(19) DANMARK

(10) DK/EP 2975024 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 D 209/88 (2006.01)* *A 61 K 31/343 (2006.01)* *A 61 K 31/381 (2006.01)*
A 61 K 31/403 (2006.01) *A 61 K 31/4439 (2006.01)* *A 61 K 31/454 (2006.01)*
A 61 K 31/4545 (2006.01) *A 61 K 31/496 (2006.01)* *A 61 K 31/5377 (2006.01)*
A 61 P 25/24 (2006.01) *A 61 P 25/28 (2006.01)* *A 61 P 35/00 (2006.01)*
A 61 P 35/02 (2006.01) *A 61 P 35/04 (2006.01)* *A 61 P 43/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2018-04-23**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2018-03-28**

(86) Europæisk ansøgning nr.: **15180863.1**

(86) Europæisk indleveringsdag: **2010-06-09**

(87) Den europæiske ansøgnings publiceringsdag: **2016-01-20**

(30) Prioritet: **2009-06-10 JP 2009139691**

(62) Stamansøgningsnr: **10786195.7**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO SE SI SK SM TR**

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(54) Benævnelse: **Tetracykliske forbindelser**

(56) Fremdragne publikationer:
WO-A1-00/69856

DESCRIPTION

[Technical field]

[0001] The present invention relates to tetracyclic compounds, salts or solvates thereof. More specifically, the present invention relates to the tetracyclic compounds and provides a medicament, pharmaceutical compositions comprising the compounds, ALK inhibitors, and pharmaceuticals for the prophylaxis or treatment of the deseases including cancer, cancer metastasis, depression or cognitive function disorder comprising the compounds. Furthermore, the compounds of the present invention can be used for the treatment of the diseases comprising administrating to the patient who is in need of the treatment of the disease the compounds described herein, salts or solvates thereof in an effective amount for the treatment of the diseases, and use of the tetracyclic compounds for the preparation of the pharmaceutical composition.

[Background art]

[0002] Anaplastic Lymphoma Kinase (ALK) is one of the receptor tyrosine kinases belonging to insulin receptor family (Non-Patent Document Nos. 1 and 2).

[0003] It was reported that, due to gene alteration of ALK (translocation, point mutation and gene amplification), an abnormal activation of ALK is eventually involved in oncogenesis.

[0004] For example, in lung cancer, ALK forms EML4-ALK due to chromosomal translocation, leading to constitutive activation of tyrosine kinase, and it acquires a tumorigenic activity (Non-Patent Document 1). In addition, the ALK translocation were reported in systemic anaplastic large cell lymphoma (ALCL) and inflammatory myofibroblastic tumors (IMTs) (Non-Patent Document Nos. 3 and 4), and esophageal cancer (Non-Patent Document 5). It was also found that active point mutation (approximately 10%) or gene amplification of ALK is involved in oncogenesis of neuroblastoma (Non-Patent Document Nos. 6 and 7).

[0005] On the other hand, it was also reported in tumors activated by pleiotrophin (PTN) or midkine (MK) (Non-Patent Document Nos. 8 and 9), both a ligand for ALK.

[0006] Further, from the study using ALK knock-out mouse, it was suggested that an inhibitor for ALK is useful as an anti-depression agent or as a preventive or therapeutic agent for cognitive function disorders (Non-Patent Document 10 and Patent Document 1).

[0007] Therefore, a compound having an inhibitory activity on ALK will be very useful for the prevention and treatment of cancer, depression and cognitive function disorders, etc.

[0008] Meanwhile, as an ALK inhibiting material, there are some compounds among multi-kinase inhibitors which have an inhibitory activity on ALK as one of their activities. For example, as an inhibitor for c-MET (mesenchymal-epithelial transition factor) and ALK, PF02341066 having a 2-aminopyridine structure was reported (Patent Document 2, Non-Patent Document Nos. 11 and 12). As an inhibitor for FAK, ZAP70, IGF-1R and ALK, etc., NVP-TAE684 having a 2,4-diaminopyrimidine structure was reported (Patent Document 3 and Non-Patent Document 13). In addition, 2,4-diaminopyrimidines and 2,4-diaminoquinazolines (Patent Document 4), pyridopyrazines (Patent Document 5), pyrazolo [3,4-C] isoquinolines (Patent Document 6), thiazoles (Patent Document 7), tricyclic compounds (Patent Document 8), and indazoles (Patent Document 9) and the like have been reported.

[0009] However, the tetracyclic compounds of the present invention are not disclosed in any of the documents described above.

[0010] As a tetracyclic compound exhibiting an anti-tumor activity, tetracyclic compounds comprising carbazole structure like ellipticine are known.

[0011] However, their action mechanism is based on interaction with DNA to exhibit cell toxicity (Non-Patent Document 15), and there is no description at all regarding the activity of inhibiting ALK by the tetracyclic compounds.

[Document list]

[0012]

[Patent Document 1] WO 2007/023310 A2

[Patent Document 2] WO 2006/021884 A2

[Patent Document 3] WO 2004/080980 A1

[Patent Document 4] WO 2009/008371 A1

[Patent Document 5] WO 2007/130468 A2

[Patent Document 6] WO 2005/009389 A2

[Patent Document 7] WO 2005/097765 A1

[Patent Document 8] WO 2008/021369 A2

[Patent Document 9] WO 2009/013126 A1

[Patent Document 10] WO 00/69856

[Non-Patent Document 1] Proc Natl Acad Sci USA, Vol. 101, pages 13306-13311, 2004

[Non-Patent Document 2] Nature, Vol. 448, pages 561-566, 2007

[Non-Patent Document 3] Blood, Vol. 72, pages 234-240, 1988

[Non-Patent Document 4] Cancer Res, Vol. 59, pages 2776-2780, 1999

[Non-Patent Document 5] World J Gastroenterol, Vol. 12, pages 7104-7112, 2006

[Non-Patent Document 6] Nature, Vol. 455, pages 930-935, 2008

[Non-Patent Document 7] Nature, Vol. 455, pages 971-974, 2008

[Non-Patent Document 8] J Biol Chem, Vol. 276, pages 16772-16779, 2001

[Non-Patent Document 9] J Biol Chem, Vol. 277, pages 35990-35999, 2002

[Non-Patent Document 10] Neuropsychopharmacology, Vol. 33, pages 685-700, 2008

[Non-Patent Document 11] Proc Am Assoc Cancer Res (AACR) 2006, 47: Abst LB-271

[Non-Patent Document 12] Proc Am Assoc Cancer Res (AACR) 2006, 47: Abst LB-273

[Non-Patent Document 13] Proc Natl Acad Sci USA Vol. 104, pages 270-275, 2007

[Non-Patent Document 14] Current Organic Chemistry, Vol. 5, Issue No. 5, pages 507-518, 2001

[Non-Patent Document 15] Current Medicinal Chemistry: Anti-Cancer Agents, Vol. 4, Issue No. 2, pages 149-172, 2004

[Summary of the invention]

[Problems to be solved by the invention]

[0013] The present invention is to provide ALK-inhibiting compounds having a novel structure. In addition, object of the present invention is to provide a pharmaceuticals for the prophylaxis or treatment comprising the ALK-inhibiting compounds that is effective for prophylaxising or treating a disease accompanied by abnormality in ALK, for example, cancer, cancer metastasis, depression and cognitive function disorder.

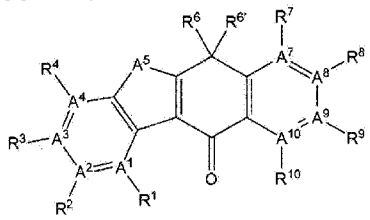
[Means for solving the problems]

[0014] As a result of extensive studies by the inventors of the present invention, it was found that the tetracyclic compounds that are represented by the following Formula (1) with a structure clearly different from any other existing pharmaceutical compounds have an excellent ALK-inhibiting activity, are useful for the treatment and prophylaxis of the diseases including cancer, cancer metastasis, depression and cognitive function disorder, and have a remarkable efficacy against said diseases. Accordingly, the present invention was completed.

[0015] Thus, according to one aspect of the present invention, the tetracyclic compounds, a medicament and a pharmaceutical

composition comprising the compounds, etc. shown below are provided.

1. [1] A compound or salt or solvate thereof represented by Formula (I):



(I)

[wherein,

A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} all represent C, or any one of A^2, A^3, A^4, A^7, A^8 and A^9 represents N (with the proviso that, when it represents N, no substituent group exists therefor) and the remainings represent C;

A^5 is selected from NR^5, O and S;

R^1 and R^{10} each independently represent [1] a hydrogen atom, [2] a cyano group, [3] a halogen atom or [4] a 4- to 10-membered heterocycloalkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s);

R^2 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group,
3. (3) a C_{2-8} alkenyl group,
4. (4) a C_{2-8} alkynyl group,
5. (5) a cyano group,
6. (6) a halogen atom,
7. (7) a $(C_{1-8}$ alkyl$)_{m2}$-amino group which may be substituted by C_{1-8} alkylsulfonyl group(s),
   m2: 0~2, and
8. (8) a nitro group;

R^3 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by [1] halogen atom(s), [2] hydroxy group(s) or [3] C_{1-8} alkoxy group(s),
3. (3) a C_{6-10} aryl group,
4. (4) a cyano group,
5. (5) a C_{1-8} alkanoyl group which may be substituted by C_{6-10} aryl group(s),
6. (6) a $(C_{1-8}$ alkyl$)_{m3a}$-aminocarbonyl group which may be substituted by one or more R^{3A},

R^{3A}: [1] a C_{6-10} aryl group, [2] a C_{1-8} alkoxy group, [3] a 5- to 14-membered heteroaryl group, or [4] a C_{6-10} aryl sulfonyl group,
m3a: 0~2,

(7) a hydroxycarbonyl group,

(8) a C_{1-8} alkoxycarbonyl group which may be substituted by [1] hydroxy group(s) or [2] C_{1-8} alkoxy group(s),

(9) a halogen atom,

(10) a $(C_{1-8}$ alkyl$)_{m3b}$-amino group which may be substituted by C_{6-10} aryl group(s),
m3b: 0~2,

(11) a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by [1] C_{6-10} aryl group(s) or [2] C_{6-10} aryloxy group(s),

(12) a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(13) a $(C_{1-8}$ alkyl$)_{m3c}$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{6-10} aryl group(s),
m3c: 0~2,

(14) a nitro group,

(15) a hydroxy group,

(16) a C_{1-8} alkoxy group which may be substituted by one or more R^{3B},

R^{3B}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, [3] a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl group, [4] a (C_{1-8} alkyl)$_{m3d}$-amino group, or [5] a halogen atom,
m3d: 0~2,

(17) a 4- to 10-membered heterocycloalkyloxy group,

(18) a 5- to 14-membered heteroaryloxy group,

(19) a (C_{1-8} alkyl)$_{m3e}$-aminocarbonyloxy group which may be substituted by C_{6-10} aryl group(s)
m3e: 0~2,

(20) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group,

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by C_{6-10} aryl group(s),

(24) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by C_{1-8} alkoxy group(s),

(25) a C_{1-8} alkoxycarbonyl (Co-8 alkyl) amino group which may be substituted by C_{1-8} alkoxy group(s),

(26) a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(27) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by one or more R^{3C},

R^{3C}: [1] a C_{1-8} alkyl group which may be substituted by halogen atom(s), or [2] a C_{1-8} alkoxy group,

(28) a C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group, and

(29) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by substituent(s) selected from the group consisting of [1] a C_{1-8} alkyl group and [2] a C_{1-8} alkoxy group;

R^4 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by halogen atom(s),
3. (3) a C_{2-8} alkenyl group,
4. (4) a C_{2-8} alkynyl group,
5. (5) a C_{3-8} cycloalkyl group,
6. (6) a cyano group,
7. (7) an aminocarbonyl group,
8. (8) a (C_{1-8} alkyl)$_{m4a}$-aminocarbonyl group,
   m4a: 1~2,
9. (9) a hydroxycarbonyl group,
10. (10) a C_{1-8} alkoxycarbonyl group,
11. (11) a halogen atom,
12. (12) a (C_{1-8} alkyl)$_{m4b}$- amino group,
    m4b: 0~2,
13. (13) a hydroxy group, and
14. (14) a C_{1-8} alkoxy group which may be substituted by hydroxy group(s);

R^5 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by one or more R^{5A},

   R^{5A}: [1] a hydroxycarbonyl group, [2] a C_{1-8} alkoxycarbonyl group, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, [5] a (C_{1-8} alkyl)$_{m5}$-amino group, [6] a C_{6-10} aryl group, or [7] a C_{1-8} alkylthio group,

m5: 0~2,

3. (3) a C_{2-8} alkenyl group,
4. (4) a C_{2-8} alkynyl group,
5. (5) a C_{3-8} cycloalkyl group, and
6. (6) a C_{1-8} alkylsulfonyl group;

R^6 and $R^{6'}$ are each independently selected from the group consisting of:

1. (1) a C_{1-8} alkyl group which may be substituted by halogen atom(s),
2. (2) a C_{2-8} alkenyl group, and
3. (3) a C_{2-8} alkynyl group; or

R^6 and $R^{6'}$ are taken together with the carbon atoms to which they are bound to form:

(4) a C_{3-8} cycloalkyl group, or

(5) a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl C_{6-10} aryl sulfonyl group(s) which may be substituted by C_{1-8} alkyl group(s);

R^7 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a halogen atom,
3. (3) a C_{1-8} alkoxy group which may be substituted by one or more R^{7A},

   R^{7A}: [1] a (C_{1-8} alkyl)m7a-amino group, [2] a hydroxy, [3] a 4- to 10-memberd heterocycloalkyl group which may be substituted by C_{1-8} alkyl group(s),

   m7a: 0~2,
4. (4) a C_{1-8} alkylsulfonyl group,
5. (5) a nitro group, and
6. (6) a hydroxyl group;

R^8 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by one or more R^{8A},

R^{8A}: [1] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8A1}, [2] a $(C_{1-8}$ alkyl$)_{m8a}$- amino group which may be substituted by a halogen atom, and [3] a hydroxy group,
m8a:0~2,

R^{8A1}: [1] a C_{1-8} alkyl group, [2] a C_{1-8} alkylsulfonyl group, [3] a $(C_{1-8}$ alkyl$)_{m8b}$-aminosulfonyl group, [4] an oxo group, [5] a C_{1-8} alkoxycarbonyl, or [6] a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) aminosulfonyl,
m8b: 0~2,

(3) a C_{2-8} alkenyl group,

(4) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B},

R^{8B}:

1. <1> a C_{1-8} alkyl group which may be substituted by one or more R^{8B1},
2. <2> a C_{2-8} alkenyl group,
3. <3> a C_{2-8} alkynyl group,
4. <4> a C_{3-8} cycloalkyl group which may be substituted by [1] cyano group(s) or [2] C_{1-8} alkyl group(s),
5. <5> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B2},
6. <6> a C_{1-8} alkoxy group which may be substituted by substituent(s) selected from the group consisting of [1] a C_{1-8} alkoxy group and [2] a C_{3-8} cycloalkyl group,
7. <7> a C_{1-8} alkoxycarbonyl group,
8. <8> a C_{1-8} alkylsulfonyl group,
9. <9> a 5- to 14-membered heteroarylsulfonyl group,

10. <10> an oxo group,
11. <11> a cyano group,
12. <12> a C_{1-8} alkanoyl group which may be substituted by one or more R^{8B3},
13. <13> a C_{3-8} cycloalkylcarbonyl group,
14. <14> a $(C_{1-8}$ alkyl$)_{m8c}$-aminosulfonyl group,
15. <15> a C_{1-8} alkylsulfonyl (C_{0-8} alkyl) amino group,
16. <16> a $(C_{1-8}$ alkyl$)_{m8d}$-amino group which may be substituted by one or more R^{8B4},
17. <17> a hydroxy group,
18. <18> a $(C_{1-8}$ alkyl$)_{m8e}$-aminocarbonyl group, or
19. <19> a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group

m8c: 0~2

m8d: 0~2

m8e: 0~2

R^{8B1}: [1] a C_{3-8} cycloalkyl group, [2] a hydroxy group, or [3] a C_{1-8} alkoxy group(s),

R^{8B2}: [1] a halogen atom, [2] a C_{1-8} alkyl group, [3] an oxo group, [4] a hydroxy group, or [5] a deuterium atom,

R^{8B3}: a $(C_{1-8}$ alkyl$)_{m8f}$-amino group,
m8f: 0~2,

R^{8B4}: [1] a C_{3-8} cycloalkyl group, or [2] a hydroxy group,

(5) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group,

(6) a $(C_{1-8}$ alkyl$)_{m8g}$-aminocarbonyl group which may be substituted by one or more R^{8C},
m8g: 0~2,

R^{8C}:[1] a hydroxy group, [2] a $(C_{1-8}$ alkyl$)_{m8h}$-amino group which may be substituted by substituent(s) selected from the group consisting of <1> a $(C_{1-8}$ alkyl$)_{m8i}$-aminosulfonyl group, <2> a C_{1-8} alkylsulfonyl group, <3> a C_{1-8} alkoxycarbonyl group and <4> a C_{1-8} alkoxycarbonyl(C_{0-8} alkyl) aminosulfonyl group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxy group which may be substituted by a hydroxy group,

m8h: 0~2,

m8i: 0~2,

(7) a 4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group which may be substituted by oxo group(s),

(8) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8D},

R^{8D}: [1] a C_{1-8} alkyl group which may be substituted by one or more R^{8D1}, [2] a hydroxy group, [3] a C_{1-8} alkylsulfonyl group, or [4] a C_{1-8} alkoxycarbonyl group,

R^{8D1}: [1] a hydroxy group, or [2] a C_{1-8} alkoxy group,

(9) a hydroxycarbonyl group,

(10) a C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted by hydroxy group(s),

(11) a halogen atom,

(12) a $(C_{1-8}$ alkyl$)_{m8j}$-amino group which may be substituted by one or more R^{8H}, m8j: 0~2,

R^{8H}: [1] a hydroxy group, or [2] a 4- to 10-membered heterocycloalkyl group,

(13) a hydroxyl group,

(14) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E},

R^{8E}:

1. <1> a hydroxy group,
2. <2> halogen atom,
3. <3> a hydroxycarbonyl group,
4. <4> a C_{1-8} alkoxycarbonyl group,
5. <5> a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8E1},
6. <6> a $(C_{1-8}$ alkyl$)_{m8k1}$-amino group which may be substituted by one or more R^{8E2},
   m8k1: 0~2,
7. <7> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8E3},
8. <8> a 5- to 14-membered heteroaryl group,
9. <9> a $(C_{1-8}$ alkyl$)_{m8k2}$-aminocarbonyl group which may be substituted by one or more R^{8E6},
   m8k2: 0~2,
10. <10> a C_{1-8} alkoxy group which may be substituted by one or more R^{8E7},
11. <11> a C_{1-8} alkylthio group,
12. <12> a C_{1-8} alkylsulfinyl group,
13. <13> a C_{1-8} alkylsulfonyl group,

R^{8E1}:

1. <1> a C_{1-8} alkoxycarbonyl group,
2. <2> a C_{1-8} alkanoyl group,
3. <3> a C_{1-8} alkylsulfonyl group,
4. <4> a $(C_{1-8}$ alkyl$)_{m8k3}$-aminosulfonyl group,
   m8k3: 0~2, or
5. <5> a 4- to 10-membered heterocycloalkyl group,

R^{8E2}:

1. <1> a hydroxy group,
2. <2> a C_{1-8} alkoxycarbonyl group which may be substituted by halogen atom(s),
3. <3> a C_{3-8} cycloalkyl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by hydroxy group(s),
4. <4> a C_{1-8} alkanoyl group which may be substituted by substituent(s) selected from the group consisting of [1] a $(C_{1-8}$ alkyl$)_{m8k4}$-amino group and [2] a halogen atom(s),
   m8k4: 0~2,
5. <5> a $(C_{1-8}$ alkyl$)_{m8k5}$-aminocarbonyl group,
   m8k5: 0~2,
6. <6> a C_{1-8} alkylsulfonyl group,
7. <7> a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by C_{1-8} alkyl group(s),
8. <8> a $(C_{1-8}$ alkyl$)_{m8k6}$-aminosulfonyl group which may be substituted by C_{1-8} alkoxycarbonyl group(s),
   m8k6: 0~2, or

R^{8E3}:

1. <1> a C_{1-8} alkyl group which may be substituted by substituent(s) selected from the group consisting of [1] a hydroxy group and [2] a C_{1-8} alkylcarbonyloxy group,
2. <2> a C_{1-8} alkylcarbonyloxy group,
3. <3> a hydroxy group,
4. <4> a C_{3-8} cycloalkyl group,
5. <5> a C_{1-8} alkoxy group,
6. <6> a C_{1-8} alkoxycarbonyl group,
7. <7> a C_{1-8} alkylsulfonyl group,
8. <8> a $(C_{1-8}$ alkyl$)_{m8k8}$-aminocarbonyl group
   m8k8: 0~2,
9. <9> a C_{1-8} alkanoyl group which may be substituted by hydroxy group(s),
10. <10> an oxo group, or
11. <11> a 4- to 10-membered heterocycloalkyl group which may be substituted by substituent(s) selected from the group

consisting of [1] a C_{1-8} alkanoyl group, [2] a C_{1-8} alkoxycarbonyl group and [3] a C_{1-8} alkylsulfonyl group,

R^{8E6}:

1. <1> a C_{2-8} alkenylcarbonyloxy group,
2. <2> a hydroxy group,
3. <3> a cyano group,
4. <4> a $(C_{1-8}$ alkyl$)_{m8k9}$-amino group which may be substituted by hydroxy group(s)
   m8k9: 0~2,
5. <5> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),
6. <6> a C_{1-8} alkylcarbonyloxy group,
7. <7> a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl group(s), or
8. <8> a 5- to 14-membered heteroaryl group,

R^{8E7}:

1. <1> a hydroxy group, or
2. <2> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

(15) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by one or more R^{8F},

R^{8F}:

<1> a C_{1-8} alkyl group which may be substituted by one or more R^{8F1},

<2> a C_{3-8} cycloalkyl group,

<3> a C_{1-8} alkanoyl group which may be substituted by halogen atom(s),

<4> a C_{1-8} alkylcarbonyloxy group,

<5> a C_{1-8} alkoxycarbonyl group,

<6> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8F2},

<7> a C_{1-8} alkyl sulfonyl group,

<8> a hydroxy group, or

[9] a C_{6-10} aryl group,

R^{8F1}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, or [3] a halogen atom,

R^{8F2}: [1] a 4- to 10-membered heterocycloalkyl group, [2] a C_{1-8} alkoxycarbonyl group, or [3] a C_{1-8} alkylsulfonyl group,

(16) a 5- to 14-membered heteroaryloxy group,

(17) a 4- to 10-membered heterocycloalkylcarbonyloxy group,

(18) a $(C_{1-8}$ alkyl$)_{m8l1}$-aminosulfonyloxy group,
m8l1: 0~2,

(19) a C_{1-8} alkyl thio group which may be substituted by [1] $(C_{1-8}$ alkyl$)_{m8l2}$-amino group(s), [2] hydroxy group(s) or [3] hydroxycarbonyl group(s),
m8l2: 0~2,

(20) a C_{1-8} alkylsulfonyl group which may be substituted by one or more R^{8G},

R^{8G}: [1] a hydroxycarbonyl group, [2] a hydroxy group, or [3] a $(C_{1-8}$ alkyl$)_{m8l3}$-amino group,
m8l3: 0~2,

(21) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group which may be substituted by C_{1-8} alkyl group(s),

(22) a C_{2-8} alkenyloxy group, and

(23) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s);

R^9 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A},

R^{9A}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9A1}, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, or [5] a hydroxycarbonyl group,

R^{9A1}: [1] a C_{1-8} alkyl group, [2] a C_{3-8} cycloalkyl group, or [3] a 4- to 10-membered heterocycloalkyl group,

(3) a C_{2-8} alkenyl group which may be substituted by one or more R^{9B},

R^{9B}: [1] a $(C_{1-8}$ alkyl$)_{m9a}$-amino group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more group R^{9B1},

R^{9B1}: [1] a C_{3-8} cycloalkyl group, or [2] a 4- to 10-membered heterocycloalkyl group,
m9a: 0~2,

(4) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C},

R^{9C}: [1] a C_{1-8} alkoxy group, [2] a $(C_{1-8}$ alkyl$)_{m9b}$-amino group which may be substituted by C_{6-10} aryl group(s), [3] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9C1}, [4] a C_{3-8} cycloalkyl group, [5] a hydroxy group, [6] a hydroxycarbonyl group, or [7] a C_{1-8} alkyloxycarbonyl group,
m9b: 0~2,

R^{9C1}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group, or [3] an oxo group,

(5) a C_{3-8} cycloalkyl group,

(6) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9D},

R^{9D}: [1] a C_{1-8} alkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s), [2] a C_{3-8} cycloalkyl group, [3] a 4- to 10-membered heterocycloalkyl group, or [4] a C_{1-6} alkylsulfonyl group, or [5] a C_{1-8} alkoxycarbonyl group,

(7) a C_{6-10} aryl group which may be substituted by one or more R^{9E},

R^{9E}: [1] a halogen atom, [2] a hydroxy group, [3] a hydroxycarbonyl group, or [4] a C_{1-8} alkyl group which may be substituted by hydroxy group(s), or [5] a C_{1-8} alkoxy group,

(8) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s),

(9) a cyano group,

(10) a C_{1-8} alkanoyl group,

(11) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by C_{1-8} alkyl group(s),

(12) a halogen atom,

(13) a $(C_{1-8}$ alkyl$)_{m9c}$- amino group which may be substituted by one or more R^{9F},
m9c: 0~2,

(14) a C_{1-8} alkylcarbonyl(C_{0-8} alkyl)amino group which may be substituted by $(C_{1-8}$ alkyl$)_{m9d}$- amino group(s),
m9d: 0~2,

(15) a C_{1-8} alkylsulfonyl(C_{0-8} alkyl)amino group,

(16) a $(C_{1-8}$ alkyl$)_{m9e}$-aminosulfonyl(C_{0-8} alkyl)amino group,
m9e: 0~2,

(17) a nitro group,

(18) a hydroxy group,

(19) a C_{1-8} alkoxy group which may be substituted by one or more R^{9G},

R^{9G}: [1] a hydroxy group, [2] a hydroxycarbonyl group, [3] a C_{6-10} aryl group which maybe substituted by C_{1-8} alkoxy group(s), [4] a $(C_{1-8}$ alkyl$)_{m9g1}$-amino group, [5] a C_{1-8} alkoxy group which may be substituted by one or more R^{9G1}, [6] a 5- to 14-membered heteroaryl group, or [7] a 4- to 10-membered heterocycloalkyloxy group which may be substituted by C_{1-8} alkyl group(s),
m9g1: 0~2,

R^{9G1}: [1] a C_{1-8} alkoxy group, or [2] a hydroxycarbonyl group,

(20) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by [1] 4- to 10-membered heterocycloalkyl group(s), or [2] C_{1-8} alkoxycarbonyl group(s),

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s),

(22) a C_{1-8} alkylthio group which may be substituted by $(C_{1-8}$ alkyl$)_{m9f}$- amino group(s),
m9f: 0~2,

(23) a C_{1-8} alkylsulfonyl group which may be substituted by $(C_{1-8}$ alkyl$)_{m9g}$-amino group(s),
m9g: 0~2,

(24) a $(C_{1-8}$ alkyl$)_{m9h}$-aminosulfonyl group,
m9h: 0~2,

(25) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by C_{1-8} alkyl group(s), and

(26) a hydroxycarbonyl group].

2. [2] The compound according to the above [1], or a salt or solvate thereof, wherein R^3 is a cyano group or a halogen atom.
3. [3] The compound according to the above [1], or a salt or solvate thereof, wherein A^5 is NR^5 and R^5 is a hydrogen atom.
4. [4] The compound according to the above [1], or a salt or solvate thereof, wherein all of the A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} are a carbon atom.
5. [5] The compound according to claim 1, or a salt or solvate thereof, wherein:

A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} all represent C, or any one of A^2, A^3, A^4, A^7, A^8 and A^9 represents N (with the proviso that, when it represents N, no substituent group exists therefor) and the remainings represent C;

A^5 is selected from NR^5, O and S;

R^1 represents [1] a hydrogen atom, [2] a cyano group, or [3] a halogen atom;

R^2 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group,
3. (3) a cyano group,
4. (4) a halogen atom, and
5. (5) a $(C_{1-8}$ alkyl$)_{m2}$-amino group which may be substituted by C_{1-8} alkylsulfonyl group(s),
   m2: 0~2;

R^3 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by halogen atom(s),
3. (3) a cyano group,
4. (4) a $(C_{1-8}$ alkyl$)_{m3a}$-aminocarbonyl group which may be substituted by one or more R^{3A},

R^{3A}: [1] a C_{6-10} aryl group, [2] a C_{1-8} alkoxy group, [3] a 5- to 14-membered heteroaryl group, or [4] a C_{6-10} aryl sulfonyl group,
m3a: 0~2,

(5) a hydroxycarbonyl group,

(6) a C_{1-8} alkoxycarbonyl group which may be substituted by hydroxy group(s),

(7) a halogen atom,

(8) a $(C_{1-8}$ alkyl$)_{m3b}$-amino group which may be substituted by C_{6-10} aryl group(s),
m3b: 0~2,

(9) a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by [1] C_{6-10} aryl group(s) or [2] C_{6-10} aryloxy group(s),

(10) a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(11) a nitro group,

(12) a hydroxy group,

(13) a C_{1-8} alkoxy group which may be substituted by one or more R^{3B},

R^{3B}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, [3] a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl group, [4] a $(C_{1-8}$ alkyl$)_{m3d}$-amino group, or [5] a halogen atom,
m3d: 0~2,

(14) a 4- to 10-membered heterocycloalkyloxy group,

(15) a 5- to 14-membered heteroaryloxy group,

(16) a $(C_{1-8}$ alkyl$)_{m3e}$-aminocarbonyloxy group which maybe substituted by C_{6-10} aryl group(s),
m3e: 0~2,

(17) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group,

(18) a C_{1-8} alkylthio group,

(19) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by C_{1-8} alkoxy group(s),

(20) a C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkoxy group(s),

(21) a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by halogen atom(s),

(22) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by C_{1-8} alkoxy group(s),

(23) a C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group, and

(24) a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by substituent(s) selected from the group consisting of [1] a C_{1-8} alkyl group and [2] a C_{1-8} alkoxy group;

R^4 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by halogen atom(s),
3. (3) a C_{3-8} cycloalkyl group,
4. (4) a cyano group,
5. (5) an aminocarbonyl group,
6. (6) a hydroxycarbonyl group,
7. (7) a halogen atom,
8. (8) a $(C_{1-8}$ alkyl$)_{m4b}$- amino group,
   m4b: 0~2,
9. (9) a hydroxy group, and
10. (10) a C_{1-8} alkoxy group which may be substituted by hydroxy group(s);

R^5 is selected from the group consisting of:

1. (1) a hydrogen atom,

2. (2) a C_{1-8} alkyl group which may be substituted by one or more R^{5A},

R^{5A}: [1] a hydroxycarbonyl group, [2] a C_{1-8} alkoxycarbonyl group, [3] a hydroxy group, [4] a C_{1-8} alkoxy group, [5] a $(C_{1-8}$ alkyl$)_{m5}$-amino group, or [6], a C_{1-8} alkylthio group, m5: 0~2, and

(3) a C_{1-8} alkylsulfonyl group;

R^6 and $R^{6'}$ are each independently:

1. (1) a C_{1-8} alkyl group, or

R^6 and $R^{6'}$ are taken together with the carbon atoms to which they are bound to form,

(2) a C_{3-8} cycloalkyl group, or

(3) a 4- to 10-membered heterocycloalkyl group;

R^7 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a halogen atom, and
3. (3) a C_{1-8} alkoxy group which may be substituted by one or more R^{7A},

R^{7A}: [1] a $(C_{1-8}$ alkyl$)_{m7a}$- amino group, or [2] a hydroxy group,
m7a:0~2;

R^8 is selected from the group consisting of:

1. (1) a hydrogen atom,
2. (2) a C_{1-8} alkyl group which may be substituted by one or more R^{8A},

R^{8A}: [1] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8A1}, [2] a $(C_{1-8}$ alkyl$)_{m8a}$- amino group which may be substituted by a halogen atom, and [3] a hydroxy group,
m8a:0~2,

R^{8A1}: [1] a C_{1-8} alkyl group, [2] a C_{1-8} alkylsulfonyl group, [3] a $(C_{1-8}$ alkyl$)_{m8b}$-aminosulfonyl group, or [4] an oxo group,
m8b: 0~2,

(3) a C_{2-8} alkenyl group,

(4) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B},

R^{8B}:

1. <1> a C_{1-8} alkyl group which may be substituted by one or more R^{8B1},
2. <2> a C_{2-8} alkynyl group,
3. <3> a C_{3-8} cycloalkyl group which may be substituted by [1] cyano group(s) or [2] C_{1-8} alkyl group(s),
4. <4> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B2},
5. <5> a C_{1-8} alkoxy group which may be substituted by substituent(s) selected from the group consisting of [1] a C_{1-8} alkoxy group and [2] a C_{3-8} cycloalkyl group,
6. <6> a C_{1-8} alkylsulfonyl group,
7. <7> an oxo group,
8. <8> a cyano group,
9. <9> a C_{1-8} alkanoyl group which may be substituted by one or more R^{8B3},
10. <10> a C_{3-8} cycloalkylcarbonyl group,
11. <11> a $(C_{1-8}$ alkyl$)_{m8c}$-aminosulfonyl group,
12. <12> a C_{1-8} alkylsulfonyl (C_{0-8} alkyl) amino group,
13. <13> a $(C_{1-8}$ alkyl$)_{m8d}$-amino group which may be substituted by one or more R^{8B4},
14. <14> a hydroxy group, or
15. <15> a $(C_{1-8}$ alkyl$)_{m8e}$-aminocarbonyl group,

m8c: 0~2,

m8d: 0~2,

m8e: 0~2,

R^{8B1}: [1] a C_{3-8} cycloalkyl group, [2] a hydroxy group, or [3] C_{1-8} alkoxy group which may be substituted by C_{1-8} alkoxy group(s),

R^{8B2}: [1] a halogen atom, [2] a C_{1-8} alkyl group, [3] an oxo group, or [4] a hydroxy group,

R^{8B3}: a $(C_{1-8}$ alkyl$)_{m8f}$-amino group,

m8f: 0~2,

R^{8B4}: [1] a C_{3-8} cycloalkyl group, or [2] a hydroxy group,

(5) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group,

(6) a $(C_{1-8}$ alkyl$)_{m8g}$-aminocarbonyl group which may be substituted by one or more R^{8C},
m8g: 0~2,

R^{8C}:[1] a hydroxy group, [2] a $(C_{1-8}$ alkyl$)_{m8h}$-amino group which may be substituted by substituent(s) selected from the group consisting of <1> a $(C_{1-8}$ alkyl$)_{m8i}$-aminosulfonyl group and <2> a C_{1-8} alkylsulfonyl group, or [3] a C_{1-8} alkylsulfonyl group,

m8h: 0~2,

m8i: 0~2,

(7) a 4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group which may be substituted by oxo group(s),

(8) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8D},

R^{8D}: [1] a C_{1-8} alkyl group which may be substituted by one or more R^{8D1}, [2] a hydroxy group, or [3] a C_{1-8} alkylsulfonyl group,

R^{8D1}: [1] a hydroxy group, or [2] a C_{1-8} alkoxy group,

(9) a hydroxycarbonyl group,

(10) a C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted by hydroxy group(s),

(11) a halogen atom,

(12) a $(C_{1-8}$ alkyl$)_{m8j}$-amino group which may be substituted by 4- to 10-membered heterocycloalkyl group(s),
m8j: 0~2,

(13) a hydroxyl group,

(14) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E},

R^{8E}:

1. <1> a hydroxy group,
2. <2> a C_{1-8} alkoxycarbonyl group,
3. <3> a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8E1},
4. <4> a $(C_{1-8}$ alkyl$)_{m8k1}$-amino group which may be substituted by one or more R^{8E2}, m8k1: 0~2,
5. <5> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8E3},
6. <6> a 5- to 14-membered heteroaryl group,
7. <7> a $(C_{1-8}$ alkyl$)_{m8k2}$-aminocarbonyl group which may be substituted by one or more R^{8E6}
   m8k2: 0~2,
8. <8> a C_{1-8} alkoxy group which may be substituted by one or more R^{8E7},
9. <9> a C_{1-8} alkylthio group,
10. <10> a C_{1-8} alkylsulfinyl group, or
11. <11> a C_{1-8} alkylsulfonyl group,

R^{8E1}:

1. <1> a C_{1-8} alkoxycarbonyl group,
2. <2> a C_{1-8} alkanoyl group,
3. <3> a C_{1-8} alkylsulfonyl group,
4. <4> a $(C_{1-8}$ alkyl$)_{m8k3}$-aminosulfonyl group
   m8k3: 0~2, or
5. <5> a 4- to 10-membered heterocycloalkyl group,

R^{8E2}:

1. <1> a hydroxy group,
2. <2> a C_{1-8} alkoxycarbonyl group,
3. <3> a C_{3-8} cycloalkyl group which may be substituted by C_{1-8} alkyl group(s) which may be substituted by hydroxy group(s),
4. <4> a C_{1-8} alkanoyl group which may be substituted by substituent(s) selected from the group consisting of [1] a $(C_{1-8}$ alkyl$)_{m8k4}$-amino group and [2] a halogen atom,
   m8k4: 0~2,
5. <5> a $(C_{1-8}$ alkyl$)_{m8k5}$-aminocarbonyl group,
   m8k5: 0~2,
6. <6> a C_{1-8} alkylsulfonyl group,
7. <7> a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by C_{1-8} alkyl group(s),
8. <8> a $(C_{1-8}$ alkyl$)_{m8k6}$-aminosulfonyl group,
   m8k6: 0~2, or

R^{8E3}:

1. <1> a C_{1-8} alkyl group which may be substituted by substituent(s) selected from the group consisting of [1] a hydroxy group and [2] a C_{1-8} alkylcarbonyloxy group,
2. <2> a hydroxy group,
3. <3> a C_{3-8} cycloalkyl group,
4. <4> a C_{1-8} alkylsulfonyl group,
5. <5> a $(C_{1-8}$ alkyl$)_{m8k8}$-aminocarbonyl group,
   m8k8: 0~2,
6. <6> a C_{1-8} alkanoyl group which may be substituted by hydroxy group(s),
7. <7> an oxo group, or
8. <8> a 4- to 10-membered heterocycloalkyl group which may be substituted by substituent(s) selected from the group consisting of [1] a C_{1-8} alkanoyl group, and [2] a C_{1-8} alkylsulfonyl group,

R^{8E6}:

1. <1> a C_{2-8} alkenylcarbonyloxy group,
2. <2> a hydroxy group,
3. <3> a cyano group,
4. <4> a $(C_{1-8}$ alkyl$)_{m8k9}$-amino group which may be substituted by hydroxy group(s),
   m8k9: 0~2,
5. <5> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),
6. <6> a 4- to 10-membered heterocycloalkyl group which may be substituted by C_{1-8} alkyl group(s), or
7. <7> a 5- to 14-membered heteroaryl group,

R^{8E7}:

1. <1> a hydroxy group, or
2. <2> a C_{1-8} alkoxy group which may be substituted by hydroxy group(s),

(15) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by one or more R^{8F}:

R^{8F}:

1. <1> a C_{1-8} alkyl group which may be substituted by one or more R^{8F1},
2. <2> a C_{3-8} cycloalkyl group,
3. <3> a C_{1-8} alkanoyl group which may be substituted by halogen atom(s),
4. <4> a C_{1-8} alkoxycarbonyl group,
5. <5> a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8F2},
6. <6> a C_{1-8} alkyl sulfonyl group, or
7. <7> a hydroxy group,

R^{8F1}: [1] a hydroxy group, [2] a C_{1-8} alkoxy group, or [3] a halogen atom,

R^{8F2}: [1] a 4- to 10-membered heterocycloalkyl group, [2] a C_{1-8} alkoxycarbonyl group, or [3] a C_{1-8} alkylsulfonyl group,

(16) a 5- to 14-membered heteroaryloxy group,

(17) a $(C_{1-8}$ alkyl$)_{m8l1}$-aminosulfonyloxy group,
m8l1: 0~2,

(18) a C_{1-8} alkylthio group which may be substituted by $(C_{1-8}$ alkyl$)_{m8l2}$-amino group(s),
m8l2: 0~2,

(19) a C_{1-8} alkylsulfonyl group which may be substituted by one or more R^{8G},

R^{8G}: [1] a hydroxycarbonyl group, [2] a hydroxy group, or [3] a $(C_{1-8}$ alkyl$)_{m8l3}$-amino group,
m8l3: 0~2,

(20) a C_{2-8} alkenyloxy group, and

(21) a C_{1-8} alkylsulfonyloxy group which may be substituted by halogen atom(s);

R^9 is selected from the group consisting of:

(1) a hydrogen atom,

(2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A},

R^{9A}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9A1}, [3] a hydroxy group, or [4] a C_{1-8} alkoxy group,

R^{9A1}: [1] a C_{1-8} alkyl group, [2] a C_{3-8} cycloalkyl group, or [3] a 4- to 10-membered heterocycloalkyl group,

(3) a C_{2-8} alkenyl group,

(4) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C},

R^{9C}: [1] a C_{1-8} alkoxy group, [2] a $(C_{1-8}$ alkyl$)_{m9b}$-amino group which may be substituted by C_{6-10} aryl group(s), [3] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9C1}, [4] a C_{3-8} cycloalkyl group, [5] a hydroxy group, or [6] a hydroxycarbonyl group,
m9b: 0~2,

R^{9C1}: [1] a C_{3-8} cycloalkyl group, [2] a 4- to 10-membered heterocycloalkyl group, or [3] an oxo group,

(5) a C_{3-8} cycloalkyl group,

(6) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9D},

R^{9D}: [1] a C_{1-8} alkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s), [2] a C_{3-8} cycloalkyl group, [3] a 4- to 10-membered heterocycloalkyl group, or [4] a C_{1-6} alkylsulfonyl group,

(7) a C_{6-10} aryl group which may be substituted by one or more R^{9E},

R^{9E}: [1] a halogen atom, [2] a hydroxy group, [3] a hydroxycarbonyl group, or [4] a C_{1-8} alkyl group which may be substituted by hydroxy group(s),

(8) a 5- to 14-membered heteroaryl group which may be substituted by C_{1-8} alkyl group(s),

(9) a cyano group,

(10) a C_{1-8} alkanoyl group,

(11) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by C_{1-8} alkyl group(s),

(12) a halogen atom,

(13) a $(C_{1-8}$ alkyl$)_{m9c}$- amino group,
m9c: 0~2,

(14) a C_{1-8} alkylcarbonyl(C_{0-8} alkyl)amino group which may be substituted by $(C_{1-8}$ alkyl$)_{m9d}$- amino group(s),
m9d: 0~2,

(15) a C_{1-8} alkylsulfonyl(C_{0-8} alkyl)amino group,

(16) a $(C_{1-8}$ alkyl$)_{m9e}$- aminosulfonyl(C_{0-8} alkyl)amino group,
m9e: 0~2,

(17) a nitro group,

(18) a hydroxy group,

(19) a C_{1-8} alkoxy group which may be substituted by one or more R^{9G},

R^{9G}: [1] a hydroxy group, [2] a hydroxycarbonyl group, [3] a C_{6-10} aryl group which maybe substituted by C_{1-8} alkoxy group(s), [4] a $(C_{1-8}$ alkyl$)_{m9g1}$-amino group, [5] a C_{1-8} alkoxy group which may be substituted by one or more R^{9G1}, or [6] a 5- to 14-membered heteroaryl group,
m9g1: 0~2,

R^{9G1}: [1] a C_{1-8} alkoxy group, or [2] a hydroxycarbonyl group,

(20) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by 4- to 10-membered heterocycloalkyl group(s),

(21) a C_{1-8} alkylthio group which may be substituted by $(C_{1-8}$ alkyl$)_{m9f}$- amino group(s),
m9f: 0~2,

(22) a C_{1-8} alkylsulfonyl group which may be substituted by $(C_{1-8}$ alkyl$)_{m9g}$-amino group(s),
m9g: 0~2,

(23) a $(C_{1-8}$ alkyl$)_{m9h}$-aminosulfonyl group,
m9h: 0~2, and

(24) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by C_{1-8} alkyl group(s);

R^{10} represents [1] a hydrogen atom, or [2] a 4- to 10-membered heterocycloalkyl group which may be substituted by 4- to 10-membered heterocycloalkyl group(s)].

6. [6] A compound according to claim 1, or salt or solvate thereof, which said compound is selected from the group consisting of:

9-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(1-isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

8-(2-tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

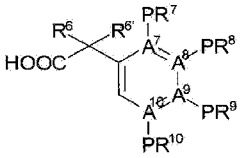
9-ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile;

6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile; and

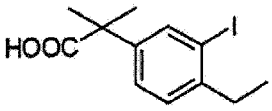
9-ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

7. [7] A medicament comprising as an active ingredient the compound according to any one of the above [1] to [5], or a salt or solvate thereof.
8. [8] An ALK inhibitor comprising as an active ingredient the compound according to any one of the above [1] to [5], or a salt or solvate thereof.
9. [9] A pharmaceutical for the prophylaxis or treatment of cancer, cancer metastasis, depression or cognitive function disorder, comprising as an active ingredient the compound according to any one of the above [1] to [5], or a salt or solvate thereof.
10. [10] A pharmaceutical composition comprising the compound according to any one of the above [1] to [5],or a salt or solvate thereof and a pharmaceutically acceptable carrier(s).
11. [11] The compounds as defined in the claims for use in the treatment of a patient suffering from the disease including cancer, cancer metastasis, depression or cognitive function disorder, comprising administering to the patient who is in need of the treatment of the disease the compound described in any one of the above [1] to [5], salt or solvate thereof in an effective amount for the treatment of the disease.
12. [12] Use of the compound described in any one of the above [1] to [5], salt or solvate thereof in the manufacture of a pharmaceutical.
13. [13] The use according to above [11] in the manufacture of a pharmaceutical composition for the treatment or prophylaxis of the disease of mammals including human, wherein the disease is related with ALK activity.
14. [14] A compound of Formula IIe:

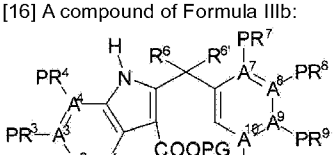


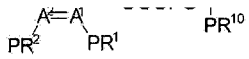
wherein, A^7 to A^{10}, R^6 and $R^{6'}$ are as defined in [1]; PR^7 to PR^{10} are the same as R^7 to R^{10} that are defined in [1] or represent a group which can be converted to R^7 to R^{10}.

15. [15] The compound of [14], wherein said Formula IIe is the following compound:



16. [16] A compound of Formula IIIb:





wherein, A^1 to A^4, A^7 to A^{10}, R^6 and R^6 are as defined in claim 1; PR^1 to PR^4 and PR^7 to PR^{10} are the same as R^1 to R^4 and R^7 to R^{10} that are defined in claim 1 or represent a group which can be converted to R^1 to R^4 and R^7 to R^{10}; PG represents a protecting group.

17. [17] A compound or a salt or a solvate thereof whereby said compound is selected from the group consisting of 6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 9-Methoxy-6,6-dimethyl-8-(4-morpholin-1-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile, 8-[4-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-piperidin-1-yl] -9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-6,6-dimethyl-8-(3-morpholin-4-yl-azetidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-8-[4-(2-hydroxy-ethylamino)-piperidin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-8-(4-ethyl-4-morpholine-4-yl-piperidine-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-8-(4-isopropyl-4-morpholine-4-yl-piperidine-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 8-(4-Amino-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-6,6-dimethyl-8-(4-2,2,3,3,5,5,6,6-d8-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 9-Ethyl-6,6-dimethyl-11-oxo-8-[4-(4-oxy-morpholin-4-yl)-piperidin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, 5,5-Dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile, 4-Fluoro-5,5-dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-pyrido[4,3-b]carbazole-8-carbonitrile, and 7-Ethyl-10,10-dimethyl-8-(4-morpholine-4-yl-piperidine-1-yl)-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile.
18. [18] 9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile or salt or solvate thereof.

[Effect of the invention]

[0016] The compounds of the present invention or salts or salvates thereof have an excellent activity of inhibiting ALK, excellent stability in organisms, and excellent solubility in water, and therefore are useful as a prophylactic or therapeutic agent for proliferative disorders (in particular, therapeutic agent). Further, the compounds of the present invention or salts salts or solvates thereof are useful as a prophylactic or therapeutic agent (in particular, therapeutic agent) for various diseases such as cancers including leukemia (acute myelogenous leukemia, chronic myelogenous leukemia, acute lymphatic leukemia, chronic lymphatic leukemia and the like), malignant lymphoma (Hodgkin lymphoma, non-Hodgkin lymphoma and the like), brain tumor, neuroblastoma, gliomatosis, thyroid cancer, myelodysplastic syndrome, head and neck cancer, esophageal cancer, stomach cancer, colon cancer, colorectal cancer, breast cancer, ovarian cancer, lung cancer, pancreatic cancer, liver cancer, gall bladder cancer, skin cancer, malignant melanoma, kidney cancer, renal pelvis-ureter cancer, bladder cancer, uterine cancer, testicle cancer, prostate cancer, and the like. Further, the compounds of the present invention are useful as a prophylactic or therapeutic agent (in particular, therapeutic agent) for infiltration/metastasis of solid tumors. Still further, the compounds of the present invention are useful as a prophylactic or therapeutic agent for other diseases that are related with ALK, for example, depression or a cognitive function disorder.

[0017] Disclosed is the use of a pharmaceutically effective amount of the pharmaceutical composition comprising the compounds of the present invention or salts or solvates thereof to a patient who is in need of such treatment or suffers from such diseases or conditions.

[Mode for carrying out the invention]

[0018] Hereinbelow, the compounds of the present invention, the method of preparing the same, and the pharmaceutical agent comprising the same will be explained.

(Definition)

[0019] According to the present invention, the "halogen atom" means a fluorine atom, a chlorine atom, a bromine atom, an iodine atom and the like. According to the present invention, when the halogen atom is a substituent group for an aromatic carbon ring, an aromatic heterocycle and the like, the preferred halogen atom includes a fluorine atom, a chlorine atom and a bromine atom. According to the present invention, when the halogen atom is a substituent group for an alkyl group or a group which comprises the alkyl as at least a part of the group (e.g., alkoxy, alkenyl, unsaturated carbocycle, unsaturated heterocycle and the like), the preferred halogen atom includes a fluorine atom. Specifically, examples thereof include a trifluoromethyl group, a pentafluoroethyl group, a heptafluoropropyl group, a nonafluorobutyl group, a trifluoromethoxy group, a pentafluoroethoxy group, a heptafluoropropoxy group, a

nonafluorobutoxy group, a trifluoroacetyl group, a pentafluoropropionyl group, a heptafluorobutyryl group and a nonafluoropentanoyl group.

[0020] The "C_{1-8} alkyl group" means a monovalent group which is derived by removing any one of hydrogen atoms from a linear or branched aliphatic hydrocarbon having 1 to 8 carbon atoms. Specifically, examples thereof include a methyl group, an ethyl group, an isopropyl group, a butyl group, a n-butyl group, an isobutyl group, a sec-butyl group, a t-butyl group, a pentyl group, an isopentyl group, a 2,3-dimethyl propyl group, a hexyl group, a 2,3-dimethyl hexyl group, a 1,1-dimethyl pentyl group, a heptyl group and an octyl group. Preferably, it is a C_{1-6} alkyl group, more preferably a C_{1-5} alkyl group, still more preferably a C_{1-4} alkyl group, and still even more preferably a C_{1-3} alkyl group.

[0021] The "C_{1-8} alkyl group which may be substituted" means an unsubtituted C_{1-8} alkyl group or a C_{1-8} alkyl group of which at least one hydrogen atom on the alkyl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkyl group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 3 substituent(s) for C_{1-6} alkyl group and a C_{1-4} alkyl group, and 1 to 2 substituent(s) for a C_{1-3} alkyl group.

[0022] The "C_{2-8} alkenyl group" means a monovalent group wherein at least one double bond (two adjacent SP2 carbon atoms) is comprised in a linear or branched aliphatic hydrocarbon group having 1 to 8 carbon atoms. Specific examples of the C_{2-8} alkenyl group include a vinyl group, an allyl group, a 1-propenyl group, a 2-propenyl group, a 1-butenyl group, a 2-butenyl group (including both cis and trans), a 3-butenyl group, a pentenyl group and a hexenyl group. Preferably, it is a C_{2-6} alkenyl group, more preferably a C_{2-5} alkenyl group, still more preferably a C_{2-4} alkenyl group, and still even more preferably a C_{2-3} alkenyl group.

[0023] The "C_{2-8} alkenyl group which may be substituted" means the unsubtituted C_{2-8} alkenyl group described above or a C_{2-8} alkenyl group of which at least one hydrogen atom on the alkenyl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the single-bonded carbon atom may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{2-8} alkenyl group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 3 substituent(s) for a C_{2-6} alkenyl group and a C_{2-4} alkenyl group, 1 to 2 substituent(s) for a C_{2-3} alkenyl group.

[0024] The "C_{2-8} alkynyl group" means a monovalent group wherein at least one triple bond (two adjacent SP carbon atoms) is comprised in a linear or branched aliphatic hydrocarbon group having 1 to 8 carbon atoms. Specific examples of the C_{2-8} alkynyl group include an ethynyl group, a 1-propynyl group, a propargyl group and a 3-butynyl group. Preferably, it is a C_{2-6} alkynyl group, more preferably a C_{2-5} alkynyl group, still more preferably a C_{2-4} alkynyl group, and still even more preferably a C_{2-3} alkynyl group.

[0025] The "C_{2-8} alkynyl group which may be substituted" means the unsubtituted C_{2-8} alkynyl group described above or a C_{2-8} alkynyl group of which at least one hydrogen atom on the alkynyl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the single-bonded carbon atom may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{2-8} alkynyl group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 3 substituent(s) for a C_{2-6} alkynyl group and a C_{2-4} alkynyl group, and 1 to 2 substituent(s) for C_{2-3} alkynyl group.

[0026] The "C_{3-8} cycloalkyl group" means an aliphatic hydrocarbon group in cyclic form. Preferably, it includes a C_{3-6} cycloalkyl group. Specifically, examples thereof include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group. Preferably, it is a C_{3-6} cycloalkyl group.

[0027] The "C_{3-8} cycloalkyl group which may be substituted" means the unsubtituted C_{3-8} cycloalkyl group described above or a C_{3-8} cycloalkyl group of which at least one hydrogen atom is substituted by a defined substituent group(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the single-bonded carbon atom may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{3-8} cycloalkyl group which may be substituted by 1 to 3 substituent(s).

[0028] The "4- to 10-membered heterocycloalkyl group" means a saturated or partially unsaturated heterocyclic group which consists of 4 to 10 ring-constituting atoms and comprises 1 to 3 hetero atoms that are selected from O, S and N. The heterocycloalkyl group can be a monocyclic, a bicyclic or a spirocyclic type heterocycloalkyl group. Specifically, examples thereof include an oxetanyl group, a tetrahydrofuryl group, a tetrahydrothienyl group, a tetrahydropyranyl group, a pyrrolidino group, a pyrrolidinyl group, a piperidino group, a piperidinyl group, a piperazino group, a piperazinyl group, a morpholino group, a morpholinyl group, a tetrahydrothiopyranyl group, a thiomorpholino group, an imidazolidinyl group, a 1,3-dioxolanyl group, a tetrahydropyranyl group, a 1,3-dioxanyl group, a 1,2,3,6-tetrahydropyridinyl group, a 1,4-Dioxa-8-aza-spiro[4.5]decanyl group, and a 1-oxa-8-aza-spiro[4.5]decanyl group. Preferably, it is a 4- to 8-membered heterocycloalkyl group, more preferably, 4- to 6-membered heterocycloalkyl group.

[0029] The "4- to 10-membered heterocycloalkyl group which may be substituted" means the unsubtituted 4- to 10-membered heterocycloalkyl group described above or a 4- to 10-membered heterocycloalkyl group of which at least one hydrogen atom on the heterocycloalkyl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkyl group which may be substituted by 1 to 4 substituent(s). More preferably, it is 1 to 4 substituent(s) for a 4- to 8-membered heterocycloalkyl group, and 1 to 3 substituent(s) for a 4- to 6-membered heterocycloalkyl group. When the substituent is an oxo group, 2 oxo group can combine with the same sulfur atom. When the salt is formed, 2 alkyl group can combine with the same nitrogen atom.

[0030] The "C_{6-10} aryl group" means a monovalent aromatic hydrocarbon ring. Specific examples of the C_{6-10} aryl group include a phenyl group, a 1-naphthyl group and a 2-naphthyl group. Preferably, it is a C_6 aryl group or a C_{10} aryl group.

[0031] The "C_{6-10} aryl group which may be substituted" means the unsubtituted C_{6-10} aryl group described above or a C_{6-10} aryl group of which at least one hydrogen atom is substituted by a defined substituent group(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{6-10} aryl group which may be substituted by 1 to 3 substituent(s).

[0032] The "5- to 14-membered heteroaryl group" means an aromatic cyclic group comprising one or more hetero atoms among 5 to 14 ring-constituting atoms. The cycle can be a monocyclic or bicyclic heteroaryl group fused to a benzene ring or a monocyclic heteroaryl ring. Specific examples thereof include a furyl group, a thienyl group, a pyrrolyl group, an imidazolyl group, a pyrazolyl group, a thiazolyl group, an isothiazolyl group, an oxazolyl group, an isooxazolyl group, an oxadiazolyl group, a thiadiazolyl group, a triazolyl group, a tetrazolyl group, a pyridyl group, a pyrimidyl group, a pyridazinyl group, a pyrazinyl group, a triazinyl group, a benzofuranyl group, a benzothienyl group, a benzothiadiazolyl group, a benzothiazolyl group, a benzoxazolyl group, a benzoxadiazolyl group, a benzoimidazolyl group, an indolyl group, an isoindolyl group, an indazolyl group, a quinolyl group, an isoquinolyl group, a cinnolinyl group, a quinazolinyl group, a quinoxalinyl group, a benzodioxolyl group, an indolizinyl group, an imidazopyridyl group and the like. Preferably, it is a 5- to 6-memebred heteroaryl group.

[0033] The "5- to 14-membered heteroaryl group which may be substituted" means the unsubtituted 5- to 14-membered ring heteroaryl group described above or a 5- to 14-membered ring heteroaryl group of which at least one hydrogen atom on the heteroaryl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a 5- to 14-membered heteroaryl group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 3 substituent(s) or 1 to 2 substituent(s) for a 5- to 6-membered heteroaryl group.

[0034] The "C_{1-8} alkanoyl group" means a C_{1-8} alkyl-C(O)- group, and the C_{1-8} alkyl group is described above. Specifically, examples thereof include acetyl, propionyl, butyryl, isobutyryl, pentanoyl, tert-butylcarbonyl and a hexanoyl group. Preferably, it is a C_{1-6} alkanoyl group, and more preferably a C_{1-3} alkanoyl group.

[0035] The "C_{1-8} alkanoyl group which may be substituted" means the unsubtituted C_{1-8} alkanoyl group described above or a C_{1-8} alkanoyl group of which at least one hydrogen atom on the alkanoyl group is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{1-8} alkanoyl group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 2 substituent(s) for a C_{1-6} alkanoyl group and a C_{1-3} alkanoyl group.

[0036] The "C_{3-8} cycloalkylcarbonyl group" means a C_{3-8} cycloalkyl-C(O)- group, and the C_{3-8} cycloalkyl group is described above. Specifically, examples thereof include a cyclopropylcarbonyl group, a cyclobutylcarbonyl group, a cyclopentylcarbonyl group, a cyclohexylcarbonyl group, a cycloheptylcarbonyl group and a cyclooctylcarbonyl group.

[0037] The "4- to 10-membered heterocycloalkylcarbonyl group" means a 4- to 10-membered heterocycloalkyl-CO- group, and the 4- to 10-membered heterocycloalkyl is described above.

[0038] The "4- to 10-membered heterocycloalkylcarbonyl group which may be substituted" means the unsubtituted 4- to 10-membered heterocycloalkylcarbonyl group described above or a 4- to 10-membered heterocycloalkylcarbonyl group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkylcarbonyl group which may be substituted by 1 to 3 substituent(s).

[0039] The "aminocarbonyl group which may be substituted" means an unsubtituted aminocarbonyl group or an aminocarbonyl group in which one or two hydrogen atoms on the nitrogen atom are substituted by a defined substituent(s). When two substituent groups are present, each substituent group can be the same or different from each other.

[0040] The "C_{3-8} cycloalkyl (C_{0-8} alkyl) aminocarbonyloxy group" means a C_{3-8} cycloalkyl-NHC(O)O- group or a C_{3-8} cycloalkyl-N(C_{1-8} alkyl) C(O)O- group, and the C_{3-8} cycloalkyl group is described above. Specifically, examples thereof include a cyclopropylaminocarbonyloxy group, a cyclobutylaminocarbonyloxy group, a cyclopentylaminocarbonyloxy group, a cyclohexylaminocarbonyloxy group, a cyclopropyl(N-methyl)aminocarbonyloxy group, and a cyclobutyl(N-methyl)aminocarbonyloxy group.

[0041] The "(C_{1-8} alkyl)$_x$-aminocarbonyl group", wherein x is a symbol defined in claims, means a $NH_2C(O)$- group, a (C_{1-8} alkyl)NH-C(O)- group, or a (C_{1-8} alkyl)$_2$N-C(O)- group. Specifically, examples thereof include a N-methyl-aminocarbonyl group, N-ethyl-aminocarbonyl group, N-n-buthyl-aminocarbonyl group, a N,N-dimethylaminocarbonyl group.

[0042] The "(C_{1-8} alkyl)$_x$-aminocarbonyl group which may be substituted" means an unsubtituted (C_{1-8} alkyl)$_x$-aminocarbonyl group described above or an (C_{1-8} alkyl)$_x$-aminocarbonyl group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety are substituted by a defined substituent(s). When plural substituent groups are present, each substituent group can be the same or different from each other.

[0043] The "C_{6-10} aryl(C_{0-8} alkyl)aminocarbonyl group"means a C_{6-10} aryl-NHC(O)-group, or a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)- group. Specifically, examples thereof include a phenyl-NHC(O)- group, or a phenyl-(N-methyl)-aminocarbonyl group, wherein the C_{6-10} aryl group and C_{1-8} alkyl are described above. Specifically, examples thereof include a phenylaminocarbonylamino group and a phenylaminocarbonyl(N-methyl)amino group.

[0044] The "4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl group" means a carbonyl group to which a 4- to 10-membered nitrogen-containig heterocycloalkyl group is bonded. Herein, the 4- to 10-membered nitrogen-containig heterocycloalkyl group (i.e., 4- to 10-membered heterocycloalkyl group comprising a nitrogen atom(s)) means a heterocycloalkyl group which consists of 4 to 10 ring-constituting atoms and comprises at least one nitrogen atom as a hetero atom. Preferably, it is bonded to the carbonyl group via a nitrogen atom that is comprised in the heterocycloalkyl ring. Specific examples of the 4- to 10-membered nitrogen-containing heterocycloalkyl group include a pyrrolidinyl group, an imidazolidinnyl group, a morpholino group, a thiomorphorino group, a piperazino group and a piperidino group. As for the 4- to 10-membered nitrogen-containig heterocycloalkylcarbonyl group, examples thereof include a pyrrolidinocarbonyl group, a piperidinocarbonyl group, a piperazinocarbonyl group and a morpholinocarbonyl group.

[0045] The "4- to 10-membered nitrogen-containig heterocycloalkylcarbonyl group, which may be substituted" means the unsubtituted 4- to 10-membered nitrogen-containig heterocycloalkylcarbonyl group as described above or a 4- to 10-membered heterocycloalkylcarbonyl group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered nitrogen-containig heterocycloalkylcarbonyl group which may be substituted by 1 to 3 substituent(s).

[0046] The "4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group" means 4- to 10-membered heterocycloalkyl NHC(O)- group, or a 4- to 10-membered heterocycloalkyl N(C_{1-8} alkyl)-C(O)- group. Specifically, examples thereof include a oxetan-3-yl amide group, and a (1,1-dioxo-tetrahydro-thiophen-3-yl)-amide group.

[0047] The "4- to 10-membered heterocycloalkyl (C_{0-8} alkyl) aminocarbonyl group which may be substituted by one or more oxo groups" means the unsubstituted 4- to 10-membered heterocycloalkylaminocarbonyl group described above or the 4- to 10-membered heterocycloalkylaminocarbonyl group in which the heterocycloalkyl moiety is substituted by at least one oxo group.

[0048] The "C_{6-10} arylsulfonyl group" means a C_{6-10} aryl-$S(O)_2$- group and the C_{6-10} aryl group is described above. Specifically, examples thereof include a phenylsulfonyl group.

[0049] The "5- to 14-membered heteroarylsulfonyl group" means a 5- to 14-membered heteroaryl-$S(O)_2$- group, and the 5- to 14-membered heteroaryl is described above. Specifically, examples thereof include a imidazol-sulfonyl group.

[0050] The "(C_{1-8} alkyl)$_x$-amino group", wherein x is a symbol defined in claims, means an amino group, a NH(C_{1-8} alkyl) group, or a N(C_{1-8} alkyl)$_2$- group. Specifically, examples thereof include amino, methylamino, ethylamino, butylamino, isopropylamino, dimethylamino and diethylamino. Preferably, it is a C_{1-3} alkylamino group.

[0051] The "(C_{1-8} alkyl)$_x$-amino group which may be substituted" means an unsubtituted (C_{1-8} alkyl)$_x$-amino group or an amino group in which one or two hydrogen atoms on the nitrogen atom or the alkyl moiety are substituted by a defined substituent(s). When two substituent groups are present, each substituent group can be the same or different from each other.

[0052] The "C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group" means a C_{1-8} alkyl-C(O)-NH-group or a C_{1-8} alkyl-C(O)-N(C_{1-8} alkyl)- group,

and the C_{1-8} alkyl is described above. Specifically, examples thereof include a methylcarbonylamino group, an ethylcarbonylamino group, a propylcarbonylamino group and a butylcarbonylamino group.

[0053] The "C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group described above or the C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atoms of the terminal alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by 1 to 3 substituent(s).

[0054] The "C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl-C(O)-NH-group or a C_{6-10} aryl-C(O)-N(C_{1-8} alkyl)- group and the C_{6-10} aryl group and the C_{1-8} alkyl group are described above. Specifically, examples thereof include a phenylcarbonylamino group.

[0055] The "C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group described above or the C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atoms of the aryl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{6-10} arylcarbonyl (C_{0-8} alkyl) amino group which may be substituted by 1 to 3 substituent(s).

[0056] The "(C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group", wherein x is a symbol defined in claims, means a $NH_2C(O)NH$-group, a (C_{1-8} alkyl)NHC(O)NH-group, a $NH_2C(O)N(C_{1-8}$ alkyl)- group, or a (C_{1-8} alkyl)NHC(O)N(C_{1-8} alkyl)- group, and the C_{1-8} alkyl is described above. Specifically, examples thereof include aminocarbonyl-(N-methyl)amino, and (N-methyl)aminocarbonyl-(N'-methyl)amino.

[0057] The "(C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted" means an unsubstituted (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group, or a (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atom on the nitrogen atom or the alkyl moiety is substituted by a defined substituent. Preferably, it is a (C_{1-8} alkyl)$_x$-aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by a phenyl group.

[0058] The "C_{1-8} alkylsulfonylamino group" means a C_{1-8} alkyl-$S(O)_2$-NH- group and the C_{1-6} alkyl group is described above. Specifically, examples thereof include a methylsulfonylamino group and an ethylsulfonylamino group.

[0059] The "(C_{1-8} alkyl)$_x$-aminosulfonyl(C_{0-8} alkyl)amino group", wherein x is a symbol defined in claims, means a $NH2S(O)_2NH$-group, a NH(C_{1-8} alkyl)-$S(O)_2NH$-group, or a N(C_{1-8} alkyl)$_2$-$S(O)_2NH$- group, a $NH_2S(O)_2N$ (C_{1-8} alkyl) - group, a NH(C_{1-8} alkyl)-$S(O)_2$ (C_{1-8} alkyl) N- group, or a N(C_{1-8} alkyl)$_2$-$S(O)_2$ (C_{1-8} alkyl) N-group, and the C_{1-8} alkyl group is described above. Specifically, examples thereof include a methylamino-sulfonylamino group and a dimethylamino-sulfonylamino group.

[0060] The "C_{1-8} alkoxy group" means a C_{1-8} alkyl-O- group. Specifically, examples thereof include a methoxy group, an ethoxy group, a 1-propoxy group, a 2-propoxy group, a n-butoxy group, an i-butoxy group, a sec-butoxy group, a t-butoxy group, a 1-pentyloxy group, a 2-pentyloxy group, a 3-pentyloxy group, a 2-methyl-1-butyloxy group, a 3-methyl-1-butyloxy group, a 2-methyl-2-butyloxy group, a 3-methyl-2-butyloxy group, a 2,2-dimethyl-1-propyloxy group, a 1-hexyloxy group, a 2-hexyloxy group, a 3-hexyloxy group, a 2-methyl-1-pentyloxy group, a 3-methyl-1-pentyloxy group, a 4-methyl-1-pentyloxy group, a 2-methyl-2-pentyloxy group, a 3-methyl-2-pentyloxy group, a 4-methyl-2-pentyloxy group, a 2-methyl-3-pentyloxy group, a 3-methyl-3-pentyloxy group, a 2,3-dimethyl-1-butyloxy group, a 3,3-dimethyl-1-butyloxy group, a 2,2-dimethyl-1-butyloxy group, a 2-ethyl-1-butyloxy group, a 3,3-dimethyl-2-butyloxy group, a 2,3-dimethyl-2-butyloxy group and a 1-methyl-cyclopropylmethoxy group. Preferably, it is a C_{1-6} alkoxy group, more preferably a C_{1-5} alkoxy group, still more preferably a C_{1-4} alkoxy group, and still even more preferably a C_{1-3} alkoxy group.

[0061] The "C_{1-8} alkoxy group which may be substituted" means an unsubtituted C_{1-8} alkoxy group or a C_{1-8} alkoxy group in which at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxy group which may be substituted by 1 to 3 substituent(s). More preferably, it is 1 to 3 substituent(s) for C_{1-6} alkoxy group and a C_{1-4} alkoxy group, and 1 to 2 substituent(s) for a C_{1-3} alkoxy group.

[0062] The "C_{1-8} alkoxycarbonyl group" means a C_{1-8} alkyl-O-C(O)- group and the C_{1-8} alkyl group is described above. Specifically, examples thereof include a methoxycarbonyl group, an ethoxycarbonyl group, a n-propoxycarbonyl group and an i-propoxycarbonyl group. Preferably, it is a C_{1-6} alkoxycarbonyl group, and more preferably a C_{1-3} alkoxycarbonyl group.

[0063] The "C_{1-8} alkoxycarbonyl group which may be substituted" means the unsubtituted C_{1-8} alkoxycarbonyl group described above

or a C_{1-8} alkoxycarbonyl group of which at least one hydrogen atom is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety of the alkoxycarbonyl group may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxycarbonyl group which may be substituted by 1 to 3 substituent(s).

[0064] The "Co-8 alkoxy (C_{0-8} alkyl) aminocarbonyl group" means a HO-NH-C(O)-group, a C_{1-8} alkyl-NH-C(O)- group, a HO-N(C_{1-8} alkyl)-C(O)- group, or a C_{1-8} alkyl-N(C_{1-8} alkyl)-C(O)- group, and has a C_{1-8} alkoxy group or a C_{1-8} alkyl group as described above. Specifically, examples thereof include a methoxyaminocarbonyl group, an ethoxyaminocarbonyl group, a n-propoxyaminocarbonyl group and an i-propoxyaminocarbonyl group. Preferably, it is a C_{1-6} alkoxyaminocarbonyl group, and more preferably a C_{1-3} alkoxyaminocarbonyl group.

[0065] The "C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted" means the unsubtituted hydroxyaminocarbonyl group described above, or a C_{1-8} alkoxyaminocarbonyl group, a hydroxy (C_{1-8} alkyl) aminocarbonyl group or a C_{1-8} alkoxy (C_{1-8} alkyl) aminocarbonyl group, wherein at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkoxy aminocarbonyl group which may be substituted by 1 to 3 substituent(s).

[0066] The "4- to 10-membered heterocycloalkyloxy group" means a 4- to 10-membered heterocycloalkyl-O- group, and the 4- to 10-membered heterocycloalkyl is described above.

[0067] The "4- to 10-membered heterocycloalkyloxy group which may be substituted" means the unsubtituted 4- to 10-membered heterocycloalkyloxy group described above or a 4- to 10-membered heterocycloalkyloxy group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkyloxy group which may be substituted by 1 to 3 substituent(s).

[0068] The "C_{6-10} aryloxy group" means a C_{6-10} aryl-O- group, and the C_{6-10} aryl group is described above.

[0069] The "5- to 14-membered heteroaryloxy group" means a 5- to 14-membered heteroaryl-O- group, and the 5- to 14-membered heteroaryl is described above. Specifically, examples thereof include a pyrimidinyloxy group.

[0070] The "C_{1-8} alkylcarbonyloxy group" means a C_{1-8} alkyl-C(O)-O- group, and the C_{1-8} alkyl is described above. Specifically, examples thereof include a methylcarbonyloxy group, an ethylcarbonyloxy group and a propylcarbonyloxy group.

[0071] The "C_{2-8} alkenylcarbonyloxy group" means a C_{2-8} alkenyl-C(O)-O- group, and the C_{2-8} alkenyl is described above. Specifically, examples thereof include a 2-methyl-2-butenoyloxy group.

[0072] The "4- to 10-membered heterocycloalkylcarbonyloxy group" means a 4- to 10-membered heterocycloalkyl-C(O)-O- group, and the 4- to 10-membered heterocycloalkyl is described above.

[0073] The "(C_{1-8} alkyl)$_x$-aminocarbonyloxy group", wherein x is a symbol defined in claims, means a NH2C(O)-O- group, a NH(C_{1-8} alkyl)-C(O)-O- group, or a N(C_{1-8} alkyl)$_2$-C(O)-O- group. Specifically, examples thereof include a methylamino-carbonyloxy group, an ethylamino-carbonyloxy group and a propylamino-carbonyloxy group.

[0074] The "(C_{1-8} alkyl)$_x$-aminocarbonyloxy group which may be substituted" means an unsubtituted (C_{1-8} alkyl)$_x$-aminocarbonyloxy group or a (C_{1-8} alkyl)$_x$-aminocarbonyloxy group group in which one or two hydrogen atoms on the nitrogen atom or the alkyl moiety are substituted by a defined substituent(s). When two substituent groups are present, each substituent group can be the same or different from each other.

[0075] The "4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group" means the 4- to 10-membered nitrogen-containing heterocycloalkyl-S(O)$_2$- group described above. Specifically, examples thereof include a morphorino-sulfonyl group.

[0076] The "4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl groupwhich may be substituted" means the unsubstituted 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group described above or the 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group in which at least one hydrogen atom of the 4- to 10-membered nitrogen-containing heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl which may be substituted by 1 to 3 substituent(s).

[0077] The "4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group" means the 4- to 10-membered nitrogen-containing heterocycloalkyl-$S(O)_2$-O-group described above. Specifically, examples thereof include a morphorino-sulfonyloxy group and a piperadino-sulfonyloxy group.

[0078] The "4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group which may be substituted" means the unsubstituted 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group described above or the 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy group in which at least one hydrogen atom of the 4- to 10-membered nitrogen-containing heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyloxy which may be substituted by 1 to 3 substituent(s).

[0079] The "C_{1-8} alkylsulfonyloxy group" means a C_{1-8} alkyl-S $(O)_2$-O- group, and the C_{1-8} alkyl is described above.

[0080] The "C_{1-8} alkylsulfonyloxy group which may be substituted" means the unsubtituted C_{1-8} alkylsulfonyloxy group described above or a C_{1-8} alkylsulfonyloxy group in which at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylsulfonyloxy group which may be substituted by 1 to 3 substituent(s). Specifically, examples thereof include a trifluoromethylsulfonyloxy group.

[0081] The "$(C_{1-8}$ alkyl$)_x$-aminosulfonyloxy group" wherein x is a symbol defined in claims, means a $NH_2S(O)_2$- group, a $N(C_{1-8}$ alkyl$)S(O)_2$- group, or a $N(C_{1-8}$ alkyl$)_2S(O)_2$- group. Specifically, examples thereof include a N-methylaminosulfonyloxy group.

[0082] The "C_{1-8} alkylthio group" means a C_{1-8} alkyl-S- group, and the C_{1-8} alkyl group is described above. Examples thereof include methylthio, ethylthio, n-propylthio, i-propylthio, n-butylthio, s-butylthio, i-butylthio, t-butylthio, n-pentylthio, 3-methylbutylthio, 2-methylbutylthio, 1-methylbutylthio, 1-ethylpropylthio, n-hexylthio, 4-methylpentylthio, 3-methylpentylthio, 2-methylpentylthio, 1-methylpentylthio, 3-ethylbutylthio, and 2-ethylbutylthio and the like. Preferably, it is a C_{1-6} alkylthio group, and more preferably a C_{1-3} alkylthio group.

[0083] The "C_{1-8} alkylthio group which may be substituted" means an unsubtituted C_{1-8} alkylthio group or a C_{1-8} alkylthio group in which at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. In addition, the alkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a C_{1-8} alkylthio group which may be substituted by 1 to 3 substituent(s).

[0084] The "C_{1-8} alkylsulfonyl group" means a C_{1-8} alkyl-$S(O)_2$- group, and the C_{1-8} alkyl group is described above. Specifically, examples thereof include a methylsulfonyl group, an ethylsulfonyl group and a n-propylsulfonyl group. Preferably, it is a C_{1-6} alkylsulfonyl group, and more preferably a C_{1-3} alkylsulfonyl group.

[0085] The "C_{1-8} alkylsulfinyl group" means a C_{1-8} alkyl-S(O)- group, and the C_{1-8} alkyl group is described above. Specifically, examples thereof include a methylsulfinyl group, an ethylsulfinyl group and a n-propylsulfinyl group. Preferably, it is a C_{1-6} alkylsulfinyl group, and more preferably a C_{1-3} alkylsulfinyl group.

[0086] The "C_{1-8} alkylsulfonyl group which may be substituted" means the unsubtituted C_{1-8} alkylsulfonyl group described above or a C_{1-8} alkylsulfonyl group in which at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{1-8} alkylsulfonyl group which may be substituted by 1 to 3 substituent(s).

[0087] The "C_{1-8} alkylsulfinyl group which may be substituted" means the unsubtituted C_{1-8} alkylsulfinyl group described above or a C_{1-8} alkylsulfinyl group in which at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{1-8} alkylsulfinyl group which may be substituted by 1 to 3 substituent(s).

[0088] The "4- to 10-membered heterocycloalkylsulfonyl group" means a 4- to 10-membered heterocycloalkyl-$S(O)_2$- group, and the 4- to 10-membered heterocycloalkyl is described above.

[0089] The "4- to 10-membered heterocycloalkylsulfonyl group which may be substituted" means the unsubtituted 4- to 10-membered heterocycloalkylsulfonyl group described above or a 4- to 10-membered heterocycloalkylsulfonyl group in which at least one hydrogen atom of the heterocycloalkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each

substituent group can be the same or different from each other. In addition, the heterocycloalkyl moiety may be substituted by a cyclic substituent group through a spiro bond. Preferably, it is a 4- to 10-membered heterocycloalkylsulfonyl group which may be substituted by 1 to 3 substituent(s).

[0090] The "(C_{1-8} alkyl)$_x$-aminosulfonyl group", wherein x is a symbl defined in claims, means a NH_2-$S(O)_2$- group,a C_{1-8} alkylamino-$S(O)_2$- group, or a (C_{1-8} alkyl)$_2$amino-$S(O)_2$- group and the C_{1-8} alkyl is described above. Specifically, examples thereof include an aminosulfonyl group, a methylaminosulfonyl group and a dimethylaminosulfonyl group.

[0091] The "(C_{1-8} alkyl)$_x$-aminosulfonyl group which may be substituted" means an unsubtituted aminosulfonyl group or a (C_{1-8} alkyl)$_x$-aminosulfonyl group in which one or two hydrogen atoms on the nitrogen atom or the alkyl moiety are substituted by a defined substituent(s). When two substituent groups are present, each substituent group can be the same or different from each other.

[0092] The "C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) amino group" means a C_{1-8} alkoxy-C(O)-NH- group or a C_{1-8} alkoxy-C(O)-N(C_{1-8} alkyl)- group, wherein the C_{1-8} alkoxy group and C_{1-8} alkyl) are described above. Specifically, examples thereof include a methoxycarbmamoyl group and an N-ethylcarbonyl-N-methyl-amino group.

[0093] The "C_{1-8} alkoxycarbony(C_{0-8} alkyl) amino group which may be substituted" means the unsubtituted C_{1-8} alkoxycarbony(C_{0-8} alkyl) amino group described above, or a C_{1-8} alkoxycarbony(C_{0-8} alkyl) amino group, wherein at least one hydrogen atom of the alkyl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{1-8} alkoxycarbony(C_{0-8} alkyl) amino group which may be substituted by 1 to 3 substituent(s).

[0094] The "C_{1-8} alkoxycarbonyl (C_{0-8} alkyl) aminosulfonyl group" means a C_{1-8} alkoxy-C(O)-NH$S(O)_2$- group or a C_{1-8} alkoxy-C(O)-N(C_{1-8} alkyl)$S(O)_2$- group, wherein the C_{1-8} alkoxy group and C_{1-8} alkyl group are described above. Specifically, examples thereof include a methoxycarbonylaminosulfonyl group and an ethoxycarbonyl-N-methyl-aminosulfonyl group.

[0095] The "C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl-O-C(O)-NH- group or a C_{6-10} aryl-O-C(O)-N(C_{1-8} alkyl)- group, wherein the C_{6-10} aryl group and C_{1-8} alkyl are described above. Specifically, examples thereof include a phenyloxycarbonylamino group and a N-methyl-N-phenyloxycarbonyl-amino group.

[0096] The "C_{6-10} aryloxycarbonyl (Co-8 alkyl) amino group which may be substituted" means the unsubstituted C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group described above or the C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atoms of the aryl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{6-10} aryloxycarbonyl (C_{0-8} alkyl) amino group which may be substituted by 1 to 3 substituent(s).

[0097] The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group" means a C_{6-10} aryl NHC(O)NH- group, a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)NH- group, a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)N(C_{1-8} alkyl)- group, or a C_{6-10} aryl-NH-C(O)N(C_{1-8} alkyl)- group, wherein the C_{6-10} aryl group and C_{1-8} alkyl are described above. Specifically, examples thereof include a phenylaminocarbonylamino group and a phenylaminocarbonyl(N-methyl)amino group.

[0098] The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted" means the unsubstituted C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group described above or the C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group in which at least one hydrogen atoms of the aryl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyl (C_{0-8} alkyl) amino group which may be substituted by 1 to 3 substituent(s).

[0099] The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group" means a C_{6-10} aryl-NHC(O)-O-, or a C_{6-10} aryl-N(C_{1-8} alkyl)-C(O)-O- group, wherein the C_{6-10} aryl group and C_{1-8} alkyl are described above. Specifically, examples thereof include a phenylaminocarbonyloxy group and a phenylaminocarbonyl(N-methyl)amino carbonyloxy group.

[0100] The "C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted" means the unsubstituted C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group described above or the C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group in which at least one hydrogen atoms of the aryl moiety is substituted by a defined substituent(s). When two or more substituent groups are present, each substituent group can be the same or different from each other. Preferably, it is a C_{6-10} aryl (C_{0-8} alkyl) aminocarbonyloxy group which may be substituted by 1 to 3 substituent(s).

[0101] The "C_{1-8} alkylsulfonyl (Co-8 alkyl) amino group" means a C_{1-8} alkyl-$S(O)_2$-NH- group, or a C_{1-8} alkyl-$S(O)_2$-N(C_{1-8} alkyl)-

group. Specifically, examples thereof include a methylsulphonylamino group and a methylsulphonyl-(N-methyl)amino group.

[0102] The "C_{2-8} alkenyloxy group" means a C_{2-8} alkenyl-O- group, wherein the C_{2-8} alkenyl group is described above. Specific examples of the C_{2-8} alkenyloxy group include a vinyloxy group and a allyloxy group.

[0103] Preferably, all of A^1, A^2, A^3, A^4, A^7, A^8, A^9 and A^{10} are C, or any one of A^2, A^4, A^7 and A^9 is N and the remainings are C (with the proviso that, when A^2, A^4, A^7 or A^9 is N, they do not have a substituent group R^2, R^4, R^7 or R^9). More preferably, all of them are C, or A^4 is N while the remainings are C, even more preferably, all of them are C, or A^4, A^7, and A^9 is N and the remainings are C (with the proviso that, when A^4, A^7, or A^9 is N, they do not have a substituent group R^4, R^7, R^9).
A^5 is preferably NR^5 or O, more preferably NR^5.,even more preferably NH.
R^1 is preferably

1. [1] a hydrogen atom,
2. [2] a halogen atom,
   and more preferably
   1. [1] a hydrogen atom,
   2. [2] a fluorine atom,
   3. [3] a chlorine atom.

      R^{10} is preferably a hydrogen atom.

[0104] R^2 is preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-5} alkyl group,
3. [3] a cyano,
4. [4] a halogen atom,

and more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group,
3. [3] a fluorine atom,
4. [4] a chlorine atom,
5. [5] a bromine atom.

And even more preferably

1. [1] a hydrogen atom,
2. [2] a halogen atom,

Still more preferably

[1] a hydrogen atom,

[0105] R^4 is preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-5} alkyl group which may be substituted by 1-11 halogen atom(s),
3. [3] a C_{3-6} cycloalkyl group,
4. [4] a cyano,
5. [5] a halogen atom,
6. [6] a $(C_{1-3}$ alkyl$)_{m4b}$-amino group (m4b: 0~2),
7. [7] a hydroxy,
8. [8] a C_{1-5} alkoxy group which may be substituted by 1-4 hydroxy(s),

and more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substituted by 1-7 halogen atom(s),

3. [3] a C_{3-5} cycloalkyl group,
4. [4] a cyano,
5. [5] a florine atom,
6. [6] a bromine atom,
7. [7] an amino (C1-3 alkyl)$_{m4b}$-amino group,
8. [8] a hydroxy,
9. [9] a C_{1-3} alkoxy group which may be substituted by 1-2 hydroxy(s).

Even more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-8} alkyl group which may be substituted by at least one halogen atom,
3. [3] a C_{3-8} cycloalkyl group,
4. [4] a cyano,
5. [5] a halogen atom,
6. [6] a hydroxy,
7. [7] a Ci-8 alkoxy group which may be substituted by a hydroxy,

Still more preferably

1. [1] a hydrogen atom,
2. [2] a halogen atom,

[0106] R^5 is preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-5} alkyl group which may be substituted by 1-5 R^{5A} substituent(s),
3. [3] a C_{1-5} alkylsulfonyl group,

and more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substituted by 1-3 R^{5A} substituent(s),
3. [3] a C_{1-3} alkylsulfonyl group.

Even more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-8} alkyl group,

Still more preferably

[1] a hydrogen atom.

[0107] R^{5A} is preferably

1. [1] a C_{1-5} alkoxycarbonyl group,
2. [2] a hydroxy,
3. [3] a C_{1-5} alkoxy group,
4. [4] a (C_{1-5} alkyl)$_{m5}$-amino group (m5: 0-2),
5. [5] a C_6 aryl,
6. [6] a C_{1-5} alkylthio group,

and more preferably

1. [1] a C_{1-3} alkoxycarbonyl group,
2. [2] a hydroxy,
3. [3] a C_{1-3} alkoxy group,
4. [4] a (C_{1-3} alkyl)$_{m5}$-amino group (m5: 0-2),
5. [5] a C_{1-3} alkylthio group,

even more preferably

1. [1] a hydroxy,
2. [2] a C_{1-5} alkoxy group,
3. [3] a $(C_{1-5}$ alkyl$)_{m5}$-amino group (m5: 0-2),
4. [4] a C_{1-5} alkylthio group.

[0108] R^6 and $R^{6'}$ are preferably

1. [1] a C_{1-8} alkyl group,
   taken together with carbon atoms to which they are bound to form
2. [2] a C_{3-8} cycloalkyl group,
3. [3] a 4- to 10-membered heterocycloalkyl group,

more preferably

1. [1] a C_{1-3} alkyl group,
   taken together with carbon atoms to which they are bound to form
2. [2] a C_{3-6} cycloalkyl group,
3. [3] a 4- to 6-membered heterocycloalkyl group,

even more preferably

1. [1] a methyl,
   taken together with carbon atoms to which they are bound to form
2. [2] a cyclopentane,
3. [3] a tetrahydropyran,
4. [4] or a piperidine.

[0109] R^7 is preferably

1. [1] a hydrogen atom,
2. [2] a fluorine atom,
3. [3] a bromine atom,
4. [4] a chlorine atom,
5. [5] a C_{1-5} alkoxy group which may be substituted by 1-4 R^{7A} substituent(s),

and more preferably

1. [1] a hydrogen atom,
2. [2] a halogen atom,

and even more preferably

1. [1] a hydrogen atom,
2. [2] a fluorine atom,
3. [3] a bromine atom,
4. [4] a chlorine atom,

and still more preferably

[1] a hydrogen atom.

[0110] R^{7a} is preferably

1. [1] a $(C_{1-5}$ alkyl$)_{m7}$-amino group (m7: 0~2),
2. [2] a hydroxy,
3. [3] a 4- to 6-memberd heterocycloalkyl group which may be substituted by C_{1-5} alkyl group(s), and more preferably
    1. [1] a $(C_{1-3}$ alkyl$)_{m7}$-amino group (m7: 2),

2. [2] a hydroxy,
3. [3] a 4- to 6-memberd heterocycloalkyl group which may be substituted by C_{1-3} alkyl group(s).

[0111] R^3 is preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-5} alkyl group which may be substitued by 1-11 halogen atom(s),
3. [3] a cyano,
4. [4] a $(C_{1-5}$ alkyl$)_{m3a}$-aminocarbonyl group (m3a: 0~2) which may be substitued by 1-5 R^{3A} substituents,
5. [5] a hydroxycarbonyl,
6. [6] a C_{1-5} alkylcarbonyl group which may be substitued by 1-4 hydroxy(s),
7. [7] a halogen atom,
8. [8] a $(C_{1-3}$ alkyl$)_{m3b}$-amino group (m3b: 0~2) which may be substituted by 1-2 C_6 aryl(s),
9. [9] a C_{1-5} alkyl carbonyl (C_{0-3} alkyl) amino group which may be substituted by 1-2 C_6 aryl(s) or 1-2 C_6 aryloxy(s),
10. [10] a C_6 arylcarbonyl (C_{0-3} alkyl) amino group which may be substituted by 1-5 C_{1-3} alkyl group(s) which may be substituted by 1-7 halogen atom(s),
11. [11] a $(C_{1-3}$ alkyl$)_{m3c}$-aminocarbonyl(C_{0-3} alkyl) amino group (m3c: 0-1) which may be substituted by a C_6 aryl,
12. [12] a nitro,
13. [13] a hydroxy,
14. [14] a C_{1-5} alkoxy group which may be substituted by 1-4 R^{3B}(s),
15. [15] a 4- to 6-membered heterocycloalkyloxy group,
16. [16] a 6-membered heteroaryloxy,
17. [17] a $(C_{1-5}$ alkyl$)_{m3e}$-aminocarbonyloxy group (m3e: 0~2) which may be substituted by 1-3 C_6 aryl(s),
18. [18] a 4- to 6-membered nitrogen-containing heterocycloalkylaminocarbonyl group,
19. [19] a C_{1-5} alkylthio group,
20. [20] a 5- to 6-membered heteroaryl group which may be substituted by 1-4 C_{1-5} alkyl group(s) which may be substituted by 1-3 C_{1-5} alkoxy group(s),
21. [21] a C_{1-3} alkoxycarbonyl (C_{0-3} alkyl) amino group which may be substituted by a C_{1-3} alkoxy group,
22. [22] a C_6 aryloxycarbonyl (C_{0-3} alkyl) amino group which maybe substituted by 1-3 C_{1-3} alkyl group(s) which may be substituted by 1-9 halogen atom(s),
23. [23] a C_6 aryloxycarbonyl (C_{0-3} alkyl) aminocarbonyl (C_{0-3} alkyl)amino group which may be substituted by 1-3 R^{3C},
24. [24] a C_{3-6} cycloalkyl (C_{0-3} alkyl) aminocarbonyloxy group, and
25. [25] a C_6 aryl (C_{0-3} alkyl) aminocarbonyloxy group which may be substituted by 1-3 substituent(s) selected from the group consisting of a C_{1-5} alkyl group and a C_{1-5} alkoxy group(s).

[0112] R^3 is more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substitued by 1-7 halogen atom(s),
3. [3]a cyano,
4. [4] a $(C_{1-4}$ alkyl$)_{m3a}$-aminocarbonyl group (m3a: 0~1) which may be substitued by 1-4 R^{3A} substituents,
5. [5] a hydroxycarbonyl,
6. [6] a halogen atom,
7. [7] a C_{1-4} alkyl carbonyl (C_{1-3} alkyl) amino group which may be substituted by 1-2 C_6 aryl(s) or 1-2 C_6 aryloxy(s),
8. [8] a C_6 arylcarbonyl (C_{0-3} alkyl) amino group which may be substituted by a C_{1-3} alkyl group which may be substituted by 1-7 halogen atom(s),
9. [9] a nitro,
10. [10] a hydroxy,
11. [11] a C_{1-4} alkoxy group which may be substituted by 1-3 R^{3B} substituent(s),
12. [12] a 4-membered heterocycloalkyloxy group,
13. [13] a $(C_{1-3}$ alkyl$)_{m3e}$-aminocarbonyloxy group (m3e:1) which maybe substituted by a C6 aryl(s),
14. [14] a 6-membered nitrogen-containing heterocycloalkylaminocarbonyl group,
15. [15] a C_{1-3} alkylthio group,
16. [16] a 5-membered heteroaryl group which may be substituted by a C_{1-5} alkyl group which may be substituted by a C_{1-3} alkoxy

group,

17. [17] a C_6 aryloxycarbonyl (C_{0-3} alkyl) aminocarbonyl (C_{0-3} alkyl)amino group which may be substituted by a R^{3C} substituent,
18. [18] a C_6 cycloalkyl (C0-2 alkyl) aminocarbonyloxy group, and
19. [19] a C_6 aryl (C_{0-3} alkyl) aminocarbonyloxy group which may be substituted by 1-2 substituent(s) selected from the group consisting of a C_{1-4} alkyl group and a C_{1-3} alkoxy group.

[0113] R^3 is still more preferably

1. [1] a hydrogen atom,
2. [2] a cyano,
3. [3] a halogen atom,

R^3 is still even more preferably

1. [1] a cyano,
2. [2] a halogen atom.

[0114] R^{3A} is preferably

1. [1] a C_6 aryl,
2. [2] a C_{1-5} alkoxy group,
3. [3] a 5- or 6-membered heteroaryl group,
4. [4] a C_6 arylsulfonyl.

[0115] R^{3B} is preferably

1. [1] a hydroxy,
2. [2] a C_{1-5} alkoxy group,
3. [3] a C_6 aryl (C_{0-3} alkyl) aminocarbonyl group,
4. [4] a $(C_{1-3}$ alkyl$)_{m3d}$-amino group (m3d: 0~2),
5. [5] a halogen atom,

more preferably

1. [1] a hydroxy,
2. [2] a C_{1-5} alkoxy group.

[0116] R^{3C} is preferably

1. [1] a C_{1-5} alkyl group which may be substituted by 1-11 halogen atom(s),
2. [2] a C_{1-5} alkoxy group,

more preferably

1. [1] a C_{1-4} alkyl group which may be substituted by 1-9 halogen atom(s),
2. [2] a C_{1-3} alkoxy group.

[0117] **R^8 is preferably**

1. [1] a hydrogen atom,
2. [2] a C_{1-5} alkyl group which may be substituted by 1-5 R^{8A} substituent(s),
3. [3] a C_{2-5} alkenyl group,
4. [4] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-4 R^{8B} substituent(s),
5. [5] a 5- to 6-membered heteroaryl group which may be substituted by 1-4 C_{1-8} alkyl group(s),

6. [6] a $(C_{1-5}$ alkyl$)_{m8g}$-aminocarbonyl group (m8g: 0~2) which may be substituted by 1-3 R^{8C} substituent(s),
7. [7] a 4- to 6-membered heterocycloalkyl (C_{0-3} alkyl) aminocarbonyl group which may be substituted by 1-2 oxo group(s),
8. [8] a 4- to 6-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by 1-4 R^{8D} substituent(s),
9. [9] a hydroxycarbonyl,
10. [10] a C_{1-5} alkoxy (C_{0-3} alkyl) aminocarbonyl group which may be substituted by 1-3 hydroxy group(s),
11. [11] a halogen atom,
12. [12] a $(C_{1-5}$ alkyl$)_{m8j}$-amino group (m8j:0~2) which may be substituted by 1-2 R^{8H} substituent(s),
13. [13] a hydroxyl,
14. [14] a C_{1-5} alkoxy group which may be substituted by 1-4 R^{8E} substituent(s),
15. [15] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by 1-5 R^{8F} substituent(s),
16. [16] a 6-membered heteroaryloxy group,
17. [17] a $(C_{1-5}$ alkyl$)_{m8l1}$-aminosulfonyloxy group (m8l1:0-2),
18. [18] a C_{1-5} alkyl thio group which may be substituted by 1-4 R^{8I} substituent(s),
19. [19] a C_{1-5} alkylsulfonyl group which may be substituted by 1-4 R^{8G} substituent(s),
20. [20] a 6-membered heterocycloalkylsulfonyl group which may be substituted by a C_{1-3} alkyl group,
21. [21] a C_{2-5} alkenyloxy group, and
22. [22] a C_{1-3} alkylsulfonyloxy group which may be substituted by 1-7 halogen atom(s).

And more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substituted by 1-3 R^{8A} substituent(s),
3. [3] a C2-4 alkenyl group,
4. [4] a 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{8B} substituent(s),
5. [5] a 5- to 6-membered heteroaryl group which maybe substituted by 1-2 C_{1-3} alkyl group(s),
6. [6] a $(C_{1-3}$ alkyl$)_{m8g}$-aminocarbonyl group (m8g: 0~2) which may be substituted by 1-2 R^{8C} substituent(s),
7. [7] a 4- to 6-membered heterocycloalkyl (C_{0-1} alkyl) aminocarbonyl group which may be substituted by 1-2 oxo group(s),
8. [8] a 6-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by 1-2 R^{8D} substituent(s),
9. [9] a hydroxycarbonyl,
10. [10] a C_{1-3} alkoxy (C_{0-3} alkyl) aminocarbonyl group which may be substituted by 1-2 hydroxy group(s),
11. [11] a bromine atom,
12. [12] a $(C_{1-3}$ alkyl$)_{m8j}$-amino group (m8j:0~2) which may be substituted by 1-2 R^{8H} substituent(s),
13. [13] a hydroxyl,
14. [14] a C_{1-5} alkoxy group which may be substituted by 1-3 R^{8E} substituent(s),
15. [15] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by 1-3 R^{8F} substituent(s),
16. [16] a 6-membered heteroaryloxy group,
17. [17] a $(C_{1-3}$ alkyl$)_{m8l1}$-aminosulfonyloxy group (m8l1:0-2),
18. [18] a C_{1-3} alkyl thio group which may be substituted by 1-2 R^{8I} substituent(s),
19. [19] a C_{1-3} alkylsulfonyl group which may be substituted by 1-2 R^{8G} substituent(s),
20. [20] a 6-membered heterocycloalkylsulfonyl group which may be substituted by a C_{1-3} alkyl group,
21. [21] a C_{2-3} alkenyloxy group, and
22. [22] a trifluoromethylsulfonyloxy group,

Even more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substituted by 1-3 R^{8A} substituent(s),
3. [3] a 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{8B} substituent(s),
4. [4] a 5- to 6-membered heteroaryl group which may be substituted by 1-2 C_{1-3} alkyl group(s),
5. [5] a 4- to 6-membered heterocycloalkyl (C0-1 alkyl) aminocarbonyl group which may be substituted by 1-2 oxo group(s),
6. [6] a 6-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by 1-2 R^{8D} substituent(s),
7. [7] a $(C_{1-3}$ alkyl$)_{m8j}$-amino group (m8j:0~2) which may be substituted by 1-2 R^{8H} substituent(s),
8. [8] a hydroxyl,
9. [9] a C_{1-5} alkoxy group which may be substituted by 1-3 R^{8E} substituent(s),
10. [10] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by 1-3 R^{8F} substituent(s),

11. [11] a 6-membered heteroaryloxy group,
12. [12] a C_{1-3} alkyl thio group which may be substituted by 1-2 R^{8I} substituent(s),
13. [13] a C_{1-3} alkylsulfonyl group which may be substituted by 1-2 R^{8G} substituent(s), and
14. [14] a C_{2-3} alkenyloxy group,

further preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-3} alkyl group which may be substituted by 1-3 R^{8A} substituent(s),
3. [3] a 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{8B} substituent(s),
4. [4] a $(C_{1-3}$ alkyl$)_{m8j}$-amino group (m8j:0~2) which may be substituted by 1-2 R^{8H} substituent(s),
5. [5] a C_{1-5} alkoxy group which may be substituted by 1-3 R^{8E} substituent(s),and
6. [6] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by 1-3 R^{8F} substituent(s),

Still more preferably

[1] a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B} described below,

Still even more preferably

[1] a 4- to 10-membered heterocycloalkyl group which may be substituted by at least one halogen atom, C_{1-8} alkyl group, or an oxo.

[0118] R^{8A} is preferably

[8A-1] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-4 R^{8A1} substituent(s),

[8A-2] a $(C_{1-5}$ alkyl$)_{m8a}$-amino group (m8a:0~2) which may be substituted by 1-11 halogen atom(s), and

[8A-3] a hydroxy;

[0119] R^{8A} is more preferably

[8A-1] a 6-membered heterocycloalkyl group which may be substituted by 1-2 R^{8A1} substituent(s),

[8A-2] a $(C_{1-3}$ alkyl$)_{m8a}$-amino group (m8a:0~2) which may be substituted by 1-11 halogen atom(s), and

[8A-3] a hydroxy;

[0120] R^{8A1} is preferably

[8A1-1] a C_{1-5} alkyl group,

[8A1-2] a C_{1-5} alkylsulfonyl group,

[8A1-3] a $(C_{1-5}$ alkyl$)_{m8b}$-aminosulfonyl group (m8b: 0~2), or

[8A1-4] an oxo group,

more preferably

[8A1-1] a C_{1-3} alkyl group,

[8A1-2] a C_{1-3} alkylsulfonyl group, or

[8A1-3] a $(C_{1-3}$ alkyl$)_{m8b}$- aminosulfonyl group (m8b: 0),

[0121] R^{8B} is preferably

[8B-1] a C_{1-6} alkyl group which may be substituted by 1-13 R^{8B1} substituent(s),

[8B-2] a C2-6 alkynyl group,

[8B-3] a C_{3-6} cycloalkyl group which may be substituted by [1] cyano(s) or [2] C_{1-6} alkyl group(s),

[8B-4] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-10 R^{8B2} substituent(s),

[8B-5] a C_{1-6} alkoxy group which may be substituted by 1-5 substituent(s) selected from the group consisting of [1] a C_{1-5} alkoxy group and [2] a C_{3-6} cycloalkyl group,

[8B-6] a C_{1-5} alkoxycarbonyl group,

[8B-7] a C_{1-5} alkylsulfonyl group,

[8B-8] a 5- to 6-membered heteroarylsulfonyl group,

[8B-9] a cyano,

[8B-10] a C_{1-6} alkanoyl group which may be substituted by 1-2 R^{8B3} substituent(s),

[8B-11] a C_{3-8} cycloalkylcarbonyl group,

[8B-12] a $(C_{1-5}$ alkyl$)_{m8c}$-aminosulfonyl group (m8c:0-2),

[8B-13] a C_{1-6} alkylsulfonyl (C_{0-6} alkyl) amino group,

[8B-14] a $(C_{1-8}$ alkyl$)_{m8d}$-amino group (m8d:0-2) which may be substituted by 1-3 R^{8B4} substituent(s),

[8B-15] a hydroxy,

[8B-16] a (C_{1-6} alkyl)m8e-aminocarbonyl group (m8e:0-2), or

[8B-17] a C_{1-4} alkoxycarbonylamino group

more preferably

[8B-1] a C_{1-5} alkyl group which may be substituted by 1-3 R^{8B1},

[8B-2] a C_{2-5} alkynyl group,

[8B-3] a C_{3-5} cycloalkyl group which may be substituted by [1] a cyano or [2] a C_{1-6} alkyl group,

[8B-4] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-8 R^{8B2} substituent(s),

[8B-5] a C_{1-5} alkoxy group which may be substituted by 1-2 substituent(s) selected from the group consisting of [1] a C_{1-3} alkoxy group and [2] a C_{3-6} cycloalkyl group,

[8B-6] a C_{1-3} alkylsulfonyl group,

[8B-7] a cyano,

[8B-8] a C_{1-6} alkanoyl group which may be substituted by a R^{8B3} substituent,

[8B-9] a C_{3-5} cycloalkylcarbonyl group,

[8B-10] a $(C_{1-3}$ alkyl$)_{m8c}$-aminosulfonyl group (m8c:1-2),

[8B-11] a C_{1-3} alkylsulfonyl (C_{0-3} alkyl) amino group,

[8B-12] a $(C_{1-5}$ alkyl$)_{m8d}$-amino group (m8d:0-1) which may be substituted by 1-2 R^{8B4} substituent(s),

[8B-13] a hydroxy, or

[8B-14] a $(C_{1-3}$ alkyl$)_{m8e}$-aminocarbonyl group (m8e:0-1).

[0122] R^{8B1} is preferably

[8B1-1] a C_{3-6} cycloalkyl group,

[8B1-2] a hydroxy,

[8B1-3] a C_{1-8} alkoxy group which may be substituted by 1-2 C_{1-5} alkoxy group(s), or

[8B1-4] a cyano,

More preferably

[8B1-1] a C_{3-5} cycloalkyl group,

[8B1-2] a hydroxy,

[8B1-3] a C_{1-8} alkoxy group which may be substituted by 1 C_{1-3} alkoxy group, or [8B1-4] a cyano,

[0123] R^{8B2} is preferably

[8B2-1] a halogen atom,

[8B2-2] a C_{1-6} alkyl group,

[8B2-3] an oxo,

[8B2-4] a hydroxy, or

[8B2-5] a deuterium atom,

more preferably

[8B2-1] a fluorine atom,

[8B2-2] a C_{1-3} alkyl group,

[8B2-3] an oxo, or

[8B2-4] a hydroxyl.

[0124] R^{8B3} is preferably

[8B3-1] a $(C_{1-6}$ alkyl$)_{m8f}$-amino group (m8f:0-2),

more preferably

[8B3-1] a $(C_{1-3}$ alkyl$)_{m8f}$-amino group (m8f: 2).

[0125] R^{8B4} is preferably

[8B4-1] a C_{3-6} cycloalkyl group, or

[8B4-2] a hydroxy;

[0126] R^{8C} is preferably

[8C-1] a hydroxyl,

[8C-2] a $(C_{1-3}$ alkyl$)_{m8h}$-amino group (m8h:0-1) which may be substituted by a $(C_{1-3}$ alkyl$)_{m8i}$-aminosulfonyl group (m8i:0-2),

[8C-3] a C_{1-3} alkylsulfonyl group,

[0127] R^{8D} is preferably

[8D-1] a C_{1-6} alkyl group which may be substituted by a R^{8D1} substituent,

[8D-2] a hydroxy group,

[8D-3] a C_{1-3} alkylsulfonyl group, or

[8D-4] a C_{1-4} alkoxycarbonyl group;

[0128] R^{8D1} is preferably

[8D1-1] a hydroxy group, or

[8D1-2] a C_{1-3} alkoxy group;

[0129] R^{8H} is preferably

[8H-1] a 4- to 6-membered heterocycloalkyl group,

[0130] R^{8E} is preferably

[8E-1] a hydroxy group,

[8E-2] a C_{1-8} alkoxy group which may be substituted by 1-2 R^{8E7} substituent(s),

[8E-3] a C_{1-3} alkylsulfonyl group,

[8E-4] a C_{1-4} alkoxycarbonyl group,

[8E-5] a 4- to 6-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by 1-2 R^{8E1} substituent(s),

[8E-6] a $(C_{1-5}$ alkyl$)_{m8k1}$-amino group (m8k1: 0~2) which may be substituted by a R^{8E2} substituent,

[8E-7] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-4 R^{8E3} substituent(s),

[8E-8] a 5- to 6-membered heteroaryl group,

[8E-9] a $(C_{1-6}$ alkyl$)_{m8k2}$-aminocarbonyl group (m8k2: 0~2) which may be substituted by 1-2 R^{8E6} substituent(s),

[8E-10] a C_{1-5} alkoxy group which may be substituted by a R^{8E7} substituent,

[8E-11] a C_{1-3} alkylthio group,

[8E-12] a C_{1-3} alkylsulfinyl group,

[8E-13] a C_{1-5} alkylsulfonyl group,

[8E-14] a C_{1-3} alkylsulfonyl (C_{0-8} alkyl) amino group,

[8E-15] a 4- to 6-membered heterocycloalkylsulfonyl (C_{0-3} alkyl) amino group which may be substituted by 1-3 C_{1-5} alkyl group(s);

more preferably

[8E-1] a $(C_{1-3}$ alkyl$)_{m8k1}$-amino group (m8k1: 2) which may be substituted by one or more R^{8E2},

[8E-2] a C_{1-8} alkoxy group which may be substituted by one or more R^{8E7},

[8E-3] a C_{1-3} alkylsulfonyl group,

[8E-4] a $(C_{1-5}$ alkyl$)_{m8k1}$-amino group (m8k1: 0~2) which may be substituted by a R^{8E2} substituent,

[8E-5] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-4 R^{8E3} substituent(s),

[8E-6] a 4- to 6-membered heterocycloalkylsulfonylamino group which may be substituted by 1-2 C_{1-3} alkyl group(s);

[0131] R^{8E1} is preferably

[8E1-1] a C_{1-4} alkoxycarbonyl group,

[8E1-2] a C_{1-3} alkanoyl group,

[8E1-3] a C_{1-5} alkylsulfonyl group,

[8E1-4] a $(C_{1-3}$ alkyl$)_{m8k3}$-aminosulfonyl group (m8k3: 0~2),

[8E1-5] a 4- to 6-membered heterocycloalkyl group;

[0132] R^{8E2} is preferably

[8E2-1] a hydroxy group,

[8E2-2] a C_{1-6} alkoxycarbonyl group,

[8E2-3] a C3-6 cycloalkyl group which may be substituted by a C_{1-8} alkyl group which may be substituted by a hydroxy,

[8E1-4] a C_{1-5} alkanoyl group which may be substituted by 1-3 substituent(s) selected from the group consisting of [1] a $(C_{1-3}$ alkyl$)_{m8k4}$-amino group (m8k4: 0~2) and [2] a halogen atom,

[8E2-5] a $(C_{1-3}$ alkyl$)_{m8k5}$-aminocarbonyl group (m8k5: 0~2),

[8E2-6] a C_{1-3} alkylsulfonyl group,

[8E2-7] a $(C_{1-3}$ alkyl$)_{m8k6}$-aminosulfonyl group (m8k6: 0-1) which may be substituted by a C_{1-4} alkoxycarbonyl group.

more preferably

[8E2-1] a hydroxy group.

[0133] R^{8E3} is preferably

[8E3-1] a C_{1-6} alkyl group which may be substituted by 1-3 substituent(s) selected from the group consisting of [1] a hydroxy group or [2] a C_{1-3} alkylcarbonyloxy group,

[8E3-2] a C_{1-4} alkylcarbonyloxy group,

[8E3-3] a hydroxy group,

[8E3-4] a C_{3-5} cycloalkyl group,

[8E3-5] a C_{1-4} alkoxycarbonyl group,

[8E3-6] a C_{1-5} alkylsulfonyl group,

[8E3-7] a $(C_{1-3}$ alkyl$)_{m8k8}$-aminocarbonyl group (m8k8: 0~2),

[8E3-8] a C_{1-3} alkanoyl group which may be substituted by a hydroxy,

[8E3-9] an oxo group, or

[8E3-10] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-3 substituent(s) selected from the group consisting of [1] a C_{1-3} alkanoyl group, [2] a C_{1-4} alkoxycarbonyl group, or [3] a C_{1-3} alkylsulfonyl group;

more preferably

[8E3-1] a $(C_{1-3}$ alkyl$)_{m8k8}$-aminocarbonyl group (m8k8: 0~2), or

[8E3-2] an oxo group;

[0134] R^{8E4} is preferably

[8E4-1] a 4- to 6-membered heterocycloalkyl group,

[8E4-2] a C_{1-3} alkanoyl group,

[8E4-3] a C_{1-3} alkoxycarbonyl group,

[8E4-4] a C_{1-3} alkylsulfonyl group,

[8E4-5] a C_{1-3} alkylaminosulfonyl group;

[0135] R^{8E6} is preferably

[8E6-1] a C_{2-3} alkenylcarbonyloxy group,

[8E6-2] a hydroxy group,

[8E6-3] a cyano,

[8E6-4] a $(C_{1-3}$ alkyl$)_{m8k9}$-amino group (m8k9: 0-2) which may be substituted by 1-2 hydroxy group(s),

[8E6-5] a C_{1-3} alkoxy group which may be substituted by a hydroxy,

[8E6-6] a C_{1-4} alkylcarbonyloxy group,

[8E6-7] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-3 C_{1-8} alkyl group(s),

[8E6-8] a 5- to 6-membered heteroaryl group;

[0136] R^{8E7} is preferably

[8E7-1] a hydroxy group,

[8E7-2] a C_{1-3} alkoxy group which may be substituted by a hydroxy;

[0137] R^{8F} is preferably

[8F-1] a C_{1-5} alkyl group which may be substituted by 1-3 R^{8F1} substituent(s),

[8F-2] a C_{3-6} cycloalkyl group,

[8F-3] a C_{1-3} alkanoyl group which may be substituted by 1-7 halogen atom(s),

[8F-4] a C_{1-5} alkylcarbonyloxy group,

[8F-5] a C_{1-5} alkoxycarbonyl group,

[8F-6] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{8F2} substituent(s),

[8F-7] a C_{1-5} alkylsulfonyl group, or

[8F-8] a hydroxy group;

More preferably

[8F-1] a C_{1-3} alkyl group which may be substituted by a R^{8F1} substituent,]

[8F-2] a C_{3-5} cycloalkyl group,

[8F-3] a 4- to 6-membered heterocycloalkyl group which may be substituted by a R^{8F2} substituent,

[8F-4] a C_{1-3} alkylsulfonyl group,

[0138] R^{8F1} is preferably

[8F1-1] a hydroxy group,

[8F1-2] a C_{1-5} alkoxy group, or

[8F1-3] a halogen atom;

[0139] R^{8F2} is preferably

[8F2-1] a 4- to 6-membered heterocycloalkyl group,

[8F2-2] a C_{1-5} alkoxycarbonyl group, or

[8F2-3] a C_{1-3} alkylsulfonyl group,

[0140] R^{8G} is preferably

[8G-1] a hydroxycarbonyl group,

[8G-2] a hydroxy group, or

[8G-3] a $(C_{1-5}$ alkyl$)_{m8l3}$-amino group (m8l3: 0~2),

[0141] R^{9} is preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-8} alkyl group which may be substituted by 1-8 R^{9A} substituent(s),
3. [3] a C2-6 alkenyl group,
4. [4] a C_{2-8} alkynyl group which may be substituted by 1-6 R^{9C} substituent(s),
5. [5] a C_{3-6} cycloalkyl group,
6. [6] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-5 R^{9D} substituent(s),
7. [7] a C_6 aryl group which may be substituted by 1-2 R^{9E} substituent(s),
8. [8] a 5- to 6-membered heteroaryl group which may be substituted by 1-3 C_{1-5} alkyl group(s),
9. [9] a cyano,
10. [10] a C_{1-6} alkanoyl group,
11. [11] a 4- to 6-membered nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by a C_{1-5} alkyl group,
12. [12] a halogen atom,
13. [13] a (C_{1-4} alkyl)m9c-amino group (m9c: 0~2) which may be substituted by a R^{9F} substituent,
14. [14] a hydroxy,
15. [15] a C_{1-6} alkoxy group which may be substituted by 1-5 R^{9G} substituent(s),
16. [16] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by one or two 4- to 6-membered heterocycloalkyl group(s),

17. [17] a C_{1-5} alkylthio group which may be substituted by $(C_{1-3}$ alkyl$)_{m9f}$-amino group(s) (m9f: 0~2),
18. [18] a C_{1-5} alkylsulfonyl group which may be substituted by $(C_{1-3}$ alkyl$)_{m9g}$-amino group(s) (m9g: 0~2),
19. [19] a $(C_{1-3}$ alkyl$)_{m9h}$-aminosulfonyl group (m9h: 0~2),
20. [20] a 4- to 6-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by a C_{1-3} alkyl group;

More preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-6} alkyl group which may be substituted by a R^{9A} substituent,
3. [3] a C_{2-5} alkenyl group,
4. [4] a C_{2-8} alkynyl group which may be substituted by a R^{9C} substituent,
5. [5] a C_{3-6} cycloalkyl group,
6. [6] a 4- to 6-membered heterocycloalkyl group which may be substituted by a R^{9D} substituent,
7. [7] a 5- to 6-membered heteroaryl group which may be substituted by a C_{1-5} alkyl group,
8. [8] a cyano,
9. [9] a C_{1-3} alkanoyl group,
10. [10] a halogen atom,
11. [11] a $(C1\text{-}4$ alkyl$)_{m9b}$-n amino group (m9b: 0),
12. [12] a hydroxy,
13. [13] a C_{1-6} alkoxy group which may be substituted by 1-3 R^{9G} substituent(s),
14. [14] a 4- to 6-membered heterocycloalkyloxy group which may be substituted by a 4- to 6-membered heterocycloalkyl group,

Even more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-8} alkyl group which may be substituted by one or more R^{9A} substituent(s),
3. [3] a C_{2-8} alkenyl group which may be substituted by one or more R^{9B} substituent(s),
4. [4] a C_{2-8} alkynyl group which may be substituted by one or more R^{9C} substituent(s),
5. [5] a C_{3-8} cycloalkyl group,
6. [6] a halogen atom,

Still more preferably

1. [1] a hydrogen atom,
2. [2] a C_{1-8} alkyl group which may be substituted by one or more R^{9A} substituent(s),
3. [3] a C_{2-8} alkynyl group which may be substituted by one or more R^{9C} substituent(s).

[0142] R^{9A} is preferably

[9A-1] a C_{3-6} cycloalkyl group,

[9A-2] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{9A1} substituent(s),

[9A-3] a hydroxy group, or

[9A-4] a C_{1-6} alkoxy group,

More preferably

[9A-1] a 4- to 6-membered heterocycloalkyl group which may be substituted by a R^{9A1} substituent,

[9A-2] a hydroxy group, or

[9A-3] a C_{1-3} alkoxy group,

[0143] R^{9A1} is preferably

[9A1-1] a C_{1-5} alkyl group,

[9A1-2] a C_{3-5} cycloalkyl group, or

[9A1-3] a 4- to 6-membered heterocycloalkyl group,

More preferably

[9A1-1] a C_{1-3} alkyl group,

[9A1-2] a C_3 cycloalkyl group, or

[9A1-3] a 4-membered heterocycloalkyl group,

[0144] R^{9C} is preferably

[9C-1] a C_{1-8} alkoxy group,

[9C-2] a (C_{1-5} alkyl)m9b-amino group (m9b: 0~2) which may be substituted by 1-2 C6 aryl group(s),

[9C-3] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-3 R^{9C1} substituent(s),

[9C-4] a C_{3-6} cycloalkyl group,

[9C-5] a hydroxy group, or

[9C-6] a hydroxycarbonyl group;

More preferably

[9C-1] a C_{1-5} alkoxy group,

[9C-2] a $(C_{1-3}$ alkyl$)_{m9b}$-amino group (m9b: 2) which may be substituted by 1-2 C_6 aryl group(s),

[9C-3] a 4- to 6-membered heterocycloalkyl group which may be substituted by 1-2 R^{9C1} substituent(s),

[9C-4] a C_{3-5} cycloalkyl group,

[9C-5] a hydroxy group.

[0145] R^{9C1} is preferably

[9C1-1] a C_{3-5} cycloalkyl group,

[9C1-2] a 4- to 6-membered heterocycloalkyl group, or

[9C1-3] an oxo group,

More preferably

[9C1-1] a C3 cycloalkyl group,

[9C1-2] a 4- to 6-membered heterocycloalkyl group, or

[9C1-3] an oxo group,

[0146] R^{9D} is preferably

[9D-1] a C_{1-5} alkyl group which may be substituted by one or two 4- to 6-membered heterocycloalkyl group(s),

[9D-2] a C_{3-5} cycloalkyl group,

[9D-3] a 4- to 6-membered heterocycloalkyl group, or [9D-4] a C_{1-3} alkylsulfonyl group;

More preferably

[9D-1] a C_{1-5} alkyl group which may be substituted by a 4- to 6-membered heterocycloalkyl group,

[9D-2] a 4- to 6-membered heterocycloalkyl group, or [9D-3] a methylsulfonyl group;

[0147] R^{9E} is preferably

[9E-1] a halogen atom,

[9E-2] a hydroxy group,

[9E-3] a hydroxycarbonyl group, or

[9E-4] a C_{1-3} alkyl group which may be substituted by a hydroxy;

[0148] R^{9F} is preferably

[9F-1] a C_{1-3} alkylsulfonyl group,

[9F-2] a $(C_{1-3}$ alkyl$)_{m9f1}$-aminosulfonyl group (m9f1: 0~2), or

[9F-3] a C_{1-3} alkanoyl group which may be substituted by $(C_{1-3}$ alkyl$)_{m9f2}$-amino group(s) (m9f2: 0~2),

[0149] R^{9G} is preferably

[9G-1] a hydroxy group,

[9G-2] a hydroxycarbonyl group,

[9G-3] a C_6 aryl group which may be substituted by C_{1-3} alkoxy group(s),

[9G-4] a $(C_{1-3}$ alkyl$)_{m9g1}$-amino group (m9g1: 0~2),

[9G-5] a C_{1-5} alkoxy group which may be substituted by 1-3 R^{9G1} substituent(s), or

[9G-6] a 5- to 6-membered heteroaryl group;

More preferably

[9G-1] a hydroxy group,

[9G-2] a $(C_{1-3}$ alkyl$)_{m9g1}$-amino group (m9g1: 0~2),

[9G-3] a C_{1-3} alkoxy group which may be substituted by a R^{9G1} substituent, or

[9G-4] a 5- to 6-membered heteroaryl group;

[0150] R^{9G1} is preferably

[9G1-1] a C_{1-3} alkoxy group, or

[9G1-2] a hydroxycarbonyl group.

[0151] Preferably, A^5 is NH, while the remaining are C, R^3 is a cyano group, R^6 and $R^{6'}$ are methyl, R^8 is (1) a hydrogen atom, (2) a C_{1-8} alkyl group which may be substituted by one or more R^{8A}, (3) a C_{2-8} alkenyl group, (4) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B}, (5) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group, (6) a $(C_{1-8}$ alkyl$)_{m8g}$-aminocarbonyl group which may be substituted by one or more R^{8C}, (7) a 4- to 10-membered

nitrogen-containing heterocycloalkylcarbonyl group which may be substituted by one or more R^{8D}, (8) a hydroxycarbonyl group, (9) a C_{0-8} alkoxy (C_{0-8} alkyl) aminocarbonyl group which may be substituted by one or more hydroxy group(s), (10) a halogen atom, (11) a hydroxy group, (12) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E}, (13) a 4- to 10-membered heterocycloalkyloxy group which may be substituted by one or more R^{8F}, (14) an aminosulfonyloxy group which may be substituted by one or more C_{1-8} alkyl group(s), (15) a C_{1-8} alkyl thio group which may be substituted by a $(C_{1-8}$ alkyl$)_n$-amino group, or (16) a C_{1-8} alkylsulfonyl group which may be substituted by R^{8G}, R^9 is (1) a hydrogen atom, (2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A}, (3) a C_{2-8} alkenyl group which may be substituted by one or more R^{9B}, (4) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C}, (5) a C_{3-8} cycloalkyl group, (6) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{9D}, (7) a C_{6-10} aryl group which may be substituted by one or more R^{9E}, (8) a 5- to 14-membered heteroaryl group which may be substituted by a C_{1-8} alkyl group, (9) a cyano group, (10) a C_{1-8} alkanoyl group, (11) a 4- to 10-membered nitrogen-containing heterocycloalkylcarbonyl groupwhich may be substituted by a C_{1-8} alkyl group, (12) a halogen atom, (13) a $(C_{1-8}$ alkyl$)_{m9c}$- amino group which may be substituted by one or more R^{9F}, (14) a C_{1-8} alkylsulfonylamino group, (15) a nitro group, (16) a hydroxy group, (17) a C_{1-8} alkoxy group which may be substituted by one or more R^{9G}, (18) a C_{1-8} alkyl thio group which may be substituted by a $(C_{1-8}$ alkyl$)_{m9f}$- amino group, (19) a C_{1-8} alkylsulfonyl group which may be substituted by a $(C_{1-8}$ alkyl$)_{m9g}$-amino group, (20) a $(C_{1-8}$ alkyl$)_{m9h}$-aminosulfonyl group, or (21) a 4- to 10-membered nitrogen-containing heterocycloalkylsulfonyl group which may be substituted by a C_{1-8} alkyl group, and R^1, R^2, R^5, R^7 and R^{10} are defined above.

[0152] More preferably, A^5 is NH while the remaining are C, R^3 is a cyano group, R^6 and R^6 are methyl groups, R^8 is (1) a hydrogen atom, (2) a C_{1-8} alkyl group which may be substituted by one or more R^{8A}, (3) a 4- to 10-membered heterocycloalkyl group which may be substituted by one or more R^{8B}, or (4) a C_{1-8} alkoxy group which may be substituted by one or more R^{8E}, R9 is (1) a hydrogen atom, (2) a C_{1-8} alkyl group which may be substituted by one or more R^{9A}, (3) a C_{2-8} alkynyl group which may be substituted by one or more R^{9C}, (4) a C_{3-8} cycloalkyl group, or (5) a halogen atom, and R^1, R^2, R^5, R^7 and R^{10} are an hydrogen atom.

[0153] According to the present invention, examples of the salts of the compounds that are represented by the Formula (I) include hydrochloric acid salt, hydrobromic acid salt, hydriodic acid salt, phosphoric acid salt, phosphonic acid salt, sulfuric acid salt, sulfonic acid salt such as methanesulfonic acid salt, p-toluene sulfonic acid salt and the like, carboxylic acid salt such as acetic acid salt, citric acid salt, malic acid salt, tartaric acid salt, succinic acid salt, salicylic acid salt and the like, or alkali metal salt such as sodium salt, potassium salt and the like, alkaline earth metal salt such as magnesium salt, calcium salt and the like, ammonium salt such as ammonium salt, alkyl ammonium salt, dialkyl ammonium salt and trialkyl ammonium salt tetraalkyl ammonium salt. Preferably, the salts are pharmaceutically acceptable salts. These salts are produced by brining the compounds described above in contact with an acid or a base which can be used for the production of a pharmaceutical product.

[0154] According to the present invention, the compounds that are represented by the Formula (I) or salts thereof can be an anhydride or a solvate such as a hydrate and the like. Herein, the term "solvate (d)" indicates a phenomenon by which solute molecules or ions contained in a solution strongly attract neighboring solvent molecules to form a huge group of molecules. When the solvent is water, it is called "hydrate (d)." The solvate can be any one of a hydrate and a non-hydrate. Preferably, the solvates are pharmaceutically acceptable solvates. For the non-hydrate, alcohol (for example, methanol, ethanol, n-propanol), dimethylformamide and the like can be used.

[0155] The compounds of the present invention and salts thereof may be present in several tautomer forms, for example, enol and imine form, keto and enamine form, and a mixture thereof. In a solution, a tautomer is present as a mixture of tautomeric set. In case of solid form, one type of tautomer is generally present in dominant ratio. In this regard, even if only one type of tautomer is described, the present invention includes all types of tautomer of the compounds of the present invention.

[0156] The present invention includes all types of stereoisomer of the compounds of the present invention that are represented by the Formula (I) (for example, enantiomer, diastereomer (including cis and trans geometric isomer)), racemate of the isomer and a mixture thereof. For example, the compounds having the Formula (I) of the present invention may have one or more asymmetric center, and the present invention includes a racemic mixture, a diastereomer mixture and enantiomer of such compound.

[0157] When the compounds of the present invention are obtained in free form, they can be converted into a salt, a hydrate or solvate thereof which can be formed from the compounds according to a method generally known in the art.

[0158] Further, when the compounds of the present invention are obtained in the form of a salt, hydrate or solvate of the compounds, they can be converted to free form according to a method generally known in the art.

[0159] The present invention include all isotopes of compounds that are represented by the Formula (I). The isotopes of the

compounds of the present invention indicate the compounds of the present invention in which at least one atom is substituted by an atom with the same atomic number (i.e., number of protons) but with different mass number (sum of the number of protons and the number of neutrons). Example of the isotopes that are included in the compounds of the present invention includes a hydrogen atom, a carbon atom, a nitrogen atom, an oxygen atom, a phosphorus atom, a sulfur atom, a fluorine atom, a chlorine atom and the like, and ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{17}O, ^{18}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, ^{36}Cl and the like are included. In particular, a radioisotope which decays by emitting radiation, for example ^{3}H and ^{14}C, are useful for determining the distribution of a pharmaceutical agent or a compound in a living tissue, etc. On the other hand, a stable isotope does not degrade and remains in almost the same amount without exhibiting radioactivity, and therefore can be safely used. Isotopes of the compounds of the present invention can be converted by replacing a chemical reagent used for synthesis with a chemical reagent comprising a corresponding radioisotope according to a method generally known in the art.

[0160] Derivatives of the compounds having the Formula (I) can be converted to the compounds having the Formula (I) or salts or solvates thereof after administration by enzymatic or non-enzymatic degradation under a physiological condition.

[0161] Such derivative converts into desired drug form at specific pH or by an enzymatic action. Such derivative is a compound having a hydrolyzable ester residue which produces a free acid in organisms. Examples of such hydrolyzable ester residue include a residue having a carboxyl moiety of which free hydrogen (for example, a free hydrogen in a carboxyl group when Y in the Formula (I) has a carboxyl group) is replaced by a C_{1-4} alkyl group, a C_{2-7} alkanoyloxymethyl group, a 1-(alkanoyloxy)ethyl group having 4 to 9 carbon atoms, a 1-methyl-1-(alkanoyloxy)-ethyl group having 5 to 10 carbon atoms, an alkoxycarbonyloxymethyl group having 3 to 5 carbon atoms, a 1-(alkoxycarbonyloxy)ethyl group having 4 to 7 carbon atoms, a 1-methyl-1-(alkoxycarbonyloxy)ethyl group having 5 to 8 carbon atoms, a N-(alkoxycarbonyl)aminomethyl having 3 to 9 carbon atoms, a 1-(N-(alkoxycarbonyl)amino)ethyl group having 4 to 10 carbon atoms, a 3-phthalidyl group, a 4-crotonolactonyl group, a γ-butyrolacton-4-yl group, a di-N,N-(C_{1-2})alkylamino-(C_{2-3})alkyl group (for example, N,N-dimethylaminoethyl group), a carbamoyl(C_{1-2})alkyl group, a N,N-di(C_{1-2})alkylcarbamoyl-(C_{1-2})alkyl group, a piperidino(C_{2-3})alkyl group, a pyrrolidino(C2-3)alkyl group, or a morpholino(C_{2-3}) alkyl group, but not limited thereto.

Representative preparation method

[0162] The compounds having the Formula (I) of the present invention can be produced by the method described below, for example. However, method of preparing the compounds of the present invention is not limited thereto. Further, depending on necessity, order of the reaction step like introduction of a substituent group, etc. can be compounds that are used for the preparation, commercially available ones can be used or they can be produced according to a method that is generally known in the art depending on necessity.

[0163] In the following reaction schemes showing the reaction step, A^1 to A^{10} and R^1 to R^{10} are as defined in the Formula (I). PR^1 to PR^{10} are the same as R^1 to R^{10} that are defined in the Formula (I) or represent a group which can be converted to R^1 to R^{10} according to modification or deprotection of a functional group.

[0164] Other abbreviated symbols described in the following reaction schemes have the general meanings that can be understood by a skilled person in the art.

[0165] PG represents a protecting group (for example, methyl, ethyl, t-butyl, benzyl, substituted benzyl, acetyl, t-butoxycarbonyl, benzyloxycarbonyl, methanesulfonyl, trifluoromethanesulfonyl, trimethylsilyl, triethylsilyl, triisopropylsilyl, t-butyldimethylsilyl, tetrahydropyranyl and the like). In the preparation method described below, when a defined group is subjected to undesirable chemical modification under a condition for implementing the method, the preparation can be carried out by using means such as protection and deprotection of a functional group, etc.

[0166] Herein, regarding selection, addition and removal of a protecting group include the methods described in "Protective Groups in Organic Synthesis" (Greene and Wuts, 4th edition, John Wiley & Sons 2007), and they can be suitably employed according to each reaction condition.

[0167] LG represents a leaving group such as fluorine, chlorine, bromine, iodine, methanesulfonate, trifluoromethanesulfonate and the like, which can be applied for the reaction described above.

[0168] In addition, abbreviated symbols that are typically used to describe the general synthetic method and examples below and names of the chemical reagents and solvents corresponding to the chemical formulae are listed in the following.

9-BBN
: 9-borabicyclo[3.3.1]nonane

AcOH
: acetic acid

BINAP

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl

BF_3OEt_2

trifluoroboron etherate

t-BuOK

potassium t-butoxy

n-BuLi

n-butyl lithium

t-BuONa

sodium t-butoxy

CDI

carbonyl diimidazole

CPME

c-pentylmethyl ether

DBU

1,8-diazabicyclo[5.4.0]-7-undecene

DCM

dichloromethane

DEAD

diethyl azodicarboxylate

DDQ

2,3-dichloro-5,6-dicyano-p-benzoquinone

DIPEA

N,N-diisopropylethylamine

DMA

N,N-dimethylacetamide

DME

dimethoxyethane

DMF

N,N-dimethyl formamide

DMSO

dimethyl sulfoxide

DPPF

bis (diphenylphosphino)ferrocene

EDC

1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

EtOAc

ethyl acetate

HOBt

1-hydroxybenzotriazole

KHMDS

potassium hexamethyldisilazide

LDA

lithium diisopropylamide

LiHMDS

lithium hexamethyldisilazide

MeCN

acetonitrile

MeI

methyl iodide

MeOH

methanol

MTBE

t-butylmethyl ether

NaHMDS

sodium hexamethyldisilazide

NMP

N-methylpyrrolidone

$Pd_2(dba)_3$

tris (dibenzylideneacetone) dipalladium (0)

$Pd(OAc)_2$

palladium acetate

$PdCl_2(CH_3CN)_2$

dichloro(bisacetonitrile) palladium (II)

$PdCl_2(PPh_3)_2$

dichlorobis (triphenylphosphine) palladium (II)

$Pd(PPh_3)_4$

tetrakis (triphenylphosphine) palladium (0)

$P(t\text{-}Bu)_3$

tri t-butylphosphine

PPh_3

triphenylphosphine

$P(o\text{-}tol)_3$

tri o-tolylphosphine

TEA

triethylamine

TEMPO

2,2,6,6-tetramethylpiperidin-1-oxyl

TFA

trifluoroacetic acid

TFAA

trifluoroacetic anhydride

TFE

trifluoroethanol

THF

tetrahydrofuran

TMAD

1,1'-azobis(N,N-dimethylformamide)

TMSCl

trimethylsilyl chloride

TMSI

trimethylsilyl iodide

DavePhos

2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

JohnPhos

2-(di-t-butylphosphino)biphenyl

c-Hexyl JohnPhos

2-(dicyclohexylphosphino)biphenyl

S-Phos

2',6'-dimethoxy-2-(dicyclohexylphosphino)biphenyl

X-Phos

2',4',6'-triisopropyl-2-(dicyclohexylphosphino)biphenyl

t-ButylX-Phos

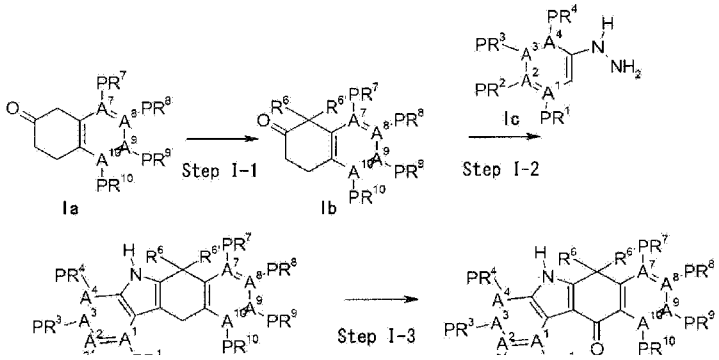
2',4',6'-triisopropyl-2-(di-t-butylphosphino)biphenyl

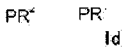
Xantphos

4,5'-bis (diphenylphosphino)-9,9'-dimethylxanthene

Preparation method I

[0169] This is one of the methods for producing the compounds of the Formula (I) in which A^5 is N and R^5 is H.





Id

Ie

Step 1-1

[0170] It is an alkylation step of a cyclic ketone derivative Ia. The step can be carried out by reacting cyclic ketone derivative Ia with an alkylating agent corresponding to R^6 and $R^{6'}$ in the presence of a base. For example, it can be carried out in view of the method described in Journal of the American Chemical Society, 115(23), 10628-36; 1993 and Organic Letters, 9(24), 5027-5029; 2007, etc. The reaction is carried out in a solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent, in the presence or the absence of a catalyst. When R^6 and $R^{6'}$ are atomic groups other than a hydrogen atom, the reaction order can be optionally selected, and separation and purification can be carried out at each step or the reaction can be carried out continuously.

[0171] As for the alkylating agent, examples thereof include an alkyl halide such as MeI, ethyl iodide, 2-iodopropane, 1,4-dibromobutane, 1,1'-oxybis (2-bromoethane) and the like, dimethyl sulfate, and sulfonic acid ester such as methylmethanesulfonate, methyl tosylate and methyltrifluoromethanesulfonate. Preferably, it is an alkyl halide such as MeI and the like. As for the catalyst, examples thereof include a phase transfer catalyst such as tetrabutylammonium chloride and tetrabutylammonium hydrogen sulfate. Preferably, it is tetrabutylammonium hydrogen sulfate. As for the base, examples thereof include an inorganic base such as sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, calcium hydride and the like or an organic base such as t-BuOK, t-BuONa, pyridine, TEA, DIPEA, LDA, LiHMDS and n-BuLi. Preferably, it is potassium hydroxide, potassium t-butoxy, or sodium t-butoxy. As for the solvent, examples thereof include toluene, xylene, n-hexane, cyclohexane, DMF, DMA, EtOAc, DMSO, dichloromethane, carbon tetrachloride, THF, dioxane, acetonitrile, water, methanol, ethanol and a mixture thereof. Preferably, it is a mixture solvent of water-THF or THF.

Step 1-2

[0172] It is the synthesis of carbazole skeleton Id according to Fischer method. This step is generally carried out by using cyclic ketone Ib in the presence of hydrazine compound Ic and an acid in a solvent or by using an acid as a solvent under the condition of a reaction temperature of 0°C to boiling point of the solvent, and also can be carried out in view of the method described in Journal of Heterocyclic Chemistry, 28(2), 321-3; 1991 and Bioorganic & Medicinal Chemistry Letters (2008), 18(24), 6479-6481. Further, when the reaction proceeds slowly, a zinc chloride catalyst and the like can be also used in view of the reaction condition disclosed in Organic Letters (2006), 8(3), 367-370. The reaction consists of a step of producing phenyl hydrazone and a step of sigmatropic rearrangement. Separation and purification can be carried out at each step or the reaction can be carried out continuously. Further, according to the structure of aryl hydrazine, which is a reacting material of this reaction step, mixture of a position isomer can be obtained as a reaction product. Such position isomer can be separated from each other or used as a mixture for the next reaction step.

[0173] As for the acid used for the reaction, examples thereof include formic acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, TFA, hydrochloric acid, sulfuric acid and pyridinium p-toluenesulfonate. Preferably, it is acetic acid, sulfuric acid, or TFA. As for the solvent, examples thereof include toluene, xylene, NMP, DMF, DMA, DMSO, sulfolane, dioxane, DME, TFE, diethylene glycol, triethylene glycol and a mixture thereof.

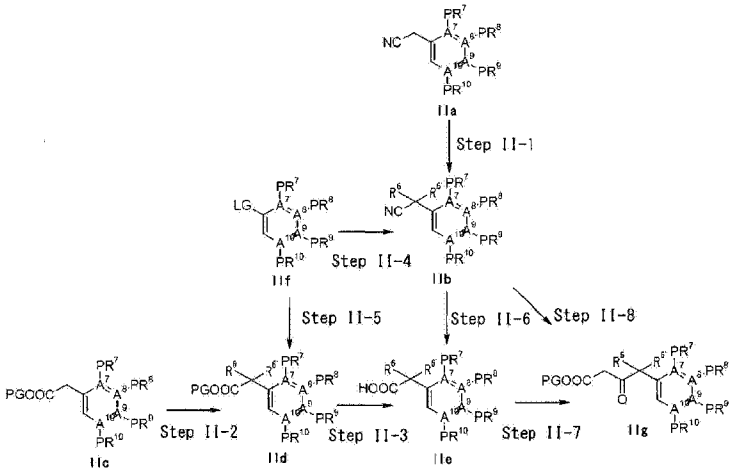
Step 1-3

[0174] It is a step of oxidation at benzyl at 11-position of carbazole skeleton Id. This step is carried out by applying an oxidizing agent to a substrate in a solvent in the presence or absence of a catalyst under the condition of a reaction temperature of -20°C to boiling point of the solvent. As for the reaction condition, the method described in Journal of Medicinal Chemistry, 51(13), 3814-3824; 2008, etc. can be considered.

[0175] As for the oxidizing agent and the catalyst used for the reaction, DDQ, peracid such as, mCPBA and the like, cerium ammonium nitrate (IV) (CAN), permanganate such as potassium permanganate, barium permanganate and the like, sodium chlorite, hydrogen peroxide, or N-hydroxyphthalimide and the like can be used alone or in a combination thereof. Preferably, it is DDQ or N-hydroxyphthalimide. As for the reaction solvent used for the reaction, examples thereof include water, t-butanol, acetonitrile, THF, dichloromethane, ethyl acetate and a mixture thereof. Preferably, it is THF.

Preparation method II

[0176] It is an exemplary method of producing β-ketoester intermediate IIg, which is used for constructing the skeleton of the compounds that are represented by the Formula (I).



Step II-1, Step II-2

[0177] It is an alkylation step at α position of carboxylic acid ester IIc or nitrile IIa. The step can be carried out by reacting with an alkylating agent corresponding to R^6 and $R^{6'}$ in a solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent, in the presence of a base. For example, it can be carried out in view of the method described in J. Org. Chem., 2007, 72 (25), 9541-9549 and European Journal of Organic Chemistry (21), 3449-3462, etc. The reagents and the condition for the reaction are the same as those described for Step 1-1.

Step II-3

[0178] It is an ester hydrolysis step of carboxylic acid ester IId. This step can be carried out by hydrolysis in an aqueous solvent at the reaction temperature of 0°C to boiling point of the solvent in the presence of an inorganic base, for example in view of the method described in Tetrahedron Lett. 3529, 1977. Alternatively, it can be carried out according to a method in which hydrolysis is carried out in the presence of an acid, in view of the method described in J. Am. Chem. Soc, 1977, 99, 2353, for example. As for the inorganic base, examples thereof include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and cesium carbonate. Preferably, it is sodium hydroxide or potassium hydroxide. As for the solvent, water, methanol, ethanol, tetrahydrofuran, dioxane, and the like can be used alone or in a combination thereof. Preferably, it is methanol comprising water or ethanol comprising water. As for the acid which can be used for acid hydrolysis, hydrochloric acid, sulfuric acid, trifluoroacetic acid and methanesulfonic acid can be used alone in a combination thereof. Preferably, it is sulfuric acid.

Step II-4, Step II-5

[0179] It is a direct (hetero)arylation step at α position of carboxylic acid ester or nitrile. This step can be carried out by S_NAr reaction in which carboxylic acid ester or nitrile is reacted with aromatic compound IIf having a leaving group in the presence of a base. It can be carried out in view of the method described in J. Am. Chem. Soc. 2000, 122, 712-713. Alternatively, it can be also carried out according to a method in which carboxylic acid ester or nitrile is reacted with aromatic compound IIf having a leaving group in the presence of a catalyst, a ligand and a base. For example, it can be carried out in view of the method described in Org. Lett, 2008, 10(8), 1545, J. Org. Chem. 2003, 68, 8003 and Angew. Chem. Int. Ed. 2003, 42, 5051, etc.

[0180] As for the base used for the reaction, sodium phosphate, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, LiHMDS, NaHMDS, LDA, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethyl pyrrolidide, KHMDS, t-BuONa, t-BuOK and the like can be used. Preferably, it is NaHMDS, KHMDS, or t-BuONa. As for the catalyst, ligand, or catalyst-ligand complex which are used for the reaction, palladium acetate, $Pd_2(dba)_3$, π-allyl palladium chloride dimer, $PdCl_2(CH_3CN)_2$, trialkylproazaphosphatrane, $\{P(t\text{-}Bu)_3PdBr\}_2$, PPh_3, $P(o\text{-}tol)_3$, BINAP, DPPF, $P(t\text{-}Bu)_3$, DavePhos, JohnPhos, c-Hexyl JohnPhos, S-Phos, X-Phos, t-ButylX-Phos, Xantphos, 4,5-bis[bis (3,5-bistrifluoromethylphenyl)phosphanyl]-9,9-dimethyl-9H-xanthene, 1,3-diallyldihydroimidazolium salt and the like can be used, for example. Preferably, it is triisobutylproazaphosphatrane.

Step II-6

[0181] It is a step of hydrolyzing nitrile IIb to carboxylic acid. This step can be carried out by hydrolysis in the presence of an acid under the condition of a reaction temperature of 0°C to boiling point of the solvent, and the reaction conditions include that described in, for example, Tetrahedron, 64(36), 8464-8475; 2008, etc. For the reaction, the acid itself can be used as a solvent or diluted with other solvent. Alternatively, it can be carried out by hydrolysis in the presence of an inorganic base under the condition of a reaction temperature of 0°C to boiling point of the solvent, and the reaction condition described in, for example, Bioorganic & Medicinal Chemistry Letters, 18(2), 749-754; 2008, etc. can be employed.

[0182] The reaction consists of the hydrolysis of nitrile IIb to acid amide and further conversion into carboxylic acid. Separation and purification can be carried out at each step or the reaction can be carried out continuously.

[0183] As for the acid which is used for the reaction, examples thereof include methanesulfonic acid, p-toluenesulfonic acid, benzenesulfonic acid, trifluoroacetic acid, hydrochloric acid and sulfuric acid. As for the solvent, examples thereof include toluene, xylene, dioxane, dimethoxyethane, diethylene glycol, triethylene glycol, TFE and the like and a mixture thereof. As for the inorganic base, examples thereof include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate and cesium carbonate.

Step II-7

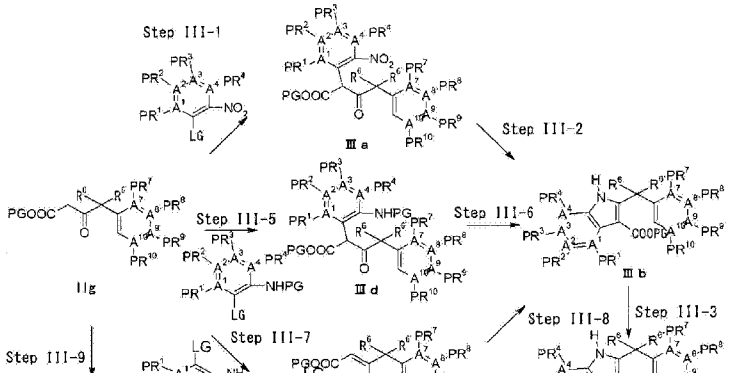
[0184] It is a step of converting carboxylic acid IIe to β-ketoester. According to this step, the carboxylic acid as a reacting material is converted into an acid chloride, active ester and the like by an action of an activating agent in a solvent under the condition of a reaction temperature of 0°C to boiling point of the solvent. Thereafter, the acid chloride or active ester is reacted with enolate of malonic acid monoester under the condition of a reaction temperature of 0°C to boiling point of the solvent to give a target compound through decarboxylation. As for the reaction condition, a method described in J. Chem. Soc. Perkin Trans. 1 1988, 2345-2352 and Synthesis 1993, 290-292 can be used, for example. As for the method of activating carboxylic acid, examples thereof include a method of converting into an acid chloride by using thionyl chloride, oxalyl chloride, phosphorus oxychloride, etc. or a method of converting into an active ester by using CDI. Preferably, thionyl chloride or CDI is used. The activated carboxylic acid itself can be subjected to separation and purification, or can be used continuously for the next reaction. As for the method of producing an enolate of malonic acid monoester, a combination of magnesium salt like magnesium chloride, etc. and malonic acid monoester (and a salt thereof) or a Grignard reagent like i-propyl magnesium chloride, etc. and malonic acid monoester (and a salt thereof), etc. can be used. In order to improve the reaction yield, an organic base such as TEA, DIPEA and the like can be also added to the reaction system. As for the solvent, examples thereof include toluene, xylene, MeCN, THF, CPME, MTBE, NMP, DMF, DMA, DMSO, sulfolane, dioxane, DME, and the like and a mixture thereof. Preferably, it is MeCN, THF or DME.

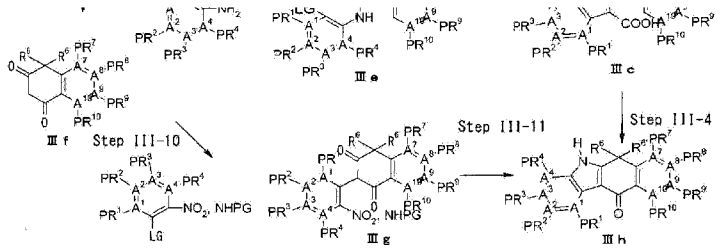
Step II-8

[0185] It is a step of converting nitrile IIb to β-ketoester. This step can be carried out by so-called Blaise reaction in which 2-halo carboxylic acid ester is reacted with nitrile in the presence of activated zinc powder under the condition of a reaction temperature of 0°C to boiling point of the solvent, and the reaction method described in, for example, SYNTHESIS 2004, No. 16, pp 2629-2632x. can be used. As for the method of activating zinc powder, a method in which acid washing and drying are carried out in advance, or a method in which a catalytic amount of an acid such as methanesulfonic acid, etc. is included in the reaction system can be employed.

Preparation method III

[0186] It is an exemplary method of preparing compound IIIh from intermediate IIg that is obtained from Preparation method II.





Step III-1

[0187] This step can be carried out by nucleophilic aromatic substitution reaction in which an aromatic nitro compound having a leaving group is reacted with β-ketoester IIg in the presence of a base under the condition of a reaction temperature of 0°C to boiling point of the solvent, and the reaction method include that described in, for example, Synlett, (5), 883-885; 2004 and Tetrahedron, 38(23), 3479-83; 1982.

[0188] As for the base used for the reaction, sodium phosphate, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, LiHMDS, NaHMDS, LDA, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethylpyrrolidide, KHMDS, t-BuOK, t-BuONa and the like can be used. Preferably, it is potassium carbonate, cesium carbonate, t-BuOK, or t-BuONa. As for the solvent, examples thereof include toluene, xylene, MeCN, THF, CPME, MTBE, NMP, DMF, DMA, DMSO, sulfolane, dioxane, DME, acetone, methylethyl ketone, and a mixture thereof. Preferably, it is THF, DMF, DMA, NMP or a mixture thereof.

[0189] Further, the present step can be also carried out in the presence of a catalyst and a base, as described in Step III-5 or Journal of Organic Chemistry, 72(14), 5337-5341; 2007.

Step III-2

[0190] It is a reductive cyclization step to form an indole ring following the reduction of a nitro group. This reaction can be carried out by reacting β-ketoester IIIa with a reducing agent under the condition of a reaction temperature of 0°C to boiling point of the solvent to reduce the nitro group. As for the reducing agent used for the reaction, the condition generally used for reduction of a nitro group, for example, iron as exemplified in Synthesis, (18), 2943-2952, 2008, zinc as exemplified in Tetrahedron, 64(40), 9607-9618, 2008, titanium (III) chloride as exemplified in Organic & Biomolecular Chemistry, 3(2), 213-215, 2005, tin (II) chloride as exemplified in Journal of Organic Chemistry, 58(19), 5209-5220,1993, sodium hydrosulphite as exemplified in Gazzetta Chimica Italiana, 121(11), 499-504, 1991, and catalytic reduction condition as exemplified in Synlett, (17), 2689-2691, 2008, etc. can be employed. Preferably, the reducing agent is iron or sodium hydrosulphite.

Step III-3

[0191] It is a step of deprotecting an ester protecting group of indole-3-carboxylic acid ester IIIb. As an example of an ester protecting group, a methyl group, an ethyl group, a t-butyl group, a benzyl group, a substituted benzyl group and the like can be used. Preferably, it is a t-butyl. As for the deprotection, examples thereof include a method described in "Protective Groups in Organic Synthesis" (Greene and Wuts, 4th edition, John Wiley & Sons 2007), and it can be appropriately used according to each reaction condition. When the ester protecting group is a t-butyl, as a deprotection condition, TMSI, TMSCl, and $BF_3 \cdot OEt_2$ can be used. As for the solvent, examples thereof include toluene, xylene, diethyl ether, THF, CPME, MTBE, NMP, DMF, DMA, DMSO, sulfolane, dioxane, DME, TFE and the like and a mixture thereof. Preferably, it is THF or TFE.

Step III-4

[0192] It is a step of cyclizing indole-3-carboxylic acid IIIc to carbazole based on Friedel-Crafts reaction. According to the reaction, a mixed acid anhydride is formed by using acetic anhydride, trifluoroacetic anhydride and the like, or acid chloride is formed by using thionyl chloride, oxalyl chloride, phosphorus oxychloride and the like, which results in activiation of the carboxylic acid. Preferably, acetic anhydride or trifluoroacetic anhydride is used. The reaction is carried out in the absence or presence of a solvent. As for the solvent, examples thereof include toluene, xylene, diethyl ether, THF, CPME, MTBE, NMP, DMF, DMA, DMSO, sulfolane, dioxane, DME and the like and a mixture thereof. Preferably, it is THF, DMF, DMA or DME. Further, an organic base such as TEA, DIPEA, pyridine and the like can be used.

[0193] Thereafter, under the condition of a reaction temperature of 0°C to boiling point of the solvent, the cyclization is carried out without a catalyst or with Bronsted acid or Lewis acid catalyst (Heterocycles 1999, 51, 2127). As for the Lewis acid catalyst, examples thereof include aluminum chloride, aluminum triflate, bismuth triflate, ytterbium triflate and $BF_3 \cdot OEt_2$. Preferably, it is $BF_3 \cdot OEt_2$. Depending on the type of a substituent group, it is also possible to carry out the reaction by applying methanesulfonic acid-phosphorus pentoxide (Eaton reagent), polyphosphoric acid and the like to indole-3-carboxylic acid ester IIIb without undergoing Step III-3.

Step III-5, III-6

[0194] The step can be carried out by reacting an aromatic acylamide compound having a leaving group with β-ketoester IIg in the presence of a base, a catalyst, and a ligand under the condition of a reaction temperature of 0°C to boiling point of the solvent, followed by deprotection of an acyl protecting group. Examples thereof include a method described in Journal of Organic Chemistry 2007, 72, 9329-9334 and Organic Letters 10(4), 625-628, 2008. As for the metal catalyst, copper (I) iodide and palladium acetate can be used. As for the ligand, (S)-proline, tri t-butylphosphine, bis (t-butyl) (2'-methyl[1,1'-biphenyl]-2-yl)phosphine and the like can be used. As for the base which is used for the reaction, sodium phosphate, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, LiHMDS, NaHMDS, LDA, lithium dicyclohexylamide, lithium 2,2,6,6-tetramethylpyrrolidide, potassium hexamethyldisilazide, t-BuONa, t-BuOK and the like can be used.

Step III-7, III-8

[0195] It is a step of reacting an aromatic amino compound with β-ketoester IIg to form an enamine intermediate followed by catalytic cyclization. Examples thereof include a method described in Journal of Organic Chemistry, 68(15), 6011-6019; 2003 and European Journal of Organic Chemistry, (24), 3977-3980; 2007.

[0196] Alternatively, the cyclization can be carried out based on an oxidative method. For example, a reaction condition described in Angewandte Chemie, International Edition, 47(38), 7230-7233; 2008 can be also employed, for example.

Step III-9

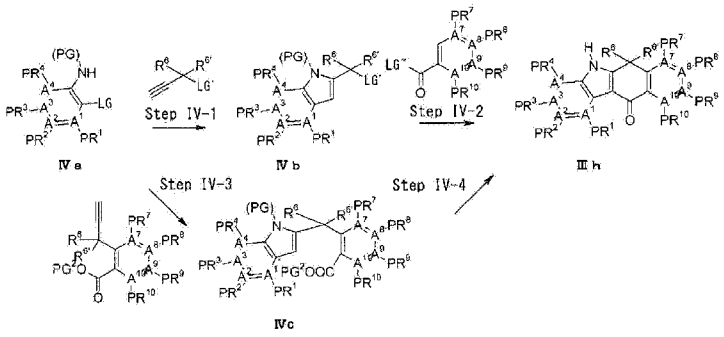
[0197] It is a step of synthesizing 1,3-diketone based on cyclization of β-keto ester IIg. As for the condition and reagents for the reaction, a method described in Bioorganic & Medicinal Chemistry Letters, 18(2), 568-570; 2008 wherein β-keto ester IIg is reacted in an solvent in the presence of Bronsted acid catalyst or Lewis acid catalyst, or a method of using a condensing agent such as methanesulfonic acid-phosphorus pentoxide (Eaton reagent), polyphosphoric acid and the like can be employed.

Step III-10, III-11

[0198] This step can be carried out in the same manner as Step III-1 and III-2 or Step III-5 and III-6.

Preparation method IV

[0199] An exemplary method of producing compound IIIh wherein formula Iva is employed as a starting material.



Step IV-1, IV-3

[0200] It is a step of constructing di-substituted indole derivatives based on Sonogashira reaction in which a terminal alkyne is reacted with aromatic amine derivative IVa having a leaving group at ortho position in the presence of a base and a catalyst with or without a catalytic amount of a copper reagent. Specifically, examples thereof include a method described in Organic Letters, 11(1), 221-224; 2009. The reaction is carried out in an appropriate solvent in the presence of a palladium catalyst and a ligand (or a complex thereof) with or without a base and a copper catalyst. Example of the copper catalyst used for the reaction include copper iodide. As an example of the catalyst and the ligand (or a complex thereof), palladium acetate, $Pd_2(dba)_3$, π-allyl palladium chloride dimer, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, trialkylproazaphosphatrane, $\{P(t\text{-}Bu)_3PdBr\}_2$, PPh_3, $P(o\text{-}tol)_3$, BINAP, DPPF, $P(t\text{-}Bu)_3$, DavePhos, JohnPhos, c-Hexyl JohnPhos, S-Phos, X-Phos, t-ButylX-Phos, Xantphos, 4,5-bis[bis (3,5-bistrifluoromethylphenyl)phosphanyl]-9,9-dimethyl-9H-xanthene, 1,3-diallyldihydroimidazolium salt and the like can be used. As for the base used for the reaction, sodium phosphate, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, TEA, DIPEA and the like can be used. Preferably, it is cesium carbonate, TEA or DIPEA.

Step IV-2

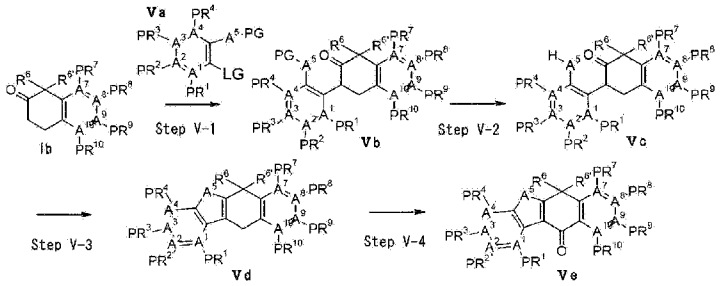
[0201] This step corresponds to a tandem Friedel-Crafts reaction in which acylation at 3-position of di-substituted indole derivative IVb is carried out in the presence of Lewis acid catalyst under the condition of a reaction temperature of 0°C to boiling point of the solvent, followed by intramolecular cyclization. As for the catalyst used for the reaction, examples thereof include aluminum chloride, aluminum triflate, bismuth triflate, ytterbium triflate and $BF_3{\cdot}OEt_2$. Preferably, it is aluminum chloride.

Step IV-4

[0202] This step consists of deprotection of carboxylic acid ester comprised in di-substituted indole derivative IVc and subsequent intramolecular cyclization at 3-position of the indole either in catalytic or non-catalytic manner. As for the deprotection, examples thereof include a method described in "Protective Groups in Organic Synthesis" (Greene and Wuts, 4th edition, John Wiley & Sons 2007), and it can be appropriately used according to the type of each protecting group. When an activated indole derivative is used for the reaction, cyclization occurs more easily so that the reaction can be carried out in a non-catalytic manner. Further, the cylclization can be also carried out by using a condensing agent such as polyphosphoric acid, methanesulfonic acid-phosphorus pentoxide (Eaton reagent) and the like. Alternatively, it is also possible that carboxylic acid is first converted into carboxylic acid chloride, a mixed acid anhydride and the like under the same condition as defined in Step III-4 and the cyclization is carried out under Friedel-Crafts condition in the presence of Lewis acid catalyst. As for the Lewis acid catalyst used for the reaction, examples thereof include aluminum chloride, aluminum triflate, bismuth triflate, ytterbium triflate and $BF_3{\cdot}OEt_2$.

Preparation method V

[0203] It is one of the methods for constructing the skeleton of the compounds having the Formula (I) in which A^5 is O, S or NH.



Step V-1

[0204] It is a step of arylation of cyclic ketone derivative Ib using aromatic compound Va having a leaving group. The reaction is catalytically carried out in the presence of a base with combination of a transition metal catalyst and a ligand, and the condition described in J. Am. Chem. Soc. 2000, 122, 1360-1370 and Journal of Organic Chemistry (2003), 68(25), 9865-9866 can be used, for example. As for the base used for the reaction, examples thereof include t-BuONa, t-BuOK, LiHMDS, NaHMDS, potassium phosphate, sodium carbonate, potassium carbonate and cesium carbonate. As for the catalyst and a ligand (or a catalyst-ligand complex), palladium acetate, $Pd_2(dba)_3$, π-allylpalladium chloride dimer, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, trialkylproazaphosphatrane, $\{P(t\text{-}Bu)_3PdBr\}_2$, PPh_3, $P(o\text{-}tol)_3$, BINAP, DPPF, $P(t\text{-}Bu)_3$, DavePhos, JohnPhos, c-Hexyl JohnPhos, S-Phos, X-Phos, t-ButylX-Phos,

Xantphos, 4,5-bis[bis (3,5-bistrifluoromethylphenyl)phosphanyl]-9,9-dimethyl-9H-xanthene 1,3-diallyldihydroimidazolium salt and the like can be used.

Step V-2

[0205] It is a step of deprotecting a protecting group. When A^5 is O or S, a t-butyl group, a benzyl group and a substituted benzyl group can be used as a protecting group. When A^5 is O, a t-butyldimethylsilyl group and a tetrahydropyranyl group can be used. When it is NH, a t-butoxycarbonyl group, a benzyloxycarbonyl group, a methanesulfonyl group, a trifluoroacetyl group and the like can be used. As for the deprotection, examples thereof include a method described in "Protective Groups in Organic Synthesis" (Greene and Wuts, 4th edition, John Wiley & Sons 2007), and it can be appropriately used according to the type of each protecting group.

Step V-3

[0206] It is a cyclization step of cyclic α-aryl ketone derivative Vc to a benzofuran derivative, benzothiophene or indole Vd. The reaction can be carried out under condition of using an acid catalyst or dehydrating condition. For example, the reaction condition described in Acta Pharmaceutica Hungarica (2003), 73(3), 171-178 can be employed. In addition, depending on the type of a protecting group for hydroxyl group, it can be carried out simultaneously with the deprotection of Step V-2, as described in Heterocycles, 26(7), 1863-71; 1987. With respect to the condition for dehydration, a combination of an organic base and an acid anhydride such as trifluoromethanesulfonic acid and the like can be used.

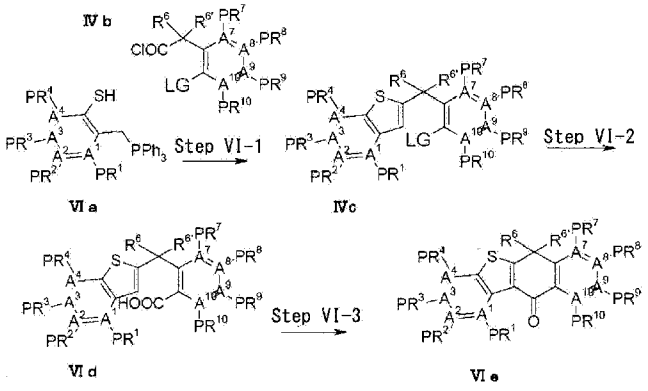
Step V-4

[0207] It is a step of oxidation at benzyl at 11-position of tetracyclic compound Vd. This step is carried out by applying an oxidizing agent to a substrate in a solvent in the presence or absence of a catalyst under the condition of a reaction temperature of -20°C to boiling point of the solvent. As for the reaction condition, the method described in Journal of Medicinal Chemistry, 51(13), 3814-3824; 2008, etc. can be employed.

[0208] As for the oxidizing agent and the catalyst used for the reaction, DDQ, peracid such as, mCPBA and the like, cerium ammonium nitrate (IV) (CAN), permanganate such as potassium permanganate, barium permanganate and the like, sodium chlorite, hydrogen peroxide, N-hydroxyphthalimide and the like can be used alone or in a combination thereof. As for the solvent used for the reaction, examples thereof include water, t-butanol, acetonitrile, tetrahydrofuran, dichloromethane, ethyl acetate and a mixture thereof.

Preparation method VI

[0209] It is an exemplary method of constructing the skeleton of the compounds that are represented by the Formula (I) in which A^5 is S.



Step VI-1

[0210] It is a reaction to construct a benzothiophene ring based on the reaction between ylide VIa having a thiol at ortho position and acyl chloride VIb. The reaction can be carried out in the presence of a base, and the condition include that described in Synthesis, (2),

155-7; 1988, for example. As for the base, examples thereof include n-butyl lithium, sodium methylate and triethylamine.

Step VI-2

[0211] It is a reaction for the synthesis of an aromatic carboxylic acid. The reaction can be carried out by metallization like addition of lithium or magnesium based on exchange between halogen and metal in the presence of a base, followed by carboxylation using carbonate gas, dry ice, etc. The reaction condition as described in Journal of Organic Chemistry (2008), 73(19), 7785-7788 can be employed. As for the base, n-butyl lithium, s-butyl lithium, t-butyl lithium, a Grignard reagent, and various ate complexes can be used. Alternatively, as described in e-EROS Encyclopedia of Reagents for Organic Synthesis 2001 (electronic edition; http://www3.interscience.wiley.com/cgi-bin/mrwhome/104554785/HOME), carboxylation condition using a transition metal catalyst can be also employed.

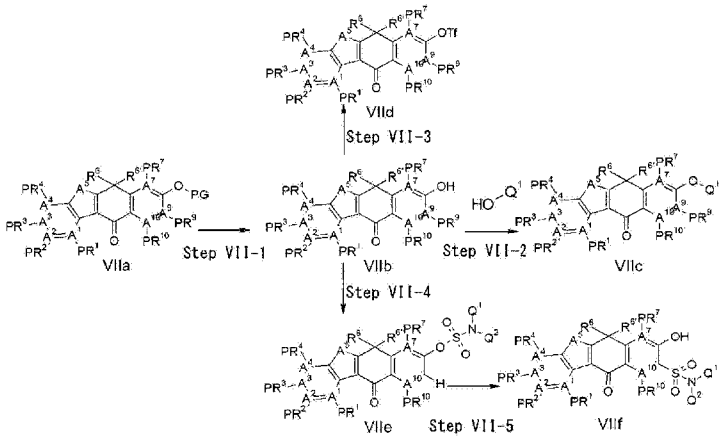
Step VI-3

[0212] This step corresponds to intramolecular cyclization at 3-position of di-substituted benzothiophene derivative VId either in catalytic or non-catalytic manner. For example, the reaction condition as described in Journal of the American Chemical Society, 130(23), 7286-7299; 2008 can be employed. The reaction can be carried out by using a condensing agent such as polyphosphoric acid, methanesulfonic acid-phosphorus pentoxide (Eaton reagent) and the like. Alternatively, it is also possible that carboxylic acid is first converted into carboxylic acid chloride, a mixed acid anhydride and the like and the cyclization is carried out under Friedel-Crafts condition in the presence of Lewis acid catalyst. As for the Lewis acid catalyst used for the reaction, examples thereof include aluminum chloride, aluminum triflate, bismuth triflate, ytterbium triflate and $BF_3 \cdot OEt_2$.

Preparation method VII Conversion and modification of functional groups

[0213] To the functional groups PR^1 to PR^{10} in the Formula (I) of the present invention, various substituent groups can be introduced based on a method of converting and modifying a functional group that is well known to a skilled person in the pertinent art. Hereinbelow, representative examples of functional group conversion will be explained. Further, although the following reaction scheme is specific in that examples of PR^8 and PR^9 are given for the tetracyclic compound that is already constructed, it can be also carried out to an intermediate during any steps explained in Preparation methods I to VI above or to a final compound. Further, it can be carried out at any substitution position of PR^1 to PR^4 and R^6 to PR^{10}.

[0214] In the following formula, Q^1 and Q^2 represent any substituent group which constitutes PR^1 to PR^4 and R^6 to PR^{10}.



Step VII-1

[0215] It is a step of deprotecting a protecting group for an aromatic hydroxyl group. As an example of the protecting group, a methyl group, a t-butyl group, a benzyl group, a substituted benzyl group, a t-butyldimethylsilyl group, a tetrahydropyranyl group and the like can be used. Preferably, it is a methyl group. As for the deprotection, examples thereof include a method described in "Protective Groups in Organic Synthesis" (Greene and Wuts, 4th edition, John Wiley & Sons 2007), and it can be appropriately used according to the type of each protecting group. When a methyl group is used as a protecting group, various reaction conditions can be used selectively for the deprotection depending on reactivity. Examples thereof include heating in the presence of pyridine hydrochloric acid

salt, heating in the presence of a solvent with dodecane thiol and sodium methylate and heating in the presence of a solvent with anhydrous lithium halide, boron tribromide, TMSI and the like.

Step VII-2

[0216] It is one of the methods for introducing a substituent group based on formation of ether bond with an aromatic hydroxyl group. For the formation of an ether bond, Mitsunobu reaction described in a known literature (Mitsunobu, et. al., Synthesis, Vol. 1, page 1, 1981) or a similar method can be used. Specifically, the reaction is carried out in the presence of a phosphorus compound and an azo compound in a solvent under the condition of a reaction temperature of -78°C to boiling point of the solvent. As for the phosphorus compound, examples thereof include PPh_3 and tri-n-butylphosphine. As for the azo compound, examples thereof include DEAD, TMAD and diisopropyl azodicarboxylic acid. Also, by using them in any combination, the target compound can be obtained.

Step VII-3

[0217] It is a step of carrying out trifluoromethane sulfonylation on an aromatic hydroxyl group. The reaction is carried out by reacting with a reacting reagent such as trifluoromethanesulfonic acid and the like in the presence of a base with or without a solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent. As for the base used for the reaction, TEA, DIPEA, pyridine, 2,6-lutidine, dimethylaminopyridine and the like can be used. Preferably, pyridine is used without any solvent. The obtained trifluoromethanesulfonic acid ester VIId is a good leaving group and can be used for various derivatization.

Step VII-4

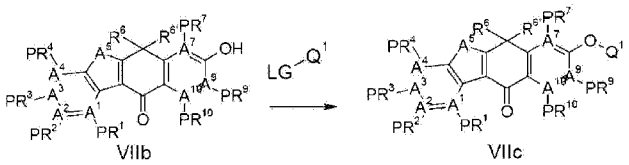
[0218] It is a step of obtaining sulfamic acid ester by carrying out sulfamoylation on an aromatic hydroxyl group. The reaction is carried out by reacting with a reacting reagent such as sulfamoyl chloride and the like in the presence of a base with a solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent. As for the base used for the reaction, sodium hydride, TEA, DIPEA, pyridine, 2,6-lutidine, dimethylaminopyridine and the like can be used. Preferably, it is sodium hydride. The obtained sulfamic acid ester VIIe is a substrate for the thiaFries rearrangement of Step VII-5 and can be used for various derivatization.

Step VII-5

[0219] This step corresponds to rearrangement of a sulfamoyl group to a neighboring position in the presence of a Lewis acid catalyst under the condition of a reaction temperature of 0°C to boiling point of the solvent when the neighboring position of the sulfamic acid ester is unsubstituted (i.e., C-H), i.e., a reaction called thiaFries rearrangement. As for the catalyst used for the reaction, aluminum chloride, aluminum triflate, bismuth triflate, ytterbium triflate, $BF_3 \cdot OEt_2$ and the like can be used. Preferably, it is aluminum chloride.

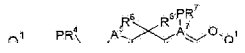
Step VII-6

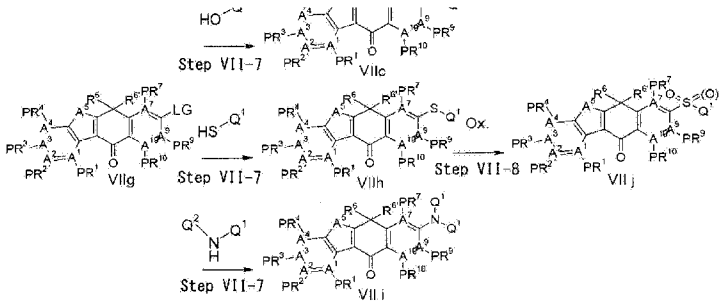
[0220]



[0221] It is another step of introducing a substituent group based on formation of an ether bond. According to the present step, a reagent having an appropriate leaving group such as alkyl halide and the like is subjected to nucleophilic reaction with the hydroxyl group of compound VIIb in the presence of an appropriate base to form an ether bond. As for the base, examples thereof include an inorganic base such as sodium carbonate, potassium carbonate, cesium carbonate, sodium hydride, potassium hydride, calcium hydride and the like or an organic base such as pyridine, TEA, DIPEA and the like.

[0222] Further, by using aryl halide, aryl borate and the like as a reagent having a leaving group, formation of an diaryl ether bond can be also achieved and used. When reactivity is not satisfactory, a catalyst such as copper powder, copper acetate, copper iodide and the like or a ligand such as phenanthroline, trans-1,2-cyclohexanediamine and the like can be used.





Step VII-7

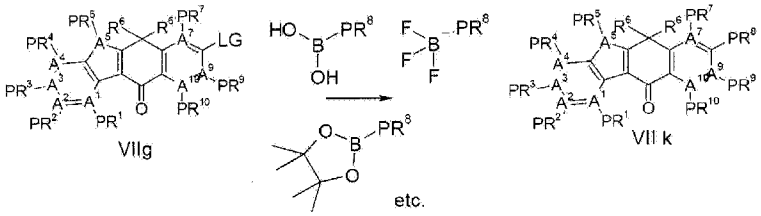
[0223] It is a reaction for forming a bond between aryl and a hetero atom by using compound VIIg having a leaving group. The reaction is carried out in an appropriate solvent inert to the reaction, in the presence of a base. As for the leaving group LG, a halogen, triflate and the like can be used. As for the solvent, examples thereof include toluene, xylene, n-hexane, cyclohexane, DMF, DMA, EtOAc, DMSO, NMP, THF, DME, dioxane, acetonitrile and the like and a mixture thereof. As for the base to be used for the reaction, examples thereof include t-BuONa, t-BuOK, LiHMDS, NaHMDS, KHMDS, potassium phosphate, sodium carbonate, potassium carbonate and cesium carbonate. This step can be also carried out by using a catalyst and a ligand. As for the catalyst and a ligand (or a catalyst-ligand complex), palladium acetate, $Pd_2(dba)_3$, π-allylpalladium chloride dimer, $PdCh(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, trialkylproazaphosphatrane, $\{P(t\text{-}Bu)_3PdBr\}_2$, PPh_3, $P(o\text{-}tol)_3$, BINAP, DPPF, $P(t\text{-}Bu)_3$, DavePhos, JohnPhos, c-Hexyl JohnPhos, S-Phos, X -Phos, t-ButylX-Phos, Xantphos, 4,5-bis[bis (3,5-bistrifluoromethylphenyl)phosphanyl]-9,9-dimethyl-9H-xanthene, 1,3-diallyldihydroimidazolium salt and the like can be used, for example.

Step VII-8

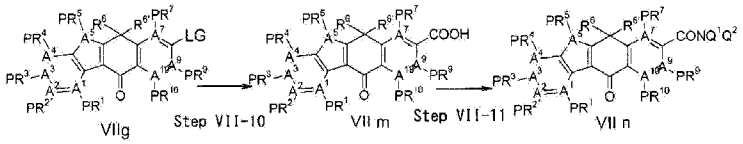
[0224] When the reaction product of Step VII-7 is thio ether VIIh, it is possible to obtain sulfoxide or sulfone compound VIIj by oxidation with m-chloro perbenzoic acid, oxone, TEMPO and the like.

Step VII-9

[0225]



[0226] It is a reaction for forming a bond between aryl and SP^2 carbon or a bond between aryl and SP^3 carbon in which compound VIIg having a leaving group is used. The reaction is carried out in an appropriate solvent inert to the reaction, in the presence of a base. As for the leaving group LG, a halogen, triflate and the like can be used. As for the solvent, examples thereof include toluene, xylene, n-hexane, cyclohexane, DMF, DMA, EtOAc, DMSO, NMP, THF, DME, dioxane, acetonitrile, water, isopropanol and the like and a mixture thereof. As for the base to be used for the reaction, examples thereof include t-BuONa, t-BuOK, LiHMDS, NaHMDS, KHMDS, potassium phosphate, sodium carbonate, potassium carbonate, cesium carbonate, TEA and DIPEA. This step can be also carried out by using a catalyst and a ligand. As for the catalyst and a ligand (or a catalyst-ligand complex), palladium acetate, $Pd_2(dba)_3$, π-allylpalladium chloride dimer, $PdCl_2(CH_3CN)_2$, $PdCl_2(PPh_3)_2$, trialkylproazaphosphatrane, $\{P(t\text{-}Bu)_3PdBr\}_2$, PPh_3, $P(o\text{-}tol)_3$, BINAP, DPPF, $P(t\text{-}Bu)_3$, DavePhos, JohnPhos, c-Hexyl JohnPhos, S-Phos, X-Phos, t-ButylX-Phos, Xantphos, 4,5-bis[bis (3,5-bistrifluoromethylphenyl)phosphanyl]-9,9-dimethyl-9H-xanthene, 1,3-diallyldihydroimidazolium salt and the like can be used, for example.



Step VII-10

[0227] It is a carboxylation reaction using compound VIIg having a leaving group. The reaction is carried out by reacting with formic acid (or a synthetic equivalent thereof) in an appropriate solvent inert to the reaction, in the presence of a base and a catalyst. As for the leaving group LG, a halogen, triflate and the like can be used. The solvent and the catalyst can be selected and used in the same manner as Step VII-9.

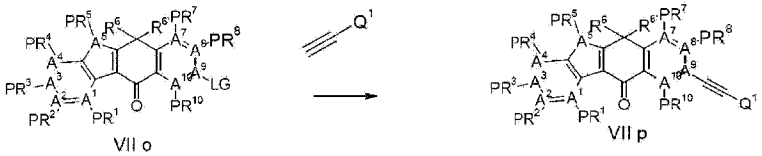
Step VII-11

[0228] It is an amidation reaction using carboxylic acid VIIm. Specifically, the reaction can be carried out by dehydrating condensation reaction using various amines such as ammonia, primary amines, secondary amines, hydrazines, substituted hydrazines and the like. The reaction is carried out in the presence of an acid halogenating agent or a dehydrating condensing agent in an aprotic solvent under the condition of a reaction temperature of -20°C to boiling point of the solvent, with or without an active esterifying agent and a base.

[0229] As for the acid halogenating agent, examples thereof include oxalyl chloride and thionyl chloride. As for the dehydrating condensing agent, examples thereof include 1,3-dicyclohexylcarbodiimide (DCC), 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ), bromo-tris (pyrrolidino)-phosphonium hexafluorophosphate (PyBrOP), EDC and (benzotriazolyloxy)tripyrrolidino-phosphonium=hexafluorophosphate (PyBOP). As for the active esterifying agent, examples thereof include HOBt, di(N-succinimidyl) carbonate and carbonyl diimidazole. As for the base, examples thereof include TEA, DIPEA and DBU. As for the solvent, examples thereof include DMF, DMA, DCM, acetone, THF, dioxane, DME, ethyl acetate, MeCN, and a mixture thereof.

Step VII-12

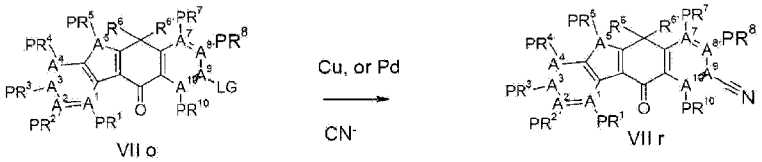
[0230]



[0231] It is a step of forming a bond between aryl and SP carbon using compound VIIo having a leaving group. The reaction is carried out by reacting terminal alkyne in an appropriate solvent in the presence of a base and a catalyst with or without a catalytic amount of a copper reagent, and the reaction is referred to as Sonogashira reaction. The reagents and the condition for the reaction are as defined in Step IV-1 and Step IV-3. As a variant of Sonogashira reaction, examples thereof include a method disclosed in Tetrahedron, 63(43), 10671-10683; 2007. Specifically, by having secondary amines and the like in a reaction system and using propargyl bromide as an alkyne, a propargyl amine can be introduced.

Step VII-13

[0232]



[0233] It is a reaction of forming a bond between aryl and CN by using compound VIIo having a leaving group. The reaction can be carried out by adding CN^- source in an appropriate solvent in the presence of a copper, zinc or palladium catalyst, with or without a ligand, in view of the reaction condition shown in Organic Letters, 10(23), 5325-5328; 2008, Tetrahedron Letters, 49(32), 4693-4694; 2008 and Bioorganic & Medicinal Chemistry, 16(13), 6489-6500; 2008. As for the CN^--source, copper (I) cyanide, zinc (II) cyanide, iron (III) hexacyanide, sodium cyanide, potassium cyanide and the like can be used.

Synthesis of starting materials

[0234] Some of the starting materials for the present invention are novel compounds, and they can be easily synthesized in the same manner as known reacting compounds or according to the method well known to a skilled person in the art.

[0235] Hereinabove, examples of a method of preparing the compounds having the Formula (I) according to the present invention are described. However, separation and purification of the target compounds that are described in detail in each reaction step can be performed by applying common chemical treatments such as extraction, concentration, removal by distillation, crystallization, filtration, recrystallization, various chromatography, etc.

Pharmaceutical of the present invention

[0236] The pharmaceutical composition of the present invention comprises a pharmaceutically acceptable carrier, in addition to the compound that is selected as being useful for the invention. In the present specification, the term "pharmaceutically acceptable carrier" means one or more type of appropriate solid or liquid vehicle, diluent or an encapsulating material which is suitable for administration to mammals. In the present specification, the term "acceptable" means that it does not cause any reaction to substantially reduce the pharmaceutical efficacy of a composition under normal condition for use, and the components of the composition and the subject compound can be mixed well with each other. The pharmaceutically acceptable carrier should have substantially high purity and substantially low toxicity so that it can be suitably administered to a subject to be treated, preferably an animal, and more preferably a mammal.

[0237] As the materials which can be used as a pharmaceutically acceptable carrier, examples thereof include sugars such as lactose, glucose, sucrose, and the like; starch such as corn starch, potato starch and the like; cellulose and cellulose derivatives such as sodium carboxy methyl cellulose, ethyl cellulose, methyl cellulose and the like; tragacanth rubber powder; malt; gelatin; talc; solid lubricating agent such as stearic acid or magnesium stearate and the like; calcium sulfate; vegetable oils such as peanut oil, cotton seed oil, sesame oil, olive oil, corn oil, plant oil, cacao oil, and the like; polyhydric alcohols such as propylene glycol, glycerin, sorbitol, mannitol, polyethylene glycol and the like; alginic acid; an emulsifying agent such as TWEEN; humectant such as lecithin and the like; colorant; flavor; tabletting agent; stabilizer, anti-oxidant; preservative; pyrogen-free water; aqueous isotonic solution and phosphate buffer solution.

[0238] When the pharmaceutical composition of the present invention is used as an ALK inhibitor or a therapeutic or prophylactic agent for a proliferative disorder, or used against depression or cognitive function disorder, as an administration route, oral, rectal, parenteral (intravenous, intramuscular, subcutaneous), intracisternal, intravaginal, intraperitoneal, intrabladder, topical (drop, powder, ointment, gel or cream) administration or administration via inhalation (mouth or nasal spray) and the like can be considered. As for the administration form, examples thereof include a tablet, a capsule, a granule, powder, a pill, an aqueous or non-aqueous oral solution and suspension, and a parenteral solution which is filled in a container suitable to be divided into several small dosages. In addition, the administration form can be modified for various administration routes including subcutaneous transplant which gives controlled release of a drug compound.

[0239] The aforementioned preparation is prepared according to a method generally known in the art by using additives such as a vehicle, a lubricating agent (i.e., coating agent), a binding agent, a disintegrating agent, a stabilizing agent, a corrigent for taste and smell, a diluent and the like.

[0240] As a vehicle, examples thereof include starch such as starch, potato starch, corn starch, lactose, crystalline cellulose and calcium hydrogen phosphate.

[0241] As a coating agent, examples thereof include ethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, shellac, talc, carnauba wax and paraffin.

[0242] As a binding agent, examples thereof include polyvinyl pyrrolidone, Macrogol and the compounds described above as a vehicle.

[0243] As a disintegrating agent, examples thereof include the compounds described as a vehicle in the above and a chemically modified starch or cellulose such as sodium croscarmellose, sodium carboxymethyl starch and crosslinked polyvinyl pyrrolidone.

[0244] As a stabilizing agent, examples thereof include paraoxy benzoic acid esters such as methyl paraben, propyl paraben and the like; alcohols such as chlorobutanol, benzyl alcohol, phenylethyl alcohol and the like; benzalkonium chloride; phenols such as phenol, cresol and the like; thimerosal; dehydroacetic acid; and sorbic acid.

[0245] As a corrigent for taste and smell, examples thereof include a sweetener, an acid tasting agent, a flavor and the like that are commonly used in the art.

[0246] Further, as a solvent to prepare a liquid preparation, examples thereof include ethanol, phenol, chlorocresol, purified water and distilled water.

[0247] As a surface active agent or an emulsifying agent, examples thereof include polysorbate 80, polyoxyl 40 stearate and lauromacrogol.

[0248] When the pharmaceutical composition of the present invention is used as an ALK inhibitor or a therapeutic or prophylactic agent for a proliferative disorder, or used against depression or cognitive function disorder, the use amount of the compounds of the present invention or salts or solvates thereof varies depending on symptom, age, body weight, relative health state of a subject, administration of other drug compounds, administration method and the like. For example, the amount which is generally effective for a patient (i.e., warm-blooded animal, in particular human) is, in an effective component (i.e., the compound of the present invention that is represented by the Formula (I)), preferably 0.001 to 1000 mg per 1 kg body weight per day, more preferably 0.01 to 300 mg per 1 kg body weight per day in case of an orally administered agent, and dosage per day is preferably in the range of 1 to 800 mg for an adult patient with normal body weight. In case of a parenterally administered agent, it is preferably 0.001 to 1000 mg per 1 kg body weight per day, and more preferably, 0.01 to 300 mg per 1 kg body weight per day. It is preferable to administer them once a day or in divided dosages a day, depending on symptom of a subject to be treated.

[Example]

[0249] Hereinbelow, the present invention will be explained in greater detail in view of the following examples. However, the present invention is not limited by the examples.

NMR analysis

[0250] NMR analysis was carried out by using JNM-EX270 (270 MHz, manufactured by JEOL), JNM-GSX400 (400 MHz, manufactured by JEOL), or 400 MR (400 MHz, manufactured by Varian). NMR data was expressed in ppm (parts per million; δ), while it was compared with the deuterium lock signal obtained from a sample solvent.

Mass spectrum

[0251] The measurement was carried out by using JMS-DX303 or JMS-SX/SX102A (both manufactured by JEOL).

High performance liquid chromatography- mass spectrum data (LC-MS)

[0252] Measurement was carried out by using Micromass (ZMD, manufactured by Micromass) equipped with 996-600E gradient high performance liquid chromatography (manufactured by Waters) or Micromass (ZQ, manufactured by Micromass) equipped with 2525 gradient high performance liquid chromatography (manufactured by Waters).

[0253] One of the following conditions that are described in the Table 1 below was taken as a condition for high performance liquid chromatography.

[Table 1]

Analysis Cond ition	Apparatus	Column used	Column Temperature	Mobile phase, Gradient	Flow Rate (mL/min)	Detection Wavelength
A	ZMD	Cadenza CD-C18 (Intakt) 3. 0mml. D. x 30mm, 3um	35deg.	A) 0. 05% TFA, H2O B) 0.05% TFA, MeCN	1.5	210-400nm
				(A/B) :95/5 => 0/100(3.5min) => 0/100 (lmin)		PDA total
B	ZMD	Cadenza CD-C18 (Intakt) 3. 0mml. D. x 30mm, 3um	35deg.	A) 0. 05% TFA, H20 B) 0. 05% TFA, MeCN	1.0	210-400nm
				(A/B) :95/5 => 0/100 (9.5min) => 0/100(2.5min)		PDA total

Analysis Cond ition	Apparatus	Column used	Column Temperature	Mobile phase, Gradient	Flow Rate (mL/min)	Detection Wavelength
C	ZQ	Chromolith Flash RP-18c (Merck KGaA) 4.6mml. D. x 25mm	Room Temp.	A) 10mM AcONH4, H2O B) MeOH	2.0	210-400nm
				(A/B) :95/5 => 0/100 (3min) => 0/100 (2min)		PDA total
D	ZQ	Chromolith Flash RP-18c (MerckKGaA) 4. 6mml. D. x 25mm	Room Temp.	A) 10mM AcONH4, H2O B) McCN	2.0	210-400nm
				(A/B) :95/5 => 0/100(3min) => 0/100(2min)		PDA total
F	ZQ	Cadenza CD-C18 (Intakt) 3. 0mml. D. x 30mm, 3um	35deg.	A) 0. 05% TFA, H2O B) 0.05% TFA, MeCN	1.5	210-400nm
				(A/B) :95/5 => 0/100 (3. 5min) => 0/100(1min)		PDA total
H	ZQ	Cadenza CD-C18 (Intakt) 3.0mml. D. x 30mm, 3um	35deg.	A) 0. 05% TFA, H2O B) 0.05% TFA, MeCN	1.0	210-400nm
				(A/B) :95/5 => 0/100(9.5min) => 0/100(2.5min)		PDA total
I	ZQ	Ascentis Express C18 (Sigma Aldrich) 2. 1mml. D. x 50mm	Room Temp.	A) 10mM AcONH4, H2O B) MeOH	1.0	210-400nm
				(A/B) : 95/5 => 0/100 (9. 5min) => 0/100(1min)		PDA total
S	ZQ	Sunfire C18 (Waters) 4.5mml. D. x50mm, 5um		A) 0. 05% TFA, H2O B) 0.05% TFA, MeCN	4.0	200-400nm
				(A/B):90/10 => 5/95 (3.5min) => 90/10(1min) => 90/10(0.5min)		PDA total
T	ZQ	Sunfire C18 (Waters) 4. 5mml. D. x50mm, 5um	Room Temp.	A) 0.05% TFA, H2O B) 0.05% TFA, MeCN	4.0	200-400nm
				(A/B):90/10 => 5/95(2min) => 5/9.5(1.5min) => 90/10(1.0min) => 90/10(0.5min)		PDA total
U	ZQ	WAKOsil 3C18 AR, (Wako Pure Chemical Industries, Ltd.) 4.6mm I.D. x 30mm	Room Temp.	A) 0. 05% TFA, H2O B) 0. 05% TFA, MeCN	2.0	210-400nm
				(A/B):90/10 => 90/10 (0. 2 min) => 5/95(3.1min) => 5/95 (1. 4min)		PDA total
W	ZMD	Sunfire C18 (Waters) 4. 5mml. D. x50mm, 5um	Room Temp.	A) 0. 05% TFA, H2O B) 0. 05% TFA, MeCN	4.0	200-400nm
				(A/B) : 90/10 => 5/95 (3.5min) => 90/10(1min) => 90/10(0.5min)		PDA total
Y	ZMD	Sunfire C18 (Waters) 4. 5mml. D. x50mm, 7um	Room Temp.	A) 0. 05% TFA, H2O B) 0.05% TFA, MeCN	2.0	210-400nm
				(A/B):90/10 => 0/100 (3.5min) => 0/100 (1min)		PDA total

Microwave reaction

[0254] The reaction was carried out by using a snap cap reaction vial together with an Explorer™ (manufactured by CEM Microwave

Technology) or an initiator (manufactured by Biotage). Maximum output setting includes cooling of the reaction vessel by air in order to avoid temperature increase caused by microwave irradiation.

[0255] Commercially available reagents were obtained and used without any further purification. The room temperature indicates the temperature range of between about 20 to 25°C. All the non-aqueous reaction was carried out in anhydrous solvent under nitrogen or argon atmosphere. For concentration under reduced pressure or removal of a solvent by distillation, a rotary evaporator was used.

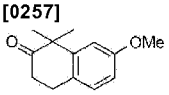
[0256] For preparing the compounds, when there is a possibility of having an undesirable side reaction, a functional group was protected using a protecting group to produce a target molecule, and the protecting group was removed later, if desired. Selection, addition and removal of a protecting group were carried out according to the method described in the literature [Greene and Wuts, "Protective Groups in Organic Synthesis" (4th edition, John Wiley & Sons 2007)], for example.

[Example 1]

Compound A2

7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[0257]



[0258] 7-Methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 209 g, 1.18 mol), tetrabutylammonium hydrogen sulfate (40 g, 0.118 mol) and methyl iodide (162 g, 2.60 mol) were suspended in THF (500 ml) at room temperature. Under stirring, the mixture was added with 50% aqueous solution of potassium hydroxide (400 g) over 5 min. Reflux occurred as the inner temperature rapidly increases. Once the inner temperature stopped to increase, stirring was continued for 45 min. The reaction solution was diluted with distilled water (1 L) and extracted twice with CPME (1.5L). The combined organic layer was washed (distilled water 1 L × 3), dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The resulting crude product was recrystallized with MeOH (1 L) and distilled water (500 ml) to obtain the title compound as a colorless needle-like crystal (177 g, 73%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 1.43 (6 H, s), 2.65 (2 H, t, 12 Hz), 3.02 (2 H, t, 12 Hz), 3.79 (3 H, s), 6.74 (1 H, m), 6.87 (1 H, m), 7.24 (1 H, m).

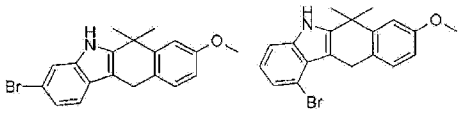
LCMS: m/z 205 $[M+H]^+$

[Example 2]

Compound A3-1, Compound A3-2

3-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole 1-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole

[0259]



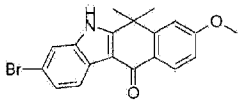
[0260] 7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 66.2 g, 324 mmol) and 3-bromophenylhydrazine hydrochloric acid salt (71.0 g, 318 mmol) were dissolved in AcOH (350 ml) and refluxed under stirring for 6 hr. The reaction solvent was removed by distillation under reduced pressure to obtain the crude product as a mixture of the title compound A3-1 and A3-2.

[Example 3]

Compound A4

3-Bromo-8-methoxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one

[0261]



[0262] The crude product obtained from the above (i.e., mixture of A3-1 and A3-2) was dissolved in a mixture solvent of THF (450 ml) and distilled water (50 ml), added once with DDQ (115 g, 509 mmol), and then stirred at room temperature for 1 hr. The reaction mixture was diluted with CPME 3L, and the organic layer was washed three times with 0.5 N aqueous solution of sodium hydroxide (1 L) and twice with distilled water (1 L) in order and dried over anhydrous sodium sulfate. The organic layer was concentrated to 500 ml under reduced pressure. The precipitated product was collected by filtration and washed with a small amount of CPME to obtain the title compound as a yellow crystal (48 g, 40%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 1.73 (6 H, s), 3.90 (3 H, s), 7.06-7.09 (1 H, m), 7.32-7.38 (2 H, m), 7.65-7.66 (1 H, m), 8.09-8.17 (2 H, m), 12.32 (1 H, br. s).

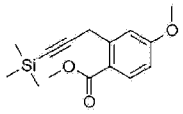
LCMS: m/z 370, 372 $[M+H]^+$

[Example 4]

Compound AA1

4-Methoxy-2-(3-trimethylsilanylprop-2-ynyl)-benzoic acid methyl ester

[0263]



[0264] To the THF (16 ml) solution of 2-bromomethyl-4-methoxy-benzoic acid methyl ester (961 mg, 4.09 mmol), triphenylphosphine (107 mg, 0.1 eq.), cesium carbonate (1.87 g, 1.4 eq.), copper iodide (59 mg, 0.076 eq.) and tris (dibenzylideneacetone) dipalladium (86 mg, 0.023 eq.) were added, degassed, flushed with nitrogen gas, added with trimethylsilylacetylene (734 µl, 1.3 eq.), and then stirred overnight at 55°C. To the reaction solution, saturated aqueous solution of ammonium chloride was added followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (brown oily substance, 606 mg, 54%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 7.93 (1 H, d, J = 8.8 Hz), 7.33 (1 H, d, J = 2. 6 Hz), 6.78 (1 H, dd, J = 8.8, 2.6 Hz), 4.09 (2 H, s), 3.86 (3 H, s), 3.84 (3 H, s), 0. 14(9 H, s).

LCMS: m/z 277 $[M+H]^+$

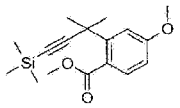
HPLC retention time: 3.30 min (analysis condition U)

[Example 5]

Compound AA2

2-(1,1-Dimethyl-3-trimethylsilanylprop-2-ynyl)-4-methoxy-benzoic acid methyl ester

[0265]



[0266] To the toluene (4 ml) solution of 4-methoxy-2-(3-trimethylsilanyl-prop-2-ynyl)-benzoic acid methyl ester (Compound AA1, 273 mg, 0.988 mmol), sodium bis (trimethylsilyl) amide (2.1 ml, 1.9 m solution, 4 eq.) and iodomethane (308 µl, 5 eq.) were added at -78°C. After allowing the reaction temperature to increase to the room temperature, the mixture was stirred for 2 hr. To the reaction solution, saturated aqueous solution of ammonium chloride was added followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (yellow oily substance, 226 mg, 75%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 7.45 (1.0 H, d, J = 8.4 Hz), 7. 09 (1.1 H, d, J = 2.6 Hz), 6.75 (1 H, m), 3.84 (3 H, s), 3.82 (3 H, s), 1.70 (6 H, s), 0.14(9 H, s)

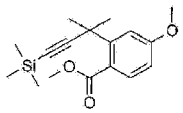
LCMS: m/z 305 $[M+H]^+$
HPLC retention time: 3.38 min (analysis condition U)

[Example 6]

Compound AA3

2-(1,1-Dimethylprop)-2-ynyl)-4-methoxy-benzoic acid methyl ester

[0267]



[0268] To the THF (18 ml) solution of 2-(1,1-dimethyl-3-trimethylsilanylprop-2-ynyl)-4-methoxy-benzoic acid methyl ester (Compound AA2, 912 mg, 3 mmol), tetrabutylammonium fluoride (2.061 g, 2.6 eq.) was added, and then stirred for 3 hr at room temperature. To the reaction solution, saturated aqueous solution of ammonium chloride was added followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (yellow oily substance, 524 mg, 75%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 7.44 (1 H, d, J = 8.4 Hz), 7.05 (1 H, d, J = 2. 3 Hz), 6.76 (1 H, dd, J = 8.4, 2.3 Hz), 3.84 (3 H, s), 3.82 (3 H, s), 1.73 (6 H, s)

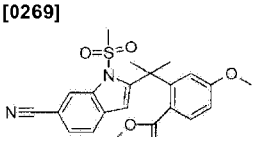
LCMS: m/z 223 $[M+H]^+$
HPLC retention time: 2.55 min (analysis condition U)

[Example 7]

Compound AA4

2-[1-(6-Cyano-1-methanesulfonyl-1H-indol-2-yl)-1-methylethyl]-4-methoxy-benzoic acid methyl ester

[0269]



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[0270] To the DMF (2 ml) solution of 2-(1,1-dimethylprop-2-ynyl)-4-methoxy-benzoic acid methyl ester (Compound AA3, 134 mg, 0.577 mmol) and N-(2-bromo-5-cyanophenyl)methanesulfonamide (Compound AA5, 167 mg, 1.05 eq.), copper iodide (9 mg, 0.08 eq.) and TEA (129 µl, 1.6 eq.) were added, degassed and flushed with nitrogen gas, added with dicholorobis (triphenylphosphine) palladium (20 mg, 0.05 eq.), and then degassed and flushed again with nitrogen gas. After stirring for 2 hr at 90°C, the reaction solution was added with water, extracted with ethyl acetate. The organic layer was washed with an brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (white solid, 152 mg, 62%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.19 (1 H, dd, J = 0.6, 0.6 Hz), 7.84 (1 H, dd, J = 8.0, 0.6 Hz), 7.67 (1 H, dd, J = 8.0, 1.3 Hz), 7.13 (1 H, d, J = 8.4 Hz), 6. 99 (1 H, s), 6.96 (1 H, br. s), 6.85 (1 H, dd, J = 8.4, 2.5 Hz), 3.78 (3 H, s), 3.12 (3 H, s), 3.09 (3 H, br. s), 1.89 (6 H, s).

LCMS: m/z 427 $[M+H]^+$

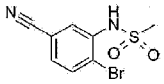
HPLC retention time: 2.77 min (analysis condition U)

[Example 8]

Compound AA5

N-(2-Bromo-5-cyanophenyl)methanesulfonamide

[0271]



[0272] To a miture of 3-amino-4-bromo-benzonitrile (1.98 g, 10 mmol), TEA (5.06 g, 50 mmol), and methylene chloride (50 ml), mesyl chloride (2.71 ml, 35 mmol) was added at 0°C and the mixture was stirred at room temperature for 30 min. Water was added to the reaction solution, which was then extracted with dichloromethane. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with tetrahydrofuran (100 ml), water (400 µl) and sodium hydride (540 mg, 15.5 mmol), and stirred at room temperature for 16 hr. To the reaction solution, saturated aqueous solution of ammonium chloride (200 ml) was added followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane/ethyl acetate) to obtain the title compound (2.48 g, 90%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 9.82 (1 H, s), 7.87 (1 H, d, J=4 Hz), 7. 75 (1 H, d, J=8 Hz), 7.70 (1 H, dd, J=8 Hz, 4 Hz), 3.14(3 H, s)

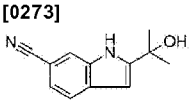
HPLC retention time: 1.63 min (analysis condition U)

[Example 9]

Compound AA6

2-(1-Hydroxy-1-methylethyl)-1H-indole-6-carbonitrile

[0273]



[0274] To N-(2-bromo-5-cyanophenyl)methanesulfonamide (Compound AA5, 230 mg, 1 mmol), 3-methyl-2-butyn-3-ol (0.15 ml, 1.5 mmol), X-Phos (72 mg, 15% mol), $PdCl_2(CH_3CN)_2$ (13 mg, 5% mol) and cesium carbonate (390 mg, 2 mmol), DMA (2 ml) was added, and the mixture was stirred at 100°C for 3 hr. Water and 5 N hydrochloric acid solution were added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the

residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane/ethyl acetate) to obtain the title compound (130 mg, 75%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 8.76 (1 H, s), 7.68 (1 H, s), 7.60 (1 H, d, J=8 Hz), 7.32 (1 H, dd, J=8 Hz, 4 Hz), 6.37(1 H, m), 1.93 (1 H, s), 1.70 (6 H, s)

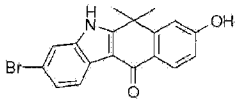
LCMS: m/z 201 $[M+H]^+$
HPLC retention time: 2.12 min (analysis condition U)

[Example 10]

Compound A5-1

3-Bromo-8-hydroxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one

[0275]



[0276] Under the same conditions as the method for synthesizing Compound A6, the title compound was synthesized from Compound A4.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.30 (1 H, s), 10.21 (1 H, s), 8.06-8.11 (1 H, m), 8.01-8. 05 (1 H, m), 7.62-7.66 (1 H, m), 7.32-7.37 (1 H, m), 7.08-7.12 (1 H, m), 6.84-6.90 (1 H, m), 1.69 (6 H, s).

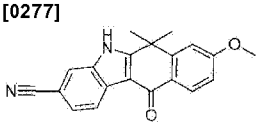
LCMS: m/z 356, 358 $[M+H]^+$
HPLC retention time: 2.30 min (analysis condition U)

[Example 11]

Compound A5-2

8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0277]



[0278] (Method 1) 3-Bromo-8-methoxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one (Compound A4, 10.45 g, 28.2 mmol) and copper (I) cyanide (5.0 g, 50.2 mmol) were dissolved in NMP (100 ml), followed by stirring at 170°C for 17 hr. The reaction mixture was suspended in ethyl acetate (500 mL) and distilled water (200 mL). The insoluble matters were removed by Celite filtration and washed twice with ethyl acetate (300 mL × 2). The organic layer was washed once with an aqueous solution of disodium EDTA (200 mL) and twice with saturated brine (200 mL) in order, and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to yield a product, which was suspended and washed with a small amount of CPME to obtain the title compound as a colorless crystal (6.58 g, 73%).

[0279] (Method 2) To the THF (5.6 ml) solution of 2-[1-(6-cyano-1-methanesulfonyl-1H-indol-2-yl)-1-methylethyl]-4-methoxy-benzoic acid methyl ester (Compound AA4, 138 mg, 0.324 mmol), tetrabutylammonium fluoride (514 mg, 6 eq.) was added, and the mixture was stirred at room temperature overnight. Thereafter, 2 M aqueous solution of sodium hydroxide (5.6 ml) was added to the mixture, which was then stirred for 4 hr, added with 1 M HCl, and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were dissolved in ethyl acetate (10 ml) and added with e 4 M HCl and ethyl acetate solution (10 ml) followed by stirring at room temperature for 30 min. The residues obtained after concentration of the reaction solution under reduced pressure

were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (89.2 mg, 62%).

[0280] (Method 3) To nitrobenzene (5 ml) and aluminum chloride (400 mg, 3 mmol), 4-methoxybenzoyl chloride (400 mg, 2.3 mmol) was added. After stirring for 30 min at room temperature, 2-(1-hydroxy-1-methyl-ethyl)-1H-indole-6-carbonitrile (Compound AA6, 200 mg, 1 mmol) was added followed by stirring at room temperature for 3 hr. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane/ethyl acetate) to obtain the title compound (127 mg, 40%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 1.71 (6 H, s), 3.89 (3 H, s), 7.07-7.09 (1 H, m), 7.34 (1 H, s), 7.58-7.60 (1 H, m), 7.99 (1 H, s), 8.14-8.16 (1 H, m), 8.30-8. 32 (1H, m), 12.32 (1 H, br. s),

LCMS: m/z 317 $[M+H]^+$

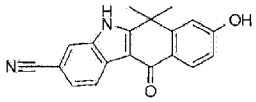
HPLC retention time: 2.56 min (analysis condition U)

[Example 12]

Compound A6

8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0281]



[0282] 8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A5-2, 6.58 g, 20.8 mmol) was dissolved in pyridine hydrochloric acid salt (25.0 g), and stirred at 170°C for 13 hr. The reaction mixture was partitioned in ethyl acetate (400 mL) and distilled water (400 mL), and the aqueous layer was extracted one more time with ethyl acetate (400 mL). The combined organic layer was washed twice with distilled water (100 mL) and once with saturated brine (100 mL) in order, and dried over anhydrous sodium sulfate. The organic layer was concentrated under reduced pressure to yield a product, which was suspended and washed with a small amount of CPME to obtain the title compound as a colorless crystal (5.91 g, 93%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 1.73 (6 H, s), 6.87-6.90 (1 H, m), 7.11 (1 H, s), 7.57-7.59 (1 H, m), 7.97 (1 H, s), 8.04-8.06 (1H, m), 8.29-8.31 (1 H, m), 10.27 (1 H, s), 12.66 (1 H, br. s),

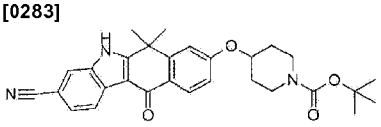
LCMS: m/z 303 $[M+H]^+$

[Example 13]

Compound A7-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-piperidine-1-carboxylic acid tert-butyl ester

[0283]



[0284] 8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 30 mg, 0.099 mmol) was dissolved in THF (1 mL), added with 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester (40 mg, 2 eq.), triphenylphosphine (52 mg, 2 eq.), and diisopropyl azodicarboxlyate (43 μL, 2 eq.) in order, and stirred at room temperature for 4 hr. The reaction solution was poured to water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (37 mg, 76%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 9.44 (1 H, s), 8.77 (1 H, d, J = 7.8 Hz), 8.62 (1 H, d, J = 8.2 Hz), 8.00 (1 H, s), 7.81 (1 H, d, J = 8.2 Hz), 7.34 (1 H, s), 7.26 (1 H, d, J = 7.8 Hz), 4.85-4.93 (1 H, m), 3.96-4.04 (2 H, m), 3.60-3.70 (2 H, m), 2.19-2. 32 (2H, m), 1.89-2.15 (8 H, m), 1.74 (9 H, s)

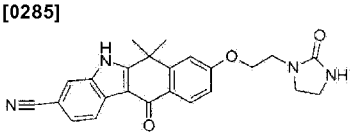
LCMS: m/z 430 $[M+H]^+$
HPLC retention time: 4.09 min (analysis condition W)

[Example 14]

Compound A7-2

6,6-Dimethyl-11-oxo-8-[2-(2-oxo-imidazolidin-1-yl)-ethoxy]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0285]



[0286] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 1-(2-hydroxy-ethyl)-imidazolidin-2-one.

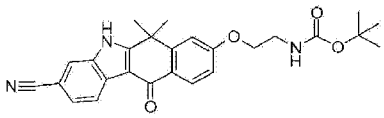
LCMS: m/z 415 $[M+H]^+$
HPLC retention time: 2.96 min (analysis condition W)

[Example 15]

Compound A7-3

[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-carbamic acid tert-butyl ester

[0287]



[0288] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and (2-hydroxy-ethyl)-carbamic acid tert-butyl ester.

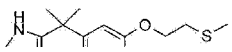
LCMS: m/z 346 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition W)

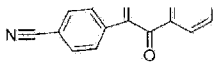
[Example 16]

Compound A7-4

6,6-Dimethyl-8-(2-methylsulfanyl-ethoxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0289]





[0290] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-methylthioethanol.

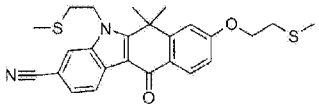
LCMS: m/z 451 $[M+H]^+$
HPLC retention time: 4.23 min (analysis condition W)

[Example 17]

Compound A7-5

6.6-Dimethyl-8-(2-methylsulfanyl-ethoxy)-5-(2-methylsulfanyl-ethyl)-11-oxo-6.11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0291]



[0292] The title compound was obtained as a by-product of the synthesis of Compound A7-4.

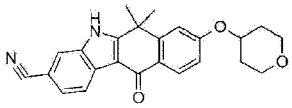
LCMS: m/z 377 $[M+H]^+$
HPLC retention time: 3.75 min (analysis condition W)

[Example 18]

Compound A7-6

6.6-Dimethyl-11-oxo-8-(tetrahydro-pyran-4-yloxy)-6.11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0293]



[0294] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and tetrahydropyran-4-ol.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.72 (1 H, br.s), 8.32 (1 H, d, 8.5 Hz), 8.15 (1 H, d, 8.5 Hz), 8.01 (1 H, s), 7.61 (1 H, d, 8.5 Hz), 7.38 (1 H, s), 7.15 (1 H, d, 8.5 Hz), 4.86-4.81 (1 H, m), 3.93-3.88 (2 H, m), 3.58-3.52 (2 H, m), 2.06-2.00 (2 H, m), 1.85 (6 H, s), 1.69-1.60 (2 H, m)

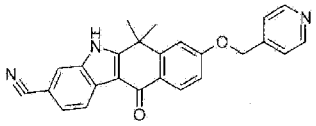
LCMS: m/z 387 $[M+H]^+$
HPLC retention time: 3.47 min (analysis condition W)

[Example 19]

Compound A7-7

6,6-Dimethyl-11-oxo-8-(pyridin-4-ylmethoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0295]



[0296] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and pyridin-4-yl-methanol.

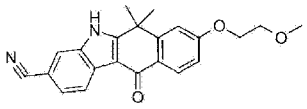
LCMS: m/z 394 $[M+H]^+$
HPLC retention time: 2.56 min (analysis condition W)

[Example 20]

Compound A7-8

8-(2-Methoxyethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0297]



[0298] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-methoxyethanol.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 11.69 (1 H, br. s), 8.27 (1 H, d, 7.9 Hz), 8.10 (1H, d, 8.5 Hz), 7.95 (1 H, s), 7.55 (1 H, d, 7.9 Hz), 7. 32 (1 H, d, 2.4 Hz), 7. 05 (1 H, d, 8.5 Hz), 4.22 (2 H, t, 4.3 Hz), 3.67 (2 H, t, 4.3 Hz), 1.72 (6 H, s)

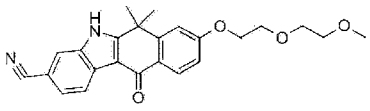
LCMS: m/z 361 $[M+H]^+$
HPLC retention time: 3.38 min (analysis condition W)

[Example 21]

Compound A7-9

8-[2-(2-Methoxyethoxy)ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0299]



[0300] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-(2-methoxyethoxy)ethanol.

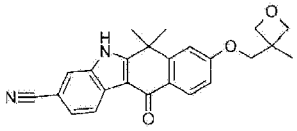
LCMS: m/z 405 $[M+H]^+$
HPLC retention time: 3.32 min (analysis condition W)

[Example 22]

Compound A7-10

6,6-Dimethyl-8-(3-methyloxetan-3-ylmethoxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0301]



[0302] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 3-chloromethyl-3-methyloxetane.

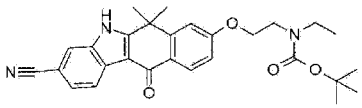
LCMS: m/z 387 $[M+H]^+$
HPLC retention time: 2.23 min (analysis condition S)

[Example 23]

Compound A7-11-1

[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)ethyl]ethyl-carbamic acid tert-butyl ester

[0303]



[0304] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and ethyl-(2-hydroxy-ethyl)-carbamic acid tert-butyl ester.

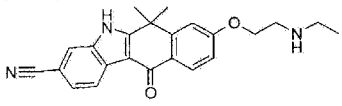
LCMS: m/z 474 $[M+H]^+$
HPLC retention time: 2.93 min (analysis condition U)

[Example 24]

Compound A7-11-2

8-(2-Ethylaminoethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0305]



[0306] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound A7-11-1.

LCMS: m/z 374 $[M+H]^+$

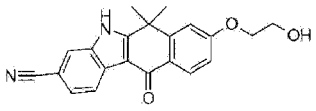
HPLC retention time: 1.35 min (analysis condition U)

[Example 25]

Compound A7-12

8-(2-Hydroxyethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0307]



[0308] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 2-bromo-ethanol.

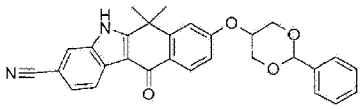
LCMS: m/z 437 $[M+H]^+$
HPLC retention time: 2.93 min (analysis condition U)

[Example 26]

Compound A7-13-1

6,6-Dimethyl-11-oxo-8-(2-phenyl-[1,3]dioxan-5-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0309]



[0310] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-phenyl-[1,3]dioxan-5-ol.

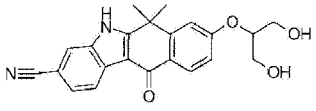
LCMS: m/z 465 $[M+H]^+$
HPLC retention time: 4.10 min (analysis condition W)

[Example 27]

Compound A7-13-2

8-(2-Hydroxy-1-hydroxymethylethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0311]



[0312] Anhydrous ferric trichloride (56 mg, 5 eq.) was added to the dichloromethane (2 mL) suspension of 6,6-dimethyl-11-oxo-8-(2-

phenyl-[1,3]dioxan-5-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A7-13-1, 13 mg, 0.028 mmol), and stirred at room temperature for 1 hr. The reaction solution was added to water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by high performance liquid chromatography to obtain the title compound (7 mg, 46%).

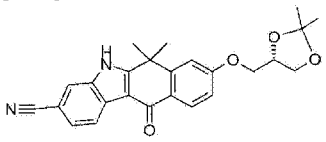
LCMS: m/z 377 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition W)

[Example 28]

Compound A7-14-1

8-((S)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0313]



[0314] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and toluene-4-sulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-ylmethyl ester.

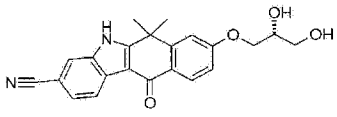
LCMS: m/z 417 $[M+H]^+$
HPLC retention time: 3.47 min (analysis condition Y)

[Example 29]

Compound A7-14-2

8-((R)-23-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0315]



[0316] To the solution of THF and water (4: 1,1 mL) of 8-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A14-1, 30 mg, 0.07 mmol), camphor sulfonic acid (36 mg, 0.14 mmol) was added at room temperature. After stirring at room temperature for 38 hr, the mixture was extracted with ethyl acetate. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the title compound (white solid, 28 mg, 72%).

^{1}H-NMR(300 MHz, DMSO-d_6) σppm ; 12.7 (s, 1 H), 8.31 (d, 1 H, J=8.01 Hz), 8.15 (d, 1H, J=8. 77 Hz), 8.00 (s, 1 H), 7.60 (d, 1 H, J=8.01 Hz), 7.12 (s, 1 H), 7. 09 (d, 1 H, J=8. 77 Hz), 4.46 (m, 1 H), 4.15 (m, 3 H), 3.78 (m, 1 H), 1.76 (s, 6 H), 1. 38 (s, 3 H), 1.32 (s, 3 H)

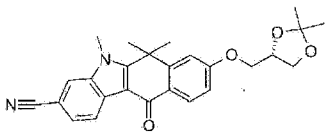
LCMS: m/z 377 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition U)

[Example 30]

Compound A7-14-3

8-((S)-2,2-Dimethyl-[1,3]dioxolan-4-ylmethoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0317]



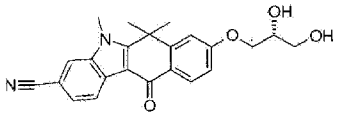
[0318] Under the same conditions as the method for synthesizing Compound B3-4, the title compound was prepared as a crude product from Compound A7-14-1.

[Example 31]

Compound A7-14-4

8-((R)-2,3-Dihydroxy-propoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0319]



[0320] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound A7-14-3 (303 mg, 98%).

LCMS: m/z 484 $[M+H]^+$

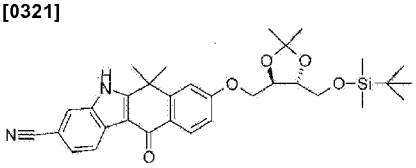
HPLC retention time: 2.08 min (analysis condition D)

[Example 32]

Compound A7-15-1

8-[(4R,5S)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0321]



[0322] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol.

LCMS: m/z 516 $[M+H]^+$

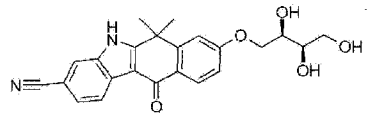
HPLC retention time: 3.97 min (analysis condition Y)

[Example 33]

Compound A7-15-2

6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0323]



[0324] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound A7-15-1.

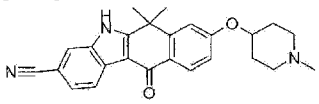
LCMS: m/z 407 $[M+H]^+$
HPLC retention time: 1.73 min (analysis condition U)

[Example 34]

Compound A7-16

6,6-Dimethyl-8-(1-methyl-piperidin-4-yloxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0325]



[0326] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 1-methylpiperidin-4-ol.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.75 (1 H, s), 8.32 (1 H, d, J = 7.9 Hz), 8.14 (1 H, d, J = 9.8 Hz), 8.00 (1 H, s), 7.60 (1 H, d, J = 7.9 Hz), 7.34 (1 H, s), 7.11 (1 H, d, J = 9.1 Hz), 4.62 (1 H, m), 2. 64 (2 H, m), 2.23 (2 H, m), 2.21(s, 3 H), 1.99 (2 H, m), 1.77(s, 6 H), 1.73 (2 H, m).

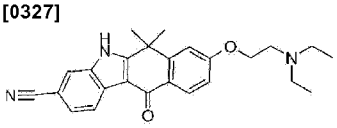
LCMS: m/z 400 $[M+H]^+$
HPLC retention time: 1.42 min (analysis condition S)

[Example 35]

Compound A7-17

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0327]



[0328] 8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 25 mg, 0.083 mmol) was dissolved in N,N-dimethylacetamide (1 mL), added with 2-chloroethyldiethylamine (16 mg, 1.1 eq.) and cesium carbonate (54 mg, 2 eq.) in order and stirred at 100°C for 4 hr. The reaction solution was poured over water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by amino silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (11 mg, 32%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.32 (1 H, d, J = 8.2 Hz), 8.15 (1 H, d, J = 8.7 Hz), 8.01 (1 H, s), 7.61 (1 H, d, J = 8.2 Hz), 7.35 (1H, d, J = 1.8 Hz), 7.09 (1 H, dd, J = 8.7, 1.8 Hz), 4.19 (2 H, t, J = 5.9 Hz), 2.83 (2 H, t, J = 5.9 Hz), 2.58 (4 H, q, J = 7.0 Hz), 1.78 (6 H, s), 1.00 (6 H, t, J = 7.0 Hz)

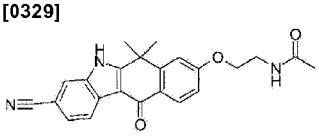
LCMS: m/z 402 $[M+H]^+$
HPLC retention time: 2.52 min (analysis condition W)

[Example 36]

Compound A7-18

N-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-acetamide

[0329]



[0330] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 2-chloroethylacetamide.

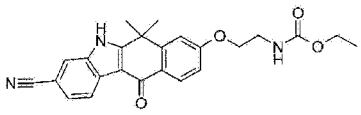
LCMS: m/z 388 $[M+H]^+$
HPLC retention time: 2.91 min (analysis condition W)

[Example 37]

Compound A7-19

[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-carbamic acid ethyl ester

[0331]



[0332] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and ethyl-2-chloroethylcarbamate.

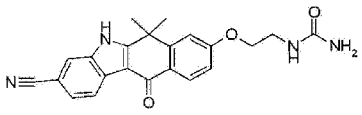
LCMS: m/z 418 $[M+H]^+$
HPLC retention time: 3.35 min (analysis condition W)

[Example 38]

Compound A7-20

[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-urea

[0333]



[0334] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 2-chloroethylurea.

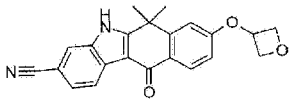
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 2.80 min (analysis condition W)

[Example 39]

Compound A7-21

6,6-Dimethyl-8-(oxetan-3-yloxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0335]



[0336] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and toluene-4-sulfonic acid oxetan-3-yl ester.

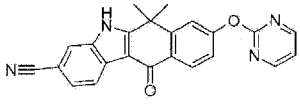
LCMS: m/z 359 $[M+H]^+$
HPLC retention time: 2.00 min (analysis condition S)

[Example 40]

Compound A7-22

6,6-Dimethyl-11-oxo-8-(pyrimidin-2-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0337]



[0338] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 2-bromopyrimidine.

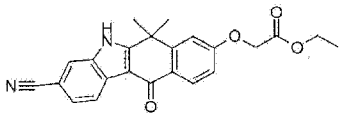
LCMS: m/z 381 $[M+H]^+$
HPLC retention time: 2.00 min (analysis condition S)

[Example 41]

Compound A7-23

(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl acetate ester

[0339]



[0340] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 3-chloro-propionic acid ethyl ester.

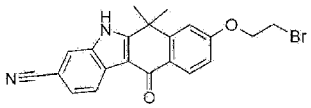
LCMS: m/z 389 $[M+H]^+$
HPLC retention time: 3.37 min (analysis condition U)

[Example 42]

Compound A7-24

8-(2-Bromo-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0341]



[0342] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-bromoethanol.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.75 (1 H, br.s), 8.32 (1 H, d, J = 8. 2 Hz), 8.17 (1 H, d, J = 8.6 Hz), 8.01 (1 H, s), 7.61 (1 H, dd, J = 8.2, 1.4 Hz), 7.40 (1 H, d, J = 2.2 Hz), 7.12 (1 H, dd, J = 8.6, 2.2 Hz), 4.50 (2 H, t, J = 5.3 Hz), 3.88 (2 H, t, J = 5.3 Hz), 1.77 (6 H, s).

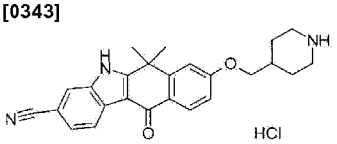
LCMS: m/z 409, 411 $[M+H]^+$
HPLC retention time: 2.48 min (analysis condition S)

[Example 43]

Compound A7-25

6,6-Dimethyl-11-oxo-8-(piperidin-4-ylmethoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloric acid salt

[0343]



[0344] Under nitrogen atmosphere, 3-cyano-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound A6, 85 mg, 0.28 mmol) and triphenylphosphine (150 mg, 2 eq.) were added with THF (2 ml), and then further added dropwise with 4-hydroxymethyl-piperidine-1-carboxylic acid tert-butyl ester (120 mg, 2 eq.) and 2.19 N toluene solution of diethyl azodicarboxylic acid

(0.26 mL, 2 eq.). The resultant was stirred at room temperature for 12 hr under nitrogen atmosphere. The residues obtained after concentrating the reaction solution under reduced pressure were purified by silica gel column chromatography (ethyl acetate/dichloromethane) to obtain 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxymethyl)-piperidine-1-carboxylic acid tert-butyl ester (white powder, 120 mg).

[0345] To the resulting compound, 4 N hydrochloric acid and dioxane solution was added under cooling. After stirring at room temperature for 2 hr, the solvent was removed under nitrogen stream. Then, the residues were washed with diethyl ether and then subjected to azeotropic treatment with toluene, followed by drying under vacuum and filtration to obtain the title compound (79 mg).

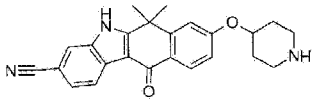
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 2.22 min (analysis condition C)

[Example 44]

Compound A8-1

6,6-Dimethyl-11-oxo-8-(piperidin-4-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0346]



[0347] THF (0.5 mL) and TFA (0.5 mL) were added to 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-piperidine-1-carboxylic acid tert-butyl ester (Compound A7-1, 35 mg, 0.072 mmol), and the mixture was stirred at room temperature until Compound A7-1 disappears. The reaction solution was concentrated under reduced pressure and the residue was desalinated by using anion exchanger PL StratoSpheres (trademark) PL-HCO3 MP to obtain the title compound (37 mg, 76%).

^{1}H-NMR (400 MHz, CD_3OD) δ : 8.38 (1 H, d, J = 7.9 Hz), 8.24 (1 H, d, J = 8.5 Hz), 7.85 (1 H, s), 7. 53 (1H, d, J = 7.9 Hz), 7. 27 (1 H, s), 7.09 (1 H, d, J = 8.5 Hz), 4.67-4.76 (1 H, m), 3.07-3.20 (2 H, m), 2.77-2.87 (2 H, m), 2.03-2.15 (2 H, m), 1.80 (6 H, s), 1.69-1.77 (2 H, m)

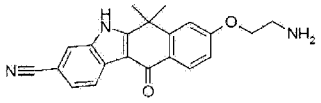
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 2.51 min (analysis condition W)

[Example 45]

Compound A8-2

8-(2-Amino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0348]



[0349] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound A7-3.

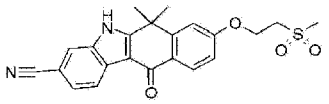
LCMS: m/z 346 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition W)

[Example 46]

Compound A8-3

8-(2-Methanesulfonyl-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0350]



[0351] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound A7-5.

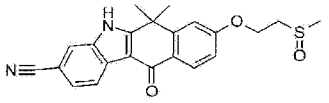
LCMS: m/z 409 $[M+H]^+$
HPLC retention time: 3.13 min (analysis condition W)

[Example 47]

Compound A8-4

8-(2-Methanesulfinyl-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0352]



[0353] The title compound was obtained as a by-product of the synthesis of Compound A8-3.

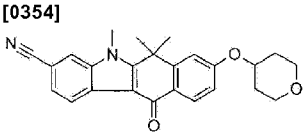
LCMS: m/z 393 $[M+H]^+$
HPLC retention time: 2.87 min (analysis condition W)

[Example 48]

Compound A8-5

5,6,6-Trimethyl-11-oxo-8-(tetrahydro-pyran-4-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0354]



[0355] Under the same conditions as the method for synthesizing Compound A10-1, the title compound was prepared from Compound A7-6.

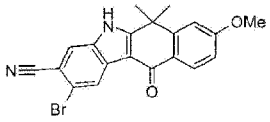
LCMS: m/z 401 $[M+H]^+$
HPLC retention time: 2.72 min (analysis condition S)

[Example 49]

Compound A8-6-1

2-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0356]



[0357] 8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A5-2, 50 mg, 0.158 mmol) was dissolved in CH_3CN (1 mL), added with NBS (56 mg, 2 eq.), and stirred at 80°C overnight. The reaction solution was added to water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with MeOH and the solid remained after dissolution was filtered to obtain the target compound (yellow powder, 20 mg, 38%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.92 (1 H, s), 8. 50 (1 H, s), 8. 16 (1 H, d, J = 8. 5 Hz), 8. 14 (1 H, s), 7. 36 (1 H, d, J = 2. 4 Hz), 7. 11 (1 H, dd, J = 8. 5, 2. 4 Hz), 3.92 (3H, s), 1. 78 (6 H, s).

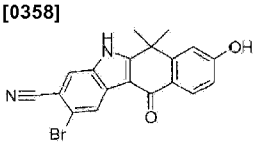
LCMS: m/z 395, 397 $[M+H]^+$
HPLC retention time: 2.57 min (analysis condition S)

[Example 50]

Compound A8-6-2

2-Bromo-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0358]



[0359] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound A8-6-1.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.46 (1 H, s), 8.10 (1H, s), 8.05 (1 H, d, J = 8.6 Hz), 7.13 (1 H, d, J = 2.1 Hz), 6.89 (1 H, dd, J = 8.5, 2.1 Hz), 1.71 (6 H, s).

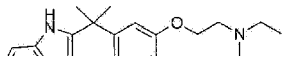
LCMS: m/z 381,383 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition S)

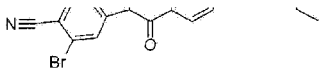
[Example 51]

Compound A8-6-3

2-Bromo-8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0360]





[0361] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A8-6-2.

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.53 (1 H, d, J = 0.5 Hz), 8.20 (1 H, d, J = 8.7 Hz), 7.88 (1 H, d, J = 0.5 Hz), 7.28 (1 H, d, J = 2.3 Hz), 7.05 (1 H, dd, J = 8.9, 2. 5 Hz), 4.24 (2 H, t, J = 5.7 Hz), 2. 96 (2 H, t, J = 5.7 Hz), 2.70 (4 H, q, J = 7. 1 Hz), 1.79 (6 H, s), 1.12 (6 H, t, J = 7.2 Hz).

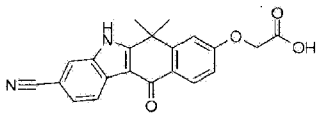
LCMS: m/z 480, 482 $[M+H]^+$
HPLC retention time: 1.73 min (analysis condition S)

[Example 52]

Compound A8-7

(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetic acid

[0362]



[0363] (3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl acetate ester (Compound A7-23, 180 mg, 0.464 mmol) and potassium hydroxide (130 mg, 2.32 mmol) were dissolved in THF (10 ml) and water (1.8 mL), and stirred at 70°C for 2 hr. After cooling to room temperature, the mixture was extracted with dichloromethane. Water layer(
日本語誤変換
) was adjusted to be acidic by using 1 N hydrochloric acid, and the precipitated solid was filtered and washed several times with water to obtain the title compound (white solid, 130 mg, 78%).

^{1}H-NMR(300 MHz, DMSO) σppm 13.09(s, 1 H), 8.31(d, 1H, J=8.1 Hz), 8. 11(d, 1H, J=8.4 Hz), 8.01(s, 1 H), 7.58(d, 1 H, J=7.8 Hz), 7.25(d, 1 H, J=2.1 Hz), 6. 97(d, 1 H, J=8.4 Hz), 4.51(s, 2 H), 1.73(s, 6 H)

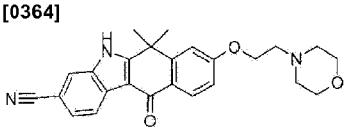
LCMS: m/z 361 $[M+H]^+$
HPLC retention time: 2.97 min (analysis condition U)

[Example 53]

Compound A8-8

6,6-Dimethyl-8-(2-morpholin-4-yl-ethoxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0364]



[0365] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound A7-24 and morpholine.

^{1}H-NMR(500 MHz, CD_3OD+$CDCl_3$) σ ppm; 8.4(d, 1 H, J=8.2 Hz), 8.3(d, 1 H, J=8.7 Hz), 7.8(s, 1 H), 7.5(dd, 1 H, J=1.1 Hz, J=8.2 Hz), 7.2(d, 1 H, J=2.3 Hz), 7.0(dd, 1 H, J=2.2 Hz, J=8. 7 Hz), 4.2(t, 2 H, J=5.3 Hz), 3.7(t, 4 H, J=4.5 Hz), 2.9(t, 2 H, J=5.3 Hz), 2.6(t, 4 H, J=4.5 Hz), 1.8(s, 6 H)

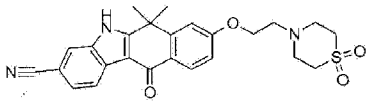
LCMS: m/z 416 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition U)

[Example 54]

Compound A8-9

8-[2-1,1-Dioxothiomorpholino)-ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0366]



[0367] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A7-24 and thiomorpholine-1,1-dioxide.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.72 (1 H, s), 8.31 (1 H, d, 8.5 Hz), 8. 15 (1 H, d, 8.5 Hz), 8.00 (1 H, s), 7.60 (1 H, d, 8.5 Hz), 7.36 (1 H, d, 1.8 Hz), 7.10 (1 H, dd, 1.8, 8.5), 4.25 (2 H, t, 5.5 Hz), 3.06-3.33 (8 H, m), 2.97 (2 H, t, 5.5), 1.77 (6 H, s)

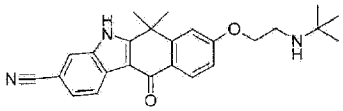
LCMS: m/z 464 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition W)

[Example 55]

Compound A8-10

8-(2-Tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0368]



[0369] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A7-24 and tert-butylamine.

^{1}H-NMR(400 MHz, DMSO-d6) δ : 12.71 (1 H, s), 8.32 (1 H, d, 7.9 Hz), 8. 15 (1 H, d, 9.1 Hz), 8.07 (1 d, 1.8 Hz), 7.60 (1 H, dd, 1.8, 7.9 Hz), 7.35 (1 H, d, 2.4 Hz), 7.09 (1 H, dd, 2.4, 9.1 Hz), 4.16 (2 H, t, 6.1 Hz), 2.91 (2 H, t, 6.1 Hz), 1.77 (6 H, s), 1.08 (9 H, s)

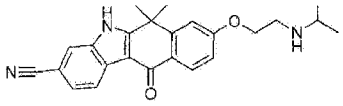
LCMS: m/z 402 $[M+H]^+$
HPLC retention time: 2.55 min (analysis condition W)

[Example 56]

Compound A8-11

8-(2-Sec-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0370]



[0371] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound A7-24 and sec-butylamine.

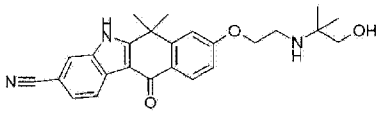
LCMS: m/z 402 $[M+H]^+$
HPLC retention time: 1.88 min (analysis condition U)

[Example 57]

Compound A8-12

8-[2-(2-Hydroxy-1,1-dimethyl-ethylamino)-ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0372]



[0373] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound A7-24 and 2-amino-2-methyl-propan-1-ol.

^{1}H-NMR(300 MHz, DMSO-d6) σppm; 12. 65(brs, 1 H), 8.31 (d, 1 H, J=8. 0 Hz), 8.15(d, 1H, J=8.8 Hz), 7.99(s, 1 H), 7.59(d, 1 H, J=8.0 Hz), 7.34(d, 1 H, J=2. 3 Hz), 7.08(dd, 1H, J=2.2 Hz, J=8.8 Hz), 4. 58(brs, 1 H), 4.16(t, 2 H, J=5.7 Hz), 3. 20(s, 2 H), 2.88(t, 2H, J=5.7 Hz), 1.76(s, 6 H), 0.97(s, 6 H)

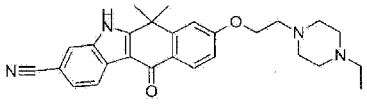
LCMS: m/z 418 $[M+H]^+$
HPLC retention time: 2.47 min (analysis condition U)

[Example 58]

Compound A8-13

8-[2-(4-Ethyl-piperazin-1-yl)-ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0374]



[0375] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound A7-24 and 1-ethyl-piperazine.

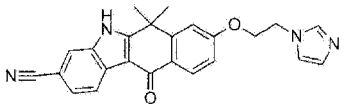
LCMS: m/z 443 $[M+H]^+$
HPLC retention time: 1.68 min (analysis condition U)

[Example 59]

Compound A8-14

8-(2-Imidazol-1-yl-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0376]



[0377] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A6 and 2-imidazol-1-yl-ethanol.

^{1}H-NMR(300 MHz, DMSO-d6) σ ppm; 12.71(s, 1 H), 8.31 (d, 1 H, J=8.3 Hz), 8.14(d, 1 H, J=8.8 Hz), 7.99(s, 1 H), 7.73(s, 1 H), 7.60(d, 1 H, J=8.3 Hz), 7. 34(s, 1 H), 7.29(s, 1 H), 7. 09(d, 1 H, J=8.8 Hz), 6.91(s, 1 H), 4.20(s, 4 H), 1.76(s, 6 H)

LCMS: m/z 387 $[M+H]^+$

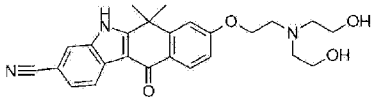
HPLC retention time: 1.77 min (analysis condition U)

[Example 60]

Compound A8-15

8-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethoxy}-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0378]



[0379] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A7-24 and 2-(2-hydroxyethylamino)-ethanol.

LCMS: m/z 434 $[M+H]^+$

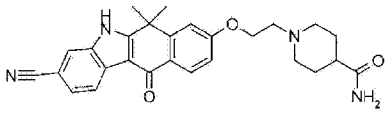
HPLC retention time: 2.40 min (analysis condition U)

[Example 61]

Compound A8-16

1-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-piperidine-4-carboxylic acid amide

[0380]



[0381] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound A7-24 and piperidine-4-carboxylic acid amide.

LCMS: m/z 457 $[M+H]^+$

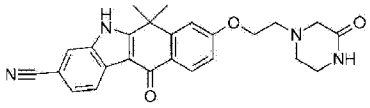
HPLC retention time: 1.28 min (analysis condition S)

[Example 62]

Compound A8-17

6,6-Dimethyl-11-oxo-8-[2-(3-oxo-piperazin-1-yl)-ethoxy]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0382]



[0383] To DMF solution (5 mL) of 8-(2-bromo-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A7-24, 30 mg, 0.07 mmol), piperazin-2-one (44.9 mg, 0.35 mmol) and N,N-diisopropylethylamine(0.061 mL, 0.35 mmol) were added at room temperature and stirred at 80°C for 18 hr. After cooling to room temperature, the mixture was extracted with ethyl acetate washed with saturated brine. The organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by preparative TLC (dichloromethane/methanol) to obtain the title compound (white solid, 24 mg, 80%).

^{1}H-NMR(300 MHz, DMSO-d6) σppm; 12.71(s, 1 H), 8.32(d, 1 H, J=8.4 Hz), 8.15(d, 1 H, J=8.8 Hz), 8.00(s, 1 H), 7.75(s, 1 H), 7.60(d, 1 H, J=8.4 Hz), 7. 37(d, 1 H, J=2.3 Hz), 7.09(dd, 1 H, J=2.3 Hz, J=8.8 Hz), 4.27(t, 2H, J=5.7 Hz), 3. 19(m, 2 H), 3.08(s, 2 H), 2.83(t, 2 H, J=5.7 Hz), 2.70(t, 2 H, J=5.7 Hz), 1.8(s, 6 H)

LCMS: m/z 429 $[M+H]^+$

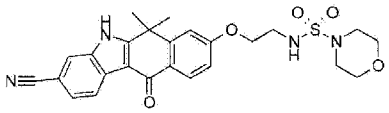
HPLC retention time: 1.29 min (analysis condition S)

[Example 63]

Compound A8-18

Morpholine-4-sulfonic acid[2-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-amide

[0384]



[0385] The title compound was obtained as a by-product of the synthesis of Compound C1-2.

LCMS: m/z 495 $[M+H]^+$

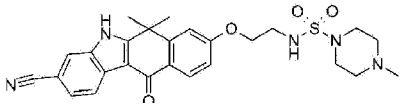
HPLC retention time: 2.00 min (analysis condition S)

[Example 64]

Compound A8-19

4-Methyl-piperazine-1-sulfonic acid[2-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-amide

[0386]



[0387] The title compound was obtained as a by-product of the synthesis of Compound C1-4.

^{1}H-NMR (300 MHz, DMSO-d6) δ : 1.77 (6 H, s), 2.16 (3 H, s), 2.34 (4 H, m), 3.08 (4 H, m), 3.35 (2 H, m), 4.19 (2 H, t, 5.34 Hz), 7.09 (1 H, dd, 8.77 Hz, 2. 99 Hz), 7.37 (1 H, bs, 1.91 Hz), 7.59 (2 H, m), 8.01 (1 H, s), 8.16 (1 H, d, 8.40 Hz), 8.32 (1 H, d, 8.01 Hz), 12.7 (1 H, s).

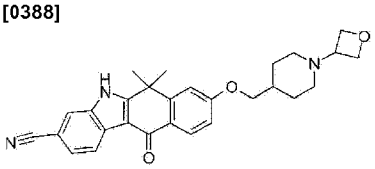
LCMS: m/z 501 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 65]

Compound A8-20

6,6-Dimethyl-8-(1-oxetan-3-yl-piperidin-4-ylmethoxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0388]



[0389] 6,6-Dimethyl-11-oxo-8-(piperidin-4-ylmethoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloric acid salt (Compound A7-25, 30 mg, 0.075 mmol) and oxetan-3-one (38 mg, 7 eq.) were dissolved in acetic acid (0.2 ml), THF (1 ml) and methanol (1 ml), added with sodium cyanoborohydride (33 mg, 7 eq.) at room temperature, and stirred overnight. The reaction solution was added with water, and then extracted with ethyl acetate. The solution was dried over sodium sulfate and the solvent was removed under vacuum and the resulting residues were purified by preparative TLC (chloroform: 2 N ammonia methanol = 9: 1) to obtain the target compound (15 mg).

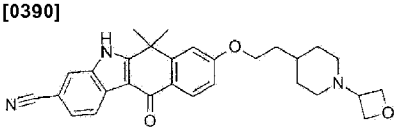
LCMS: m/z 456 $[M+H]^+$
HPLC retention time: 2.78 min (analysis condition C)

[Example 66]

Compound A8-21

6,6-Dimethyl-8-[2-(1-oxetan-3-yl-piperidin-4-yl)-ethoxy]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0390]



[0391] Under the same conditions as the method for synthesizing Compound A7-25, and Compound A8-20, the title compound was prepared from Compound A6 and 4-(2-hydroxy-ethyl)-piperidine-1-carboxylic acid tert-butyl ester (15 mg).

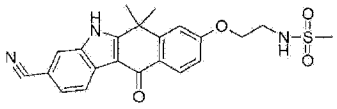
LCMS: m/z 470 $[M+H]^+$
HPLC retention time: 2.85 min (analysis condition C)

[Example 67]

Compound A9-1

N-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-methanesulfonamide

[0392]



[0393] Trifluoroacetic acid salt of 8-(2-amino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A8-2, 19 mg, 0.044 mmol) was suspended in dichloromethane (0.5 mL), added with diisopropylethylamine (0.0157 mL, 2 eq.) and methanesulfonyl chloride (0.0034 mL, 1 eq.), and then stirred at room temperature for 2 hr. The reaction solution was added to water, and then extracted with dichloromethane. After washing with saturated brine, the organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were separated by silica gel preparative TLC (ethyl acetate 100%) to obtain the target compound (5.5 mg, 29%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.47 (1 H, d, J = 8.2 Hz), 8.32 (1 H, d, J = 8.7 Hz), 8.16 (1 H, s), 7.76 (1 H, d, J = 8.2 Hz), 7.53-7. 46 (2 H, m), 7.26 (1 H, d, J = 8.7 Hz), 4.39-4.33 (2 H, m), 3.58-3.51 (2 H, m), 3.12 (3 H, s), 1.93 (6 H, s)

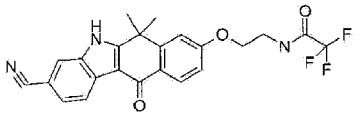
LCMS: m/z 424 $[M+H]^+$
HPLC retention time: 3.10 min (analysis condition W)

[Example 68]

Compound A9-2

N-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-ethyl]-2,2,2-trifluoro-acetamide

[0394]



[0395] The title compound was obtained as a by-product of the synthesis of Compound A9-1.

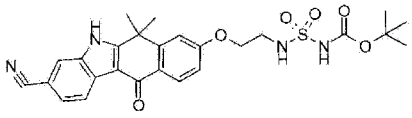
LCMS: m/z 442 $[M+H]^+$
HPLC retention time: 3.45 min (analysis condition W)

[Example 69]

Compound A9-3-1

8-{2-(Tert-butyloxycarbonylaminosulfonyl)amino-ethoxyl}-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0396]



[0397] Trifluoroacetic acid salt of 8-(2-amino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A8-2, 20 mg, 0.044 mmol) was dissolved in pyridine (0.5 mL), added with N-(tert-butoxycarbonyl)-N-[4-(dimethyl azaniumylidene)-1,4-dihydropyridin-1-yl sulfonyl]azanide (13.5 mg, 1 eq.), and then stirred at room temperature for 14 hr. The reaction solution was added to water, and then extracted with ethyl acetate. After washing with saturated brine, the organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were separated by silica gel preparative TLC(ethyl acetate) to obtain the title compound (16.1 mg, 68%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.74 (1 H, s), 10.94 (1 H, s), 8.33 (1 H, d, J = 8.5 Hz), 8.16 (1 H, d, J = 9.1 Hz), 8.02 (1 H, s), 7.84(1 H, br. s), 7.62 (1 H, d, J = 7.9 Hz), 7.36 (1 H, s), 7.10 (1 H, d, J = 7.9 Hz). 4.24-4.18 (2 H, m), 1.78 (6 H, s), 1.32 (9 H, s)

LCMS: m/z 525 $[M+H]^+$

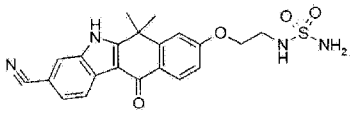
HPLC retention time: 3.48 min (analysis condition W)

[Example 70]

Compound A9-3-2

8-{2-(Methylaminosulfonyl)amino-ethoxy}-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0398]



[0399] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound A9-3-1.

LCMS: m/z 425 $[M+H]^+$

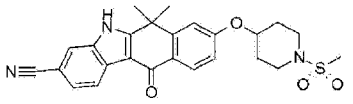
HPLC retention time: 2.95 min (analysis condition W)

[Example 71]

Compound A9-4

8-(1-Methanesulfonyl-piperidin-4-yloxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0400]



[0401] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A8-1 and methanesulfonyl chloride.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.72 (1 H, s), 8.30 (1 H, d, J = 8.5 Hz), 8.14 (1 H, d, J = 8.5 Hz), 8.00 (1 H, s), 7.59 (1 H, d, J = 7.9 Hz), 7.38 (1 H, s), 7. 13 (1 H, d, J = 8.5 Hz), 4.81 (1 H, s), 3.39-3.38 (2 H, m), 3.19-3.13 (2 H, m), 2.93 (3 H, s), 2.11-2.04 (2 H, m), 1.83-1.75 (8 H, m).

LCMS: m/z 464 $[M+H]^+$

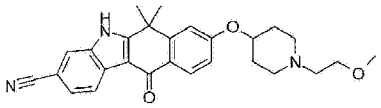
HPLC retention time: 3.41 min (analysis condition U)

[Example 72]

Compound A9-5

8-[1-(2-Methoxy-ethyl)-piperidin-4-yloxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0402]



[0403] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound A8-1 and 1-bromo-2-methoxy-ethane.

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 8.48-8.53 (1 H, m), 8.32-8.38 (1 H, m), 7. 74-7.77 (1 H, m), 7.50-7.55 (1 H, m), 7.07-7.10 (1H, m), 6.95-7.00 (1 H, m), 4.43-4.51 (1 H, m), 3.53 (2 H, t, J = 5.6 Hz), 3. 36 (3 H, s), 2.77-2.87 (2 H, m), 2.62 (2 H, t, J = 5.6 Hz), 2.35-2.47 (2 H, m), 2.02-2.12 (2 H, m), 1.78-1.95 (2 H, m), 1.82 (6 H, s).

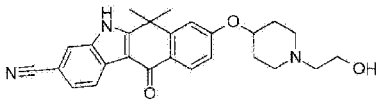
LCMS: m/z 444 $[M+H]^+$
HPLC retention time: 2.00 min (analysis condition U)

[Example 73]

Compound A9-6-2

8-[1-(2-Hydroxy-ethyl)-piperidin-4-yloxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0404]



[0405] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A8-1 and (2-bromoethoxy)-tert-butyldimethylsilane, followed by treatment with tetrabutylammonium fluoride.

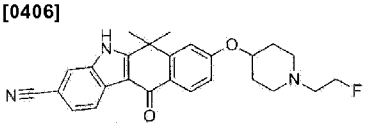
LCMS: m/z 430 $[M+H]^+$
HPLC retention time: 1.45 min (analysis condition S)

[Example 74]

Compound A9-7

8-[1-(2-Fluoro-ethyl)-piperidin-4-yloxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0406]



[0407] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A8-1 and methanesulfonic acid 2-fluoroethyl ester.

^{1}H-NMR (300 MHz, DMSO-d6) δ : 1.67 (2 H, m), 1.76 (6 H, s), 2.01 (2 H, m), 2.37 (2 H, t, 11.0 Hz), 2.61 (1 H, t, 4.20 Hz), 2.70 (1 H, t, 4.58), 2.78 (2 H, m), 4.46 (1 H, t, 4.58 Hz), 4.62 (2 H, t, 5.34 Hz), 7.10 (1 H, dd, 9.16 Hz, 2.29 Hz), 7.34 (1 H, bs, 1.53 Hz), 7.60 (1 H,

dd, 8.40 Hz, 1.53 Hz), 7.99 (1 H, s), 8.13 (1 H, d, 8. 39 Hz), 8.30 (1H, d, 8.39 Hz), 12.7 (1 H, s).

LCMS: m/z 432 $[M+H]^+$

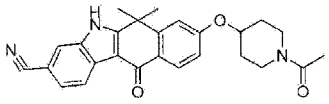
HPLC retention time: 1.52 min (analysis condition S)

[Example 75]

Compound A9-8

8-(1-Acetyl-piperidin-4-yloxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0408]



[0409] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A8-1 and acetyl chloride.

LCMS: m/z 428 $[M+H]^+$

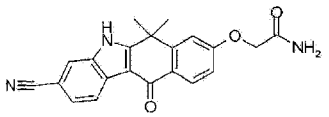
HPLC retention time: 1.91 min (analysis condition S)

[Example 76]

Compound A9-9

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carabazol-8-yloxy)-acetamide

[0410]



[0411] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A6 and 2-bromo-acetamide.

LCMS: m/z 360 $[M+H]^+$

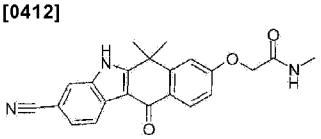
HPLC retention time: 2.83 min (analysis condition U)

[Example 77]

Compound A9-10

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-N-methyl-acetamide

[0412]



[0413] (3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetic acid (Compound A8-7, 30 mg, 0.0838 mmol), methylamine hydrochloric acid salt (28.1 mg, 0.417 mmol), EDC (32 mg, 0.167 mmol) and HOBT (0.023 mg, 0.167 mmol) were dissolved in DMF (1 mL), and added with diisopropylethylamine (0.145 mL, 0.833 mmol) at room temperature. After stirring at room temperature for 18 hr, water was added and the extraction was carried out with ethyl acetate. After washing with saturated brine, the organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were dissolved in dichloromethane, added with diethyl ether, and the precipitated title compound was obtained (white solid, 19.7 mg, 63%).

^{1}H-NMR(300 MHz, DMSO) σ ppm 12.73(s, 1 H), 8.33(d, 1 H, J=8.1 Hz), 8. 17(d, 1 H, J=8.7 Hz), 8.13(s, 1 H), 8.00(s, 1 H), 7. 62(d, 1H, J=8.1 Hz), 7.39(d, 1 H, J=2.4 Hz), 7.11(dd, 1 H, J=8.7 Hz, 2.4 Hz), 4.64(s, 2 H), 3.17(d, 1 H, J=5.4 Hz), 2. 69(d, 1 H, J=4.5 Hz), 1.76(s, 6 H)

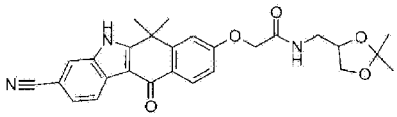
LCMS: m/z 374 $[M+H]^+$
HPLC retention time: 2.43 min (analysis condition U)

[Example 78]

Compound A9-11

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-N-(2,2-dimethyl-[1,3]dioxolan-4-ylmethyl)-acetamide

[0414]



[0415] Under the same conditions as the method for synthesizing Compound A9-10, the title compound was prepared from Compound A8-7 and C-(2,2-dimethyl-[1,3]dioxolan-4-yl)-methylamine.

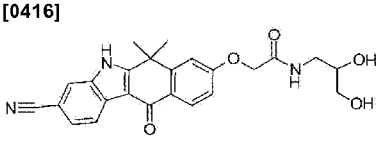
LCMS: m/z 474 $[M+H]^+$
HPLC retention time: 2.20 min (analysis condition U)

[Example 79]

Compound A9-12

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-N-(2,3-dihydroxy-propyl)-acetamide

[0416]



[0417] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound A9-11.

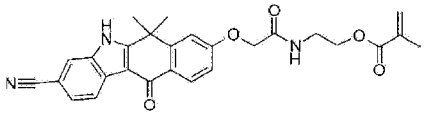
LCMS: m/z 434 $[M+H]^+$
HPLC retention time: 1.72 min (analysis condition U)

[Example 80]

Compound A9-13

2-Methyl-acrylic acid 2-[2-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetylamino]-ethyl ester

[0418]



[0419] Under the same conditions as the method for synthesizing Compound A9-10, the title compound was prepared from Compound A8-7 and 2-methyl-acrylic acid 2-amino-ethyl ester.

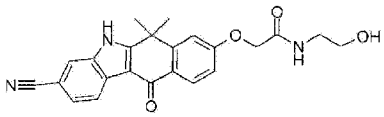
LCMS: m/z 472 $[M+H]^+$
HPLC retention time: 3.30 min (analysis condition U)

[Example 81]

Compound A9-14

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-N-(2-hydroxy-ethyl)-acetamide

[0420]



[0421] 2-Methyl-acrylic acid 2-[2-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetylamino]-ethyl ester (Compound A9-13, 40 mg, 0.085 mmol) was dissolved in a mixture solvent of methanol (2 mL) and water (2 mL), added with potassium hydroxide (48 mg, 0.85 mmol), and then stirred at room temperature for 18 hr. After the neutralization with 1 N hydrochloric acid, the reaction solution was concentrated under reduced pressure. The resulting residues were purified by amino silica gel to obtain the title compound (white solid, 8.9 mg, 26%).

^{1}H-NMR(300 MHz, DMSO) σ ppm 12.75(s, 1 H), 8.32(d, 1 H, J=8.1 Hz), 8. 17-8.13(m, 2 Hz), 7.99(s, 1 H), 7.60(d, 1 H, J=8.1 Hz), 7.38(d, 1 H, J=1.8 Hz), 7. 11(dd, 1 H, J=2.1 Hz, 8.7 Hz), 4.72(t, 1H, J=5.7 Hz), 4.65(s, 1H), 3.48(dd, 2 H, J=12.0 Hz, 6.0 Hz), 3.26(dd, 2 H, J=12.0 Hz, 6.0 Hz), 1.76(s, 6 H)

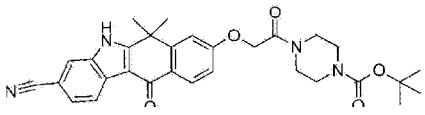
LCMS: m/z 404 $[M+H]^+$
HPLC retention time: 2.83 min (analysis condition U)

[Example 82]

Compound A9-15-1

4-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester

[0422]



[0423] (3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetic acid (Compound A8-7, 30 mg, 0.083 mmol), piperazine-1-carboxylic acid tert-butyl ester (31 mg, 2 eq.), and HOBt (30 mg, 3 eq.) were dissolved in 0.5 ml DMF, added with EDC (48 mg, 3 eq.), and stirred at room temperature overnight. Thereafter, the solvent was removed under reduced pressure and the resulting residues were purified by preparative TLC to obtain the title compound (20 mg).

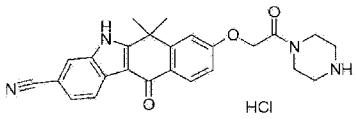
LCMS: m/z 527, 471, 427$[M-H]^-$
HPLC retention time: 2.77 min (analysis condition C)

[Example 83]

Compound A9-15-2

6,6-Dimethyl-11-oxo-8-(2-oxo-2-piperazin-1-yl-ethoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile hydrochloric acid salt

[0424]



[0425] 4-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester (Compound A9-15-1, 20 mg) was added with 4 N hydrochloric acid and dioxane solution (1 ml), and stirred in an water bath at 10°C for 4 hr. Water was added to the reaction solution and the resulting precipitates were filtered and dried to obtain the title compound (15 mg, white powder).

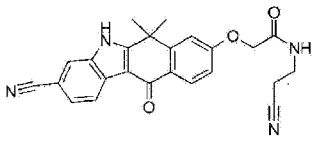
LCMS: m/z 429 $[M+H]^+$
HPLC retention time: 0.81 min (analysis condition I)

[Example 84]

Compound A9-16

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]yloxy)-N-(2-cyano-ethyl)-acetamide

[0426]



[0427] (3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetic acid (Compound A8-7, 30 mg, 0.083 mmol), 3-aminopropionitrile (12 mg, 2 eq.) and HOBt (30 mg, 3 eq.) were dissolved in 0.5 ml DMF, added with EDC (48 mg, 3 eq.), and stirred at room temperature overnight. Thereafter, the solvent was removed under reduced pressure and the resulting residues were purified by preparative TLC to obtain the title compound (23 mg).

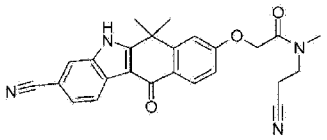
LCMS: m/z 411 $[M+H]^+$
HPLC retention time: 2.27 min (analysis condition C)

[Example 85]

Compound A9-17

2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-N-(2-cyano-ethyl)-N-methyl-acetamide

[0428]



[0429] (3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-acetic acid (Compound A8-7, 30 mg, 0.083 mmol), N-methyl-3-aminopropionitrile (14 mg, 2 eq.) and HOBt (30 mg, 3 eq.) were dissolved in 0.5 ml DMF, added with EDC (48 mg, 3 eq.), and stirred at room temperature overnight. Thereafter, the solvent was removed under reduced pressure and the resulting residues were purified by preparative TLC to obtain the title compound (7 mg).

LCMS: m/z 411 $[M+H]^+$

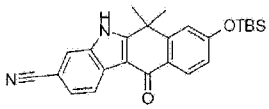
HPLC retention time: 2.33 min (analysis condition C)

[Example 86]

Compound A10

8-(Tert-butyl-dimethyl-silanyloxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0430]



[0431] The DMF solution of 8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 100 mg, 0.331 mmol), imidazole (67.5 mg, 3 eq.) and tert-butylchlorodimethylsilane (92.4 mg, 1.5 eq.) was stirred overnight at room temperature. To the reaction solution, saturated aqueous solution of sodium hydrogen carbonate was added followed by extraction with tert-butylmethyl ether. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (white solid, 170 mg, 100%).

LCMS: m/z 417 $[M+H]^+$

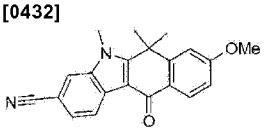
HPLC retention time: 3.38 min (analysis condition S)

[Example 87]

Compound A10-1

8-Methoxy-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0432]



[0433] To the THF solution of triphenylphosphine (260 mg, 3 eq.), azodicarboxylic acid diisopropyl ester (0.195 ml, 3 eq.) was added and the mixture was stirred at room temperature for 1 hr. Thereafter, 8-(tert-butyldimethylsilanyloxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A10, 138 mg, 0.331 mmol) and methanol (1 ml) were added and stirred overnight. The reaction solution was purified by HPLC to obtain the target compound (44.8 mg, 41%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8. 44 (1 H, d, J = 8. 1 Hz), 8.33 (1 H, s), 8. 14 (1 H, d, J = 8.7 Hz), 7.66 (1 H, dd, J = 8.2, 1.1 Hz), 7.39 (1 H, d, J = 2.3 Hz), 7. 09 (1 H, dd, J = 8.7, 2.3 Hz), 4.17 (3 H, s), 3.92 (3 H, s), 1.88 (6 H, s).

LCMS: m/z 331 $[M+H]^+$

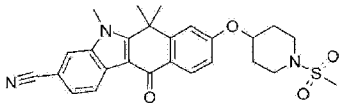
HPLC retention time: 2.35 min (analysis condition S)

[Example 88]

Compound A10-2

8-(1-Methanesulfonyl-piperidin-4-yloxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0434]



[0435] Under the same conditions as the method for synthesizing Compound B3-4, the title compound was prepared from Compound A9-4.

LCMS: m/z 478 $[M+H]^+$

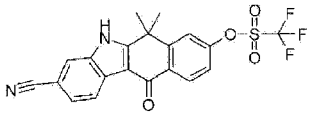
HPLC retention time: 2.68 min (analysis condition U)

[Example 89]

Compound B1

Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0436]



[0437] 8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 550 mg, 0.189 mmol) was dissolved in pyridine (18 mL), added with anhydrous trifluoromethanesulfonic acid (0.758 ml, 3 eq.), and stirred at room temperature for 30 min. The reaction solution was added to water and then extracted with dichloromethane. The organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (white powder, 641 mg, 81%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.89 (1 H, br. s), 8.36 (1 H, d, J = 8.8 Hz), 8.31 (1 H, dd, J = 8.1, 0.7 Hz), 8.11 (1 H, d, J = 2.3 Hz), 8.04 (1 H, dd, J = 1.5, 0.7 Hz), 7.65-7.60 (2 H, m). 1.76 (6 H, s)

LCMS: m/z 435 $[M+H]^+$

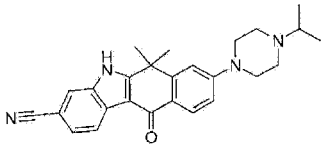
HPLC retention time: 3.10 min (analysis condition U)

[Example 90]

Compound B2-1

8-(4-Isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0438]



[0439] Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 40 mg, 0.0921 mmol) was dissolved in NMP (1 ml) and added with 1-isopropylpiperazine (236 mg, 20 eq.). The mixture was stirred at 120°C for 3 hr. After cooling to room temperature, purification was carried out by HPLC to obtain the target compound (white powder, 12.8 mg, 34%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, 8.1 Hz), 8.03 (1 H, d, 8.6 Hz), 7.98 (1 H, s), 7.56 (1 H, d, 8.6 Hz), 7.21 (1 H, s), 7.04 (1 H, d, 9.1 Hz), 3.40-3. 37 (4 H, m), 2.73-2.65 (1 H, m), 2.61-2.58 (4 H, m), 1.75 (6 H, s), 1.02 (6 H, d, 6.6 Hz)

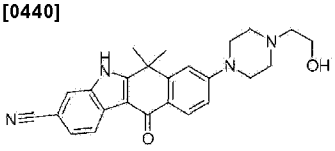
LCMS: m/z 413 $[M+H]^+$

[Example 91]

Compound B2-2

8-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0440]



[0441] According to the same method as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and N-(2-hydroxyethyl)piperazine.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, 8.1 Hz), 8. 03 (1 H, d, 8.7 Hz), 7.99 (1 H, s), 7.58 (1 H, d, 7.9 Hz), 7.21 (1 H, s), 7.04 (1 H, d, 8.7 Hz), 4.50-4. 46 (1 H, br m), 3.59-3.53 (2 H, m), 3.39-3.35 (4 H, m), 2.59-2.56 (4 H, m), 2.45 (2 H, t, 6.1 Hz), 1.76 (6 H, s)

LCMS: m/z 415 $[M+H]^+$

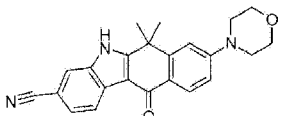
HPLC retention time: 1.27 min (analysis condition S)

[Example 92]

Compound B2-3

6,6-Dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0442]



[0443] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and morpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.62 (1 H, br. s), 8.29 (1 H, d, 8.2 Hz), 8.04 (1 H, d, 9.0 Hz), 7.96 (1 H, s), 7.56 (1 H, d, 8.2 Hz), 7.22 (1 H, s), 7.04 (1 H, d, 9.0 Hz), 3.77-3.75 (4 H, m), 3.35-3.30 (4 H, m), 1.74 (6 H, s)

LCMS: m/z 372 $[M+H]^+$

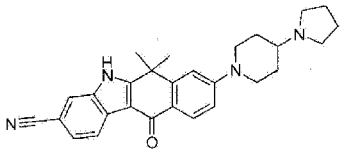
HPLC retention time: 2.45 min (analysis condition U)

[Example 93]

Compound B2-4

6,6-Dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0444]



[0445] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and 4-pyrrolidin-1-yl-piperidine.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, 8.1 Hz), 8.01 (1 H, d, 8.7 Hz), 7.97 (1 H, s), 7.56 (1 H, d, 8.6 Hz), 7.20 (1 H, s), 3.94-3.90 (2 H, m), 3.30-3. 28 (4 H, m), 2.95 (2 H, t, 11.8 Hz), 2.24-2.20 (1 H, m), 1.95-1.91 (2 H, m), 1.75 (6 H, s), 1.70-1.66 (4 H, m), 1.54-1.52 (2 H, m)

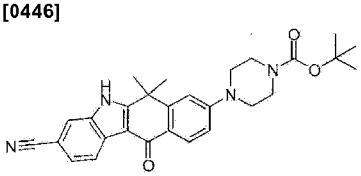
LCMS: m/z 439 $[M+H]^+$

[Example 94]

Compound B2-5-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0446]



[0447] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and piperazine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 471 $[M+H]^+$

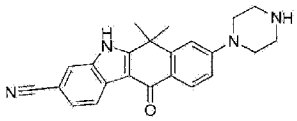
HPLC retention time: 2.67 min (analysis condition S)

[Example 95]

Compound B2-5-2

6,6-Dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0448]



[0449] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B2-5-1.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.32 (1 H, d, 8.5 Hz), 8.03 (1 H, d, 9.1 Hz), 7.99 (1 H, s), 7.59 (1 H, dd, 8.2, 1.5 Hz), 7.20 (1 H, d, 2.4 Hz), 7.04 (1 H, dd, 8.8, 2.1 Hz), 3.32-3.30 (4 H, m), 2.88-2.87 (4 H, m), 1.77 (6 H, s)

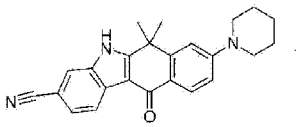
LCMS: m/z 371 $[M+H]^+$

[Example 96]

Compound B2-6

6,6-Dimethyl-11-oxo-8-piperidin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0450]



[0451] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and piperidine.

LCMS: m/z 370 $[M+H]^+$

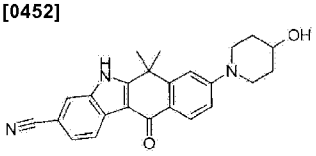
HPLC retention time: 2.40 min (analysis condition U)

[Example 97]

Compound B2-7-1

8-(4-Hydroxy-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0452]



[0453] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and piperidin-4-ol.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, 8.1 Hz), 8.01 (1 H, d, 8.7 Hz), 7.97 (1 H, s), 7.56 (1 H, d, 7.7 Hz), 7.19 (1 H, s), 7.04 (1

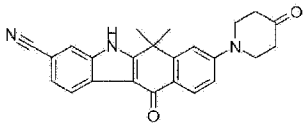
H, d, 10.6 Hz), 4.76-4.71 (1 H, br m), 3.81-3.75 (3 H, m), 3.08 (2 H, t, 10.2 Hz), 1.86-1.82 (2 H, m), 1. 75 (6 H, s), 1.49-1.42 (2 H, m)
LCMS: m/z 386 $[M+H]^+$

[Example 98]

Compound B2-7-2

6,6-Dimethyl-11-oxo-8-(4-oxo-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0454]



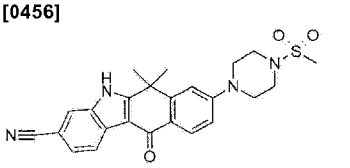
[0455] 8-(4-Hydroxy-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound B2-7-1, 210 mg, 0.545 mmol), was dissolved in the DCM (2 mL) and DMF (0.6 mL) mixture solvent, added with 1,1,1-triacetoxy-1,1-dihydro-1,2-benzoiodoxol-3(1H)-one (300 mg, 1.3 eq.), and the mixture was stirred at room temperature for 2 hr. To the reaction solution, 0.25 mol/L aqueous solution of sodium thiosulfate, saturated sodium bicarbonate solution and CPME were added followed by further stirring at room temperature for 1 hr. The reaction solution was filtered and the filtrate was subjected to liquid seperation. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (yellowish white powder, 109 mg, 52%).
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition U)

[Example 99]

Compound B2-8

8-(4-Methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0456]



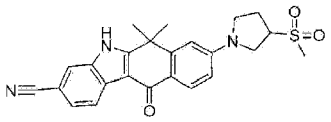
[0457] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and 1-methanesulfonylpiperazine.
^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.66 (1 H, br.s), 8.31 (1 H, d, J = 8.2 Hz), 8.06 (1 H, d, J = 8.7 Hz), 7.99 (1 H, s), 7.59 (1 H, d, J = 8.2 Hz), 7.30 (1 H, d, J = 1.8 Hz), 7.09 (1 H, dd, J = 8.7, 1. 8 Hz), 3.53 (4 H, t, J = 4.8 Hz), 3.27 (4 H, t, J = 4.8 Hz), 2.94 (3 H, s), 1.77 (6 H, s).
LCMS: m/z 449 $[M+H]^+$
HPLC retention time: 1.98 min (analysis condition S)

[Example 100]

Compound B2-9

8-(3-Methanesulfonyl-pyrrolidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0458]



[0459] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and 3-methanesulfonylpyrrolidine.

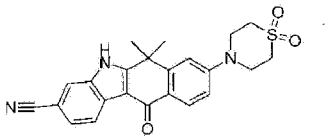
LCMS: m/z 434 $[M+H]^+$
HPLC retention time: 1.83 min (analysis condition S)

[Example 101]

Compound B2-10

8-(1,1-Dioxothiomorpholino)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0460]



[0461] Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 30 mg, 0.069 mmol) was dissolved in 1,4-dioxane (1 mL), added with thiomorpholine 1,1-dioxide (19 mg, 2 eq.), Pd2 (dba)3 (6.3 mg, 0.1 eq.), BINAP (8.6 mg, 0.2 eq.) and K_3PO_4 (29 mg, 2 eq.), and stirred at 100°C overnight. The reaction solution was added to water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (white powder, 2.1 mg, 7%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 8.6 Hz), 8.07 (1 H, d, J = 8.9 Hz), 8.00 (1 H, s), 7.55 (1 H, dd, J = 8.5, 1.7 Hz), 7.34 (1 H, d, J = 2.0 Hz), 7. 15 (1 H, dd, J = 9.1, 2. 7 Hz), 4.01 (4 H, s), 3.16 (4 H, s), 1.77 (6 H, s).

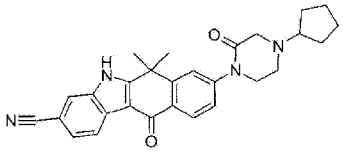
LCMS: m/z 420 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition S)

[Example 102]

Compound B2-11

8-(4-Cyclopentyl-2-oxo-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0462]



[0463] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound B1 and 4-cyclopentylpiperazin-2-one.

LCMS: m/z 453 $[M+H]^+$

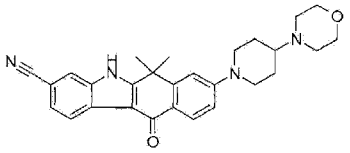
HPLC retention time: 1.30 min (analysis condition S)

[Example 103]

Compound B2-12

6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0464]



[0465] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and 4-piperidin-4-yl morpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.73 (1 H, s), 8.27-8.31 (1 H, m), 7.98-8.02 (1 H, m), 7.95-7.97 (1 H, m), 7.53-7.58 (1 H, m), 7.17-7.21 (1 H, m), 6.99-7. 05 (1 H, m), 3.97-4. 05 (2 H, m), 3.53-3.59 (4 H, m), 2.80-2.90 (2 H, m), 2.43-2.51 (4 H, m), 2.31-2.40 (1 H, m), 1.83-1.92 (2 H, m), 1.74 (6 H, s), 1.39-1.52 (2 H, m)

LCMS: m/z 455 $[M+H]^+$

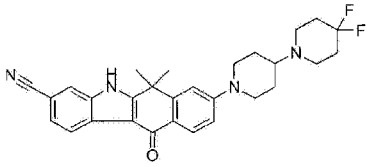
HPLC retention time: 1.73 min (analysis condition U)

[Example 104]

Compound B2-13

8-(4,4-Difluoro-1,4'-bipiperidin-1'-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0466]



[0467] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-7-2 and 4,4-difluoropiperidine hydrochloric acid salt.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.59 (1 H, s), 8.25-8.32 (1 H, m), 7.97-8.02 (1 H, m), 7.96 (1 H, s), 7.52-7.59 (1 H, m), 7.16-7.21 (1 H, m), 6.99-7.05 (1 H, mz), 4.00-4.09 (2 H, m), 3.55-3.62 (2 H, m), 2.79-2.90 (2 H, m), 2.55-2.67 (4 H, m), 1.78-1.98 (5 H, m), 1.74 (6 H, s), 1.44-1.58 (2 H, m)

LCMS: m/z 489 $[M+H]^+$

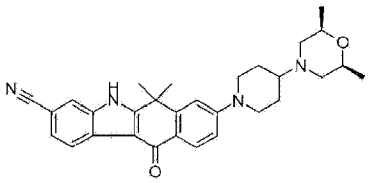
HPLC retention time: 1.88 min (analysis condition U)

[Example 105]

Compound B2-14

8-[4-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-piperidin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0468]



[0469] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-7-2 and (2R,6S)-2,6-dimethylmorpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.60 (1 H, s), 8.25-8.31 (1 H, m), 7.97-8.02 (1 H, m), 7.95 (1 H, s), 7.51-7.58 (1 H, m), 7.18 (1 H, s), 6.99-7.05 (1 H, m), 3. 96-4.06 (2 H, m), 3.45-3.55 (2 H, m), 2.80-2.91 (2 H, m), 2.72-2. 79 (2 H, m), 2.29-2.41 (1 H, m), 1.70-1.90 (10 H, m), 1.40-1.53 (2 H, m), 1.03 (6 H, d, 6.3 Hz)

LCMS: m/z 483 $[M+H]^+$

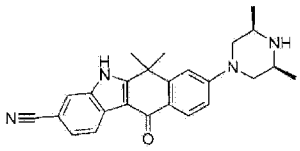
HPLC retention time: 1.83 min (analysis condition U)

[Example 106]

Compound B2-15

8-((3R,5S)-3,5-Dimethylpiperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0470]



[0471] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound B1 and 2,6-dimethylpiperazine.

LCMS: m/z 399 $[M+H]^+$

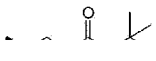
HPLC retention time: 1.76 min (analysis condition U)

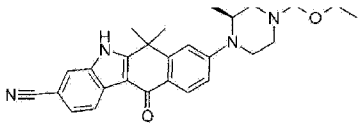
[Example 107]

Compound B2-16-1

(S)-4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3-methyl-piperazine-1-carboxylic acid tert-butyl ester

[0472]





[0473] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound B1 and (S)-3-methylpiperazine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 485 $[M+H]^+$

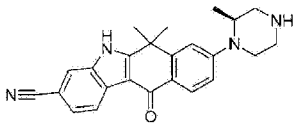
HPLC retention time: 3.97 min (analysis condition W)

[Example 108]

Compound B2-16-2

6,6-Dimethyl-8-((S)-2-methyl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0474]



[0475] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound 2-16-1.

LCMS: m/z 385 $[M+H]^+$

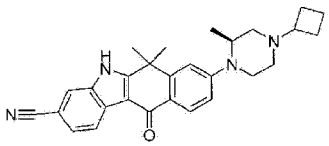
HPLC retention time: 2.43 min (analysis condition W)

[Example 109]

Compound B2-16-3

8-((S)-4-Cyclobutyl-2-methyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0476]



[0477] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-16-2 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8. 31(1 H, d, 8 Hz), 8.03(1 H, d, 12 Hz), 7. 98(1 H, s), 7.59(1 H, d, 12 Hz), 7.13(1 H, s), 6.98(1 H, d, 8 Hz), 4.35-4.28(1 H, m), 3. 70(1 H, d, 12 Hz), 3.02(1 H, ddd, 12, 12, 4 Hz), 2.87(1 H, d, 8 Hz), 2.74-2.67(2 H, m), 2.08-1.99(2 H, m), 1.92-1.64(10 H, m), 1.70-1.62(2 H, m), 1.12(3 H, d, 8 Hz)

LCMS: m/z 439 $[M+H]^+$

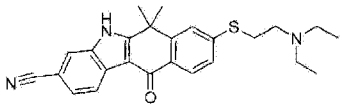
HPLC retention time: 2.59 min (analysis condition W)

[Example 110]

Compound B2-17

8-(2-Diethylamino-ethylsulfanyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0478]



[0479] Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 25 mg, 0.057 mmol) was dissolved in dimethoxyethane (0.5 mL), added with 2-diethylaminoethanethiol hydrochloric acid salt (19.6 mg, 2 eq.), $Pd_2(dba)_3$(2.6 mg, 0.05 eq.), Xantphos (3.3 mg, 0.1 eq.) and DIPEA (0.06 mg, 6 eq.), and the mixture was stirred at 160°C for 30 min. The reaction solution was added to water, extracted with ethyl acetate, and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the target compound (white amorphous, 22.4 mg, 93%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 9.60 (1 H, s), 8.53-8.48 (1 H, m), 8.32 (1 H, d, J = 8.4 Hz), 7.77 (1 H, s), 7.53-7. 50 (2 H, m), 7.38-7.35 (1 H, m), 3.18-3.12 (2 H, m), 2.81-2.75 (2 H, m), 2.65-2.57 (4 H, m), 1.76 (6 H, s), 1.08-1.04 (6 H, m)

LCMS: m/z 418 $[M+H]^+$

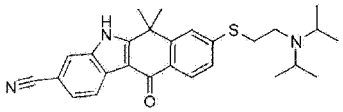
HPLC retention time: 2.10 min (analysis condition U)

[Example 111]

Compound B2-18

8-(2-Diisopropylamino-ethylsulfanyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0480]



[0481] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound B1 and 2-diisopropylaminoethanethiol hydrochloric acid salt.

LCMS: m/z 446 $[M+H]^+$

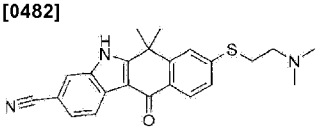
HPLC retention time: 2.22 min (analysis condition U)

[Example 112]

Compound B2-19

8-(2-Dimethylamino-ethylsulfanyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0482]



[0483] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound B1 and 2-dimethylaminoethanethiol hydrochloric acid salt.

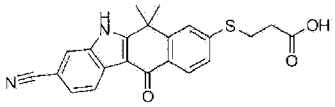
LCMS: m/z 390 $[M+H]^+$
HPLC retention time: 1.98 min (analysis condition U)

[Example 113]

Compound B2-20

3-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl sulfanyl)-propionic acid

[0484]



[0485] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound B1 and 3-mercaptopropionic acid.

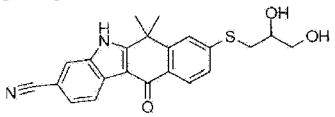
LCMS: m/z 391 $[M+H]^+$
HPLC retention time: 2.45 min (analysis condition U)

[Example 114]

Compound B2-21

8-(2,3-Dihydroxy-propylsulfanyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0486]



[0487] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound B1 and 3-mercaptopropane-1,2-diol.

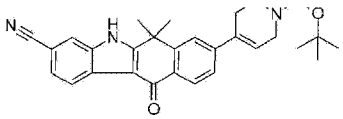
LCMS: m/z 393 $[M+H]^+$
HPLC retention time: 2.15 min (analysis condition U)

[Example 115]

Compound B2-22-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

[0488]



[0489] To trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 7.80 g, 18.0 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (6.11 g, 19.8 mmol, 1.1 eq.), $Pd(PPh_3)_2Cl_2$ (630 mg, 0.898 mmol, 0.05 eq.), and sodium carbonate (5.71 g, 53.9 mmol, 3.0 eq.), DME (125 ml) and water (25 ml) were added. The mixture was subjected to reduced pressure under ultrasonication treatment, followed by flushing with nitrogen gas. This procedure was repeated five times and then degassed. After further stirring at 80°C for 2 hr under nitrogen atmosphere, the mixture was cooled to room temperature, added with water (250 ml), and further stirred for 30 min. The precipitates were filtered and washed with water (50 ml). They were further washed with CH_3CN (50 ml) to obtain the target compound as a crude product (gray powder, 7.54 g, 90%).

LCMS: m/z 468 $[M+H]^+$

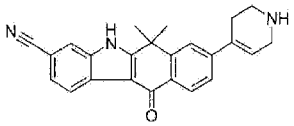
HPLC retention time: 2.90 min (analysis condition S)

[Example 116]

Compound B2-22-2

6,6-Dimethyl-11-oxo-8-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0490]



[0491] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B2-22-1.

LCMS: m/z 368 $[M+H]^+$

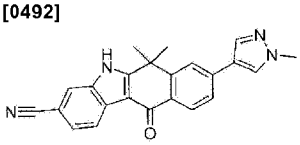
HPLC retention time: 1.47 min (analysis condition S)

[Example 117]

Compound B2-23

6,6-Dimethyl-8-(1-methyl-1H-pyrazol-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0492]



[0493] Under the same conditions as the method for synthesizing Compound B2-22-1, the title compound was prepared from Compound B1 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

LCMS: m/z 367 $[M+H]^+$

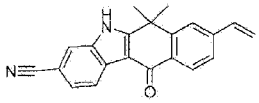
HPLC retention time: 2.42 min (analysis condition U)

[Example 118]

Compound B2-24

6,6-Dimethyl-11-oxo-8-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0494]



[0495] Under nitrogen atmosphere, trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 1.00 g, 2.302 mmol) was added with n-propanol (20 mL), potassium vinyltrifluoroborate (854 mg, 3.0 eq.), dichloro-((bis-diphenylphosphino)ferrocenyl)palladium (217 mg, 0.1 eq.) and triethylamine (1.11 ml, 3.0 eq.) in order and the resultant was stirred at 60°C for 4 hr. Upon the completion of the reaction, water was added to the reaction solution. The resulting precipitates were filtered and washed with distilled water, and the residues were dried to obtain the title compound (666 mg, 80%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 8.90 (1 H, s), 8.55 (1 H, d, J = 7.9 Hz), 8.40 (1 H, d, J = 8.5 Hz), 7.79 (1 H, s), 7.58-7.61 (3 H, m), 6.85 (1 H, dd, J = 17.7, 11.0 Hz), 5.95 (1 H, d, J = 17.1 Hz), 5.46 (1 H, d, J = 11.0 Hz), 1.84 (6 H, s)

LCMS: m/z 313 $[M+H]^+$

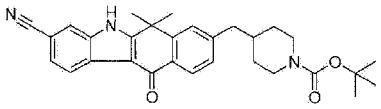
HPLC retention time: 3.75 min (analysis condition W)

[Example 119]

Compound B2-25-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl methyl)-piperidine-1-carboxylic acid tert-butyl ester

[0496]



[0497] 4-Methylene-piperidine-1-carboxylic acid tert-butyl ester (409 mg, 2.07 mmol, 1.2 eq.) was dissolved in THF (2 ml), added under nitrogen atmosphere with 9-BBN (0.5 M THF solution, 4.83 ml, 2.42 mmol, 1.4 eq.) and then stirred at 60°C for 1 hr. Thereafter, 9-BBN (0.5 M THF solution, 5.52 ml, 2.77 mmol, 1.6 eq.) was further added and the mixture was stirred at 60°C for 1 hr. The resulting mixture was cooled to room temperature, added with cesium fluoride (1.31 g, 8.60 mmol, 5.0 eq.), and stirred at room temperature for 30 min.

[0498] To the solution obtained from the above, DMF (18 ml) suspension comprising trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 750 mg, 1.73 mmol) and dichloro-((bisdiphenylphosphino)ferrocenyl)palladium (70.5 mg, 0.0863 mmol, 0.05 eq.) was added, and the mixture was stirred at 100°C for 3 hr. After cooling to the room temperature, water (50 ml) was added, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl methyl)-piperidine-1-carboxylic acid tert-butyl ester (yellow powder, 763 mg, 91%).

LCMS: m/z 484 $[M+H]^+$

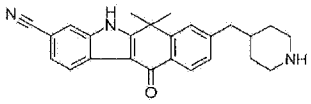
HPLC retention time: 2.97 min (analysis condition S)

[Example 120]

Compound B2-25-2

6,6-Dimethyl-11-oxo-8-piperidin-4-yl methyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0499]



[0500] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B2-25-1.

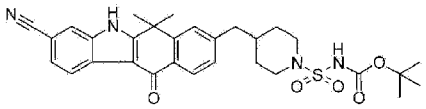
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 1.40 min (analysis condition S)

[Example 121]

Compound B2-26-1

Tert-butyl 4-((3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)methyl)piperidin-1-yl sulfonylcarbamic acid

[0501]



[0502] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B2-25-2 and N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-yl sulfonyl]azanide (CAS No. 872496-91-8).

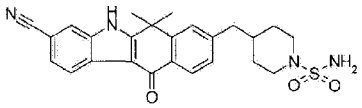
LCMS: m/z 563 $[M+H]^+$
HPLC retention time: 2.63 min (analysis condition S)

[Example 122]

Compound B2-26-2

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl methyl)-piperidine-1-sulfonic acid amide

[0503]



[0504] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B2-26-1.

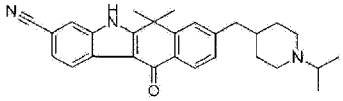
LCMS: m/z 463 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition S)

[Example 123]

Compound B2-27

8-(1-Isopropyl-piperidin-4-yl methyl)-6,6-dimethyl-1-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0505]



[0506] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-25-2 and acetone.

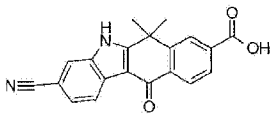
^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.80 (1 H, s), 8.32 (1 H, d, 7.9 Hz), 8. 12 (1 H, d, 7.9 Hz), 8.01 (1 H, s), 7.65 (1 H, s), 7.61 (1 H, d, 9.1 Hz), 7. 30 (1 H, d, 7. 9 Hz), 2.75 (2 H, d, 11.0 Hz), 2.65 (3 H, q, 6.5 Hz), 2.04 (2 H, t, 11.0 Hz), 1.77 (6 H, s), 1.60-1.57 (3 H, m), 1.22 (2 H, t, 11.6 Hz), 0.94 (6 H, d, 6.7 Hz)

LCMS: m/z 426 $[M+H]^+$

[Example 124]

Compound B2-28 3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid

[0507]



[0508] Under nitrogen atmosphere, to the dimethyl formamide (3 ml) solution comprising trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-ll-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound B1, 150 mg, 0.345 mmol), lithium formate monohydrate (90 mg, 5.0 eq.), 4,5-bis (diphenylphosphino)-9,9-dimethylxanthene (Xantphos) (20 mg, 0.1 eq.), $Pd_2(dba)_3$ (32 mg, 0.1 eq.), lithium chloride (88 mg, 6.0 eq.), N,N-diisopropylethylamine (241 µl, 4.0 eq.), and acetic anhydride (131 µl, 4.0 eq.) were added, and the mixture was stirred at 80°C for 15 hr. Upon the completion of the reaction, ethyl acetate was added to the reaction solution. The organic layer was washed in order with 1 M hydrochloric acid, distilled water, and brine. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (88 mg, 76%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 13.17 (1 H, s), 8.35 (1 H, d, J = 7.9 Hz), 8.34 (1 H, s), 8.23 (1 H, d, J = 7.9 Hz), 8.07 (1 H, s), 8.02 (1 H, d, J = 9.1 Hz), 7.64 (1 H, d, J = 7.9 Hz), 1.80 (6 H, s)

LCMS: m/z 331 $[M+H]^+$

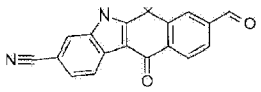
HPLC retention time: 3.08 min (analysis condition W)

[Example 125]

Compound B2-29

8-Formyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0509]



[0510] To the THF (24 ml) and distilled water (6 ml) suspension of 6,6-dimethyl-11-oxo-8-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound B2-24, 600 mg, 1.920 mmol), t-butanol solution of osmium tetraoxide (192 µl, 0.1 eq.) and sodium meta periodate (821 mg, 2.0 eq.) were added and the mixture was stirred at room temperature for 3 hr. Aqueous solution of sodium thiosulfate (0.3 M) was added to the solution, which was then extracted with an ethyl acetate. The organic layer was washed with 10% aqueous solution of disodium ethylenediamine tetraacetic acid. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (470 mg, 77%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.95 (1 H, s), 10.20 (1 H, s), 8.48 (1 H, s), 8.42 (1 H, d, J = 8.5 Hz), 8.36 (1 H, d, J = 8.5 Hz), 8.07 (1 H, s), 8.02 (1 H, d, J = 7.9 Hz), 7.67 (1 H, d, J = 7.9 Hz), 1.85 (6 H, s)

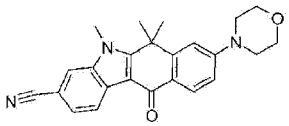
LCMS: m/z 315 $[M+H]^+$
HPLC retention time: 3.38 min (analysis condition W)

[Example 126]

Compound B3-1

5,6,6-Trimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0511]



[0512] Under the same conditions as the method for synthesizing Compound A10-1, the title compound was prepared from Compound B2-3.

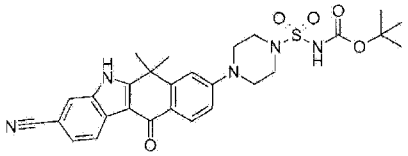
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 2.62 min (analysis condition U)

[Example 127]

Compound B3-2-1

Tert-butyl 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)piperazin-1-yl sulfonylcarbamic acid

[0513]



[0514] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B2-5-2 and N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-yl sulfonyl]azanide (CAS No. 872496-91-8).

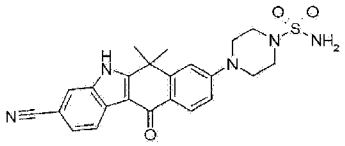
LCMS: m/z 550 $[M+H]^+$
HPLC retention time: 2.39 min (analysis condition S)

[Example 128]

Compound B3-2-2

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-sulfonic acid amide

[0515]



[0516] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B3-2-1.

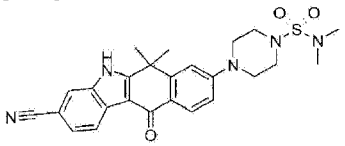
LCMS: m/z 450 $[M+H]^+$
HPLC retention time: 1.82 min (analysis condition S)

[Example 129]

Compound B3-3

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-sulfonic acid dimethylamide

[0517]



[0518] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B2-5-2 and dimethylsulfamoyl chloride.

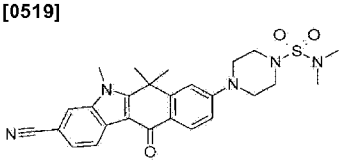
LCMS: m/z 478 $[M+H]^+$
HPLC retention time: 2.45 min (analysis condition S)

[Example 130]

Compound B3-4

4-(3-Cyano-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-sulfonic acid dimethylamide

[0519]



[0520] To the DMF suspension of 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-sulfonic acid amide (Compound B3-2-2, 20 mg, 0.04 mmol) and sodium hydride (21.4 mg, 12 eq.), iodomethane (28 µl, 10 eq.) was added and stirred at room temperature overnight. Water was added to the reaction solution, followed by filtration to obtain the target compound (25.8 mg, 100%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.43 (1 H, d, J = 8.2 Hz), 8.31 (1 H, s), 8.03 (1 H, d, J = 8.9 Hz), 7.64 (1 H, dd, J = 8.1, 1.3 Hz), 7.30 (1 H, d, J = 2.0 Hz), 7. 08 (1 H, dd, J = 8.9, 2.0 Hz), 4.16 (3 H, s), 3.43-3.53 (4 H, t, J = 4.7 Hz), 3.26-3.41 (4H, s), 2.82 (6 H, s), 1.87 (6 H, s).

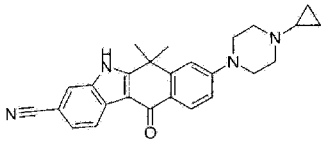
LCMS: m/z 492 $[M+H]^+$
HPLC retention time: 2.69 min (analysis condition S)

[Example 131]

Compound B3-5

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0521]



[0522] The title compound was obtained as a by-product of the synthesis of Compound F5-36.

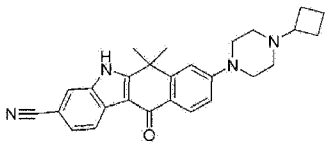
LCMS: m/z 411 $[M+H]^+$
HPLC retention time: 1.31 min (analysis condition S)

[Example 132]

Compound B3-6

8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0523]



[0524] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-5-2 and cyclobutanone.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 8.2 Hz), 8.01 (1 H, d, J = 8.8 Hz), 7.96 (1 H, s), 7.55 (1 H, d, J = 8.2 Hz), 7.19 (1 H, d, J = 2. 2 Hz), 7.03 (1 H, dd, J = 2.4, 8.8 Hz), 2.71-2.75(1 H, m), 2.37-2. 39(4 H, m), 1.98-2.00(2 H, m), 1. 77-1.85(2 H, m), 1.74 (6 H, s), 1.63-1.68(2 H, m).

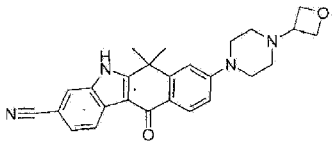
LCMS: m/z 425 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition U)

[Example 133]

Compound B3-7

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0525]



[0526] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-5-2 and 3-oxetanone.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 8.29 (1 H, dd, J = 8.2, 0.59 Hz), 8.02 (1 H, d, J = 9.0 Hz), 7.97(1 H, d, J = 0.59 Hz), 7.56(1 H, dd, J = 8.0, 1.4 Hz), 7.22(1 H, d, J = 2.3 Hz), 7.04(1 H, dd, J = 8.8, 2.2 Hz), 4.56-4.59(2 H, m), 4.47-4.50(2 H, m), 3.43-3.48(1 H, m), 3.39-3.42(4 H, m), 2.40-2.42(4 H, m), 1.74 (6 H, s)

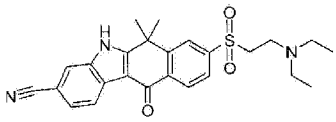
LCMS: m/z 427 $[M+H]^+$
HPLC retention time: 1.67 min (analysis condition U)

[Example 134]

Compound B3-8

8-(2-Diethylamino-ethanesulfonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0527]



[0528] 8-(2-Diethylamino-ethylsulfanyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound B2-17, 16.8 mg, 0.0402 mmol) was dissolved in methanol (1.5 mL), added with oxone (54.3 mg, 2.2 eq.) which had been dissolved in water (0.5 mL), and then stirred at room temperature for 2 hr. The reaction solution was concentrated, extracted with ethyl acetate, washed with saturated sodium hydrogen carbonate, and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the target compound (white solid, 5.8 mg, 32%).

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 9.29 (1 H, s), 8.61 (1 H, d, J = 8.2 Hz), 8. 52 (1 H, d, J = 8.0 Hz), 8.21 (1 H, s), 8.01 (1 H, d, J = 8.2 Hz), 7.81 (1 H, s), 7.61 (1 H, d, J = 8.2 Hz), 3.33 (2 H, t, J = 7.4 Hz), 2.95 (2 H, t, J = 7.4 Hz), 2.41 (4 H, q, J = 7.2 Hz), 1.86 (6 H, s), 0.89 (4 H, t, J = 7.1 Hz)

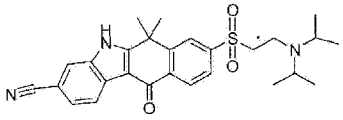
LCMS: m/z 450 $[M+H]^+$
HPLC retention time: 2.05 min (analysis condition U)

[Example 135]

Compound B3-9

8-(2-Diisopropylamino-ethanesulfonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0529]



[0530] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound B2-18.

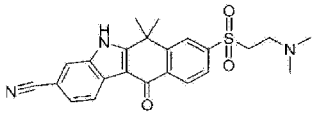
LCMS: m/z 478 $[M+H]^+$
HPLC retention time: 2.18 min (analysis condition U)

[Example 136]

Compound B3-10

8-(2-Dimethylamino-ethanesulfonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0531]



[0532] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound B2-19.

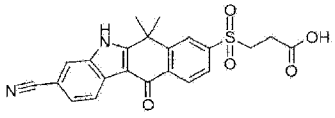
LCMS: m/z 422 $[M+H]^+$
HPLC retention time: 2.03 min (analysis condition U)

[Example 137]

Compound B3-11

3-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-sulfonyl)-propionic acid

[0533]



[0534] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound B2-20.

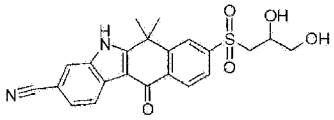
LCMS: m/z 423 $[M+H]^+$
HPLC retention time: 2.28 min (analysis condition U)

[Example 138]

Compound B3-12

8-(2,3-Dihydroxy-propane-1-sulfonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0535]



[0536] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound B2-21.

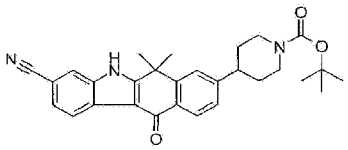
LCMS: m/z 425 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition U)

[Example 139]

Compound B3-13-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidine-1-carboxylic acid tert-butyl ester

[0537]



[0538] 4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (Compound B2-22-1, 16.2 g, 34.6 mmol) was dissolved in THF (800 ml) and methanol (230 ml), added with 10 wt% Pd/C (3.2 g), and stirred under hydrogen atmosphere for 19 hr. The solid was filtered through Celite, eluted with a mixture solvent (400 ml; THF/methanol = 4/1), and concentrated under reduced pressure. The residues were dissolved in ethyl acetate (400 ml), and then washed with 1% aqueous solution of N-acetylcysteine, saturated aqueous solution of $NaHCO_3$ and saturated brine. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues were concentrated under reduced pressure to obtain the title compound as a crude product (white powder, 14.0 g, 86%).

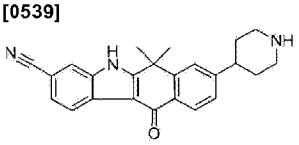
LCMS: m/z 470 $[M+H]^+$
HPLC retention time: 2.88 min (analysis condition S)

[Example 140]

Compound B3-13-2

6,6-Dimethyl-11-oxo-8-piperidin-4-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0539]



[0540] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B3-13-1.

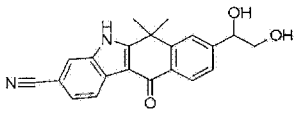
LCMS: m/z 370 $[M+H]^+$
HPLC retention time: 1.30 min (analysis condition S)

[Example 141]

Compound B3-14

8-(1,2-Dihydroxy-ethyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0541]



[0542] To the THF (1 ml) solution of 6,6-dimethyl-11-oxo-8-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound B2-24, 20 mg, 0.064 mmol), t-butanol solution of osmium tetraoxide (19 µl, 0.3 eq.) and 50% aqueous solution of N-methylmorpholine-N-oxide (30 µl, 2.0 eq.) were added and the mixture was stirred at room temperature for 3 hr. To the reaction solution, 10% aqueous solution of disodium ethylenediamine tetraacetic acid was added, followed by extraction with ethyl acetate. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by high performance liquid chromatography to obtain the title compound (21 mg, 63%).

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.41 (1 H, d, J = 7.9 Hz), 8.29 (1 H, d, J = 7.9 Hz), 7.87 (1 H, s), 7.86 (1 H, s), 7.57 (1 H, d, J = 7.9 Hz), 7.52 (1 H, d, J = 6.7 Hz), 4.85 (1 H, dd, J = 7.0, 4.6 Hz), 3.73 (1 H, dd, J = 11.3, 4.6 Hz), 3.68 (1 H, dd, J = 11.3, 7.0 Hz), 1.83 (6 H, s)

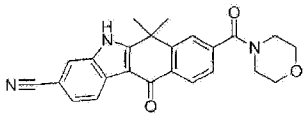
LCMS: m/z 347 $[M+H]^+$
HPLC retention time: 2.68 min (analysis condition W)

[Example 142]

Compound B3-15

6,6-Dimethyl-8-(morpholine-4-carbonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0543]



[0544] To the tetrahydrofuran (1 ml) solution of 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (Compound B2-28, 15 mg, 0.045 mmol), morpholine (6 µl, 1.5 eq.), hexafluorophosphoric acid uronium 2-(1H-7-azabenzotriazol-1-yl)-1,1,3,3-tetramethylmethane aminium (HATU) (26 mg, 1.5 eq.), and N,N-diisopropylethylamine (24 µl, 3.0 eq.) were added and the mixture was stirred at room temperature for 3 hr. The reaction solution was filtered to remove insoluble matters and the residues obtained after concentration under reduced pressure were purified by high performance liquid chromatography to obtain the title compound (11 mg, 55%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.85 (1 H, s), 8.33 (1 H, d, J = 8.5 Hz), 8.27 (1 H, d, J = 7.9 Hz), 8.03 (1 H, s), 7.92 (1 H, s), 7.63 (1 H, d, J = 8.5 Hz), 7.54 (1 H, d, J = 7.9 Hz), 3.52-3.77 (6 H, m), 3.30-3.42 (2 H, m), 1.79 (6 H, s)

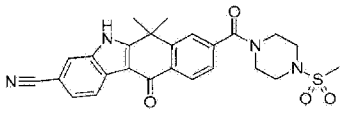
LCMS: m/z 400 $[M+H]^+$
HPLC retention time: 2.96 min (analysis condition W)

[Example 143]

Compound B3-16

8-(4-Methanesulfonyl-piperazin-1-carbonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0545]



[0546] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 1-methanesulfonylpiperazine.

LCMS: m/z 477 $[M+H]^+$

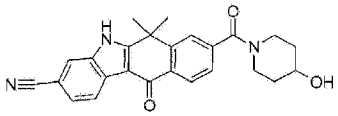
HPLC retention time: 3.03 min (analysis condition W)

[Example 144]

Compound B3-17

8-(4-Hydroxy-piperidin-1-carbonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0547]



[0548] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and piperidin-4-ol.

LCMS: m/z 414 $[M+H]^+$

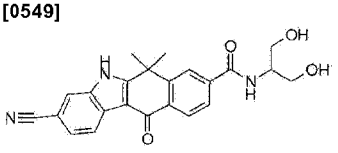
HPLC retention time: 2.75 min (analysis condition W)

[Example 145]

Compound B3-18

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-hydroxy-1-hydroxymethyl-ethyl)-amide

[0549]



[0550] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 2-aminopropane-1,3-diol.

LCMS: m/z 404 $[M+H]^+$

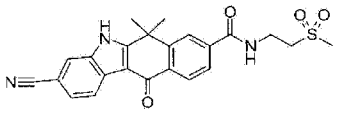
HPLC retention time: 2.60 min (analysis condition W)

[Example 146]

Compound B3-19

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-methanesulfonyl-ethyl)-amide

[0551]



[0552] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 2-methanesulfonylethylamine.

LCMS: m/z 436 $[M+H]^+$

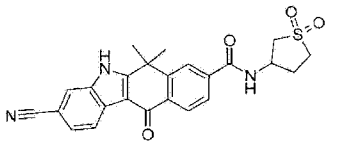
HPLC retention time: 2.87 min (analysis condition W)

[Example 147]

Compound B3-20

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (1,1-dioxo-tetrahydro-thiophen-3-yl)-amide

[0553]



[0554] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and (1,1-dioxotetrahydrothiophen-3-yl)amine

LCMS: m/z 448 $[M+H]^+$

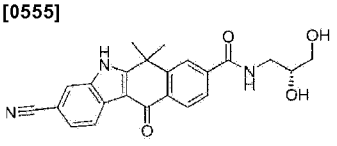
HPLC retention time: 1.70 min (analysis condition S)

[Example 148]

Compound B3-21

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid ((R)-2,3-dihydroxy-propyl)-amide

[0555]



[0556] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and (R)-(+)-3-amino-1,2-propanediol.

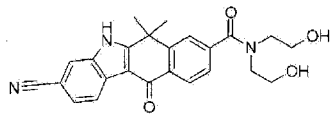
LCMS: m/z 404 $[M+H]^+$
HPLC retention time: 1.38 min (analysis condition S)

[Example 149]

Compound B3-22

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid bis-(2-hydroxy-ethyl)-amide

[0557]



[0558] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and N,N-diethanolamine.

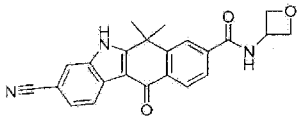
LCMS: m/z 418 $[M+H]^+$
HPLC retention time: 1.35 min (analysis condition S)

[Example 150]

Compound B3-23

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid oxetan-3-yl amide

[0559]



[0560] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and oxetan-3-yl amine.

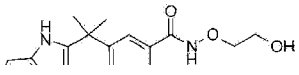
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 1.63 min (analysis condition S)

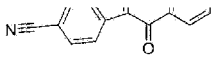
[Example 151]

Compound B3-24

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-hydroxy-ethoxy)-amide

[0561]





[0562] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 2-aminooxy-ethanol.

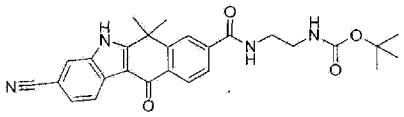
LCMS: m/z 390 $[M+H]^+$
HPLC retention time: 1.54 min (analysis condition S)

[Example 152]

Compound B3-25-1

2-[(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carbonyl)-amino]-ethyl}-carbamic acid tert-butyl ester

[0563]



[0564] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and (2-amino-ethyl)-carbamic acid tert-butyl ester.

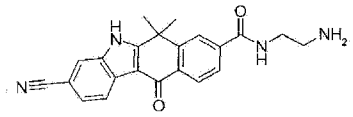
LCMS: m/z 473 $[M+H]^+$
HPLC retention time: 2.08 min (analysis condition S)

[Example 153]

Compound B3-25-2

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-amino-ethyl)-amide

[0565]



[0566] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B3-25-1.

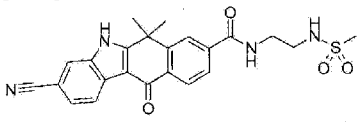
LCMS: m/z 373 $[M+H]^+$
HPLC retention time: 1.19 min (analysis condition S)

[Example 154]

Compound B3-25-3

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-methanesulfonylamino-ethyl)-amide

[0567]



[0568] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-25-2.

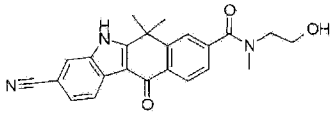
LCMS: m/z 451 $[M+H]^+$
HPLC retention time: 1.62 min (analysis condition S)

[Example 155]

Compound B3-26

3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carboxylic acid (2-hydroxy-ethyl)-methyl-amide

[0569]



[0570] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 2-methylamino-ethanol.

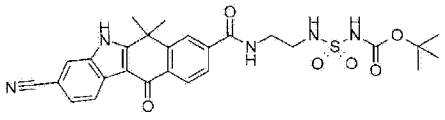
LCMS: m/z 388 $[M+H]^+$
HPLC retention time: 1.53 min (analysis condition S)

[Example 156]

Compound B3-27-1

Tert-butyl N-(2-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8carboxamide)ethylsulfamoylcarbamic acid

[0571]



[0572] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-25-2 and N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridin-1-yl sulfonyl]azanide (CAS No. 872496-91-8).

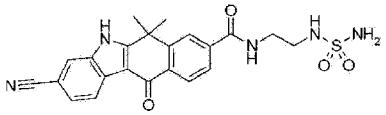
LCMS: m/z 552 $[M+H]^+$
HPLC retention time: 2.03 min (analysis condition S)

[Example 157]

Compound B3-27-2

3-Cyano-6,6-dimethyl-11-oxo-N-(2-(sulfamovlamino)ethyl)-6,11-dihydro-5H-benzo[b]carbazol-8-carboxamide

[0573]



[0574] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B3-27-1.

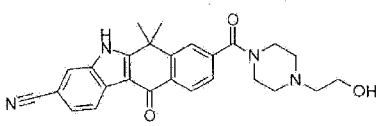
LCMS: m/z 452 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition S)

[Example 158]

Compound B3-28

8-[4-(2-Hydroxy-ethyl)-piperazin-1-carbonyl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0575]



[0576] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 2-piperazin-1-yl ethanol.

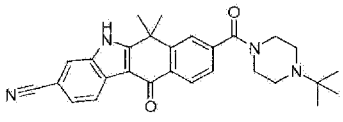
LCMS: m/z 443 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition U)

[Example 159]

Compound B3-29

8-(4-Tert-butyl-piperazin-1-carbonyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0577]



[0578] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 1-tert-butylpiperazine.

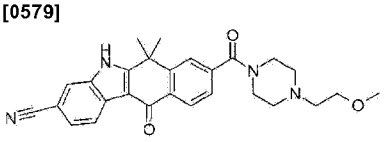
LCMS: m/z 455 $[M+H]^+$
HPLC retention time: 1.88 min (analysis condition U)

[Example 160]

Compound B3-30

8-[4-(2-Methoxy-ethyl)-piperazin-1-carbonyl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0579]



[0580] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and 1-(2-methoxyethyl)piperazine.

LCMS: m/z 457 $[M+H]^+$

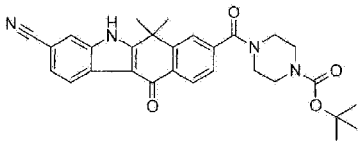
HPLC retention time: 1.83 min (analysis condition U)

[Example 161]

Compound B3-31-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-carbonyl)-piperazine-1-carboxylic acid tert-butyt ester

[0581]



[0582] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound B2-28 and piperazine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 499 $[M+H]^+$

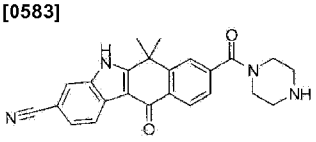
HPLC retention time: 2.63 min (analysis condition U)

[Example 162]

Compound B3-31-2

6,6-Dimethyl-11-oxo-8-(piperazin-1-carbonyl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0583]



[0584] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B3-31-1.

LCMS: m/z 399 $[M+H]^+$

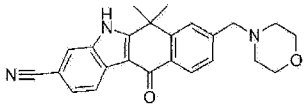
HPLC retention time: 1.78 min (analysis condition U)

[Example 163]

Compound B3-32

6,6-Dimethyl-8-morpholin-4-yl methyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0585]



[0586] To the THF (1 ml) solution of Compound B2-29 (30 mg, 0.095 mmol), morpholine (6 µl, 1.5 eq.) and sodium triacetoxyborohydride (81 mg, 2.0 eq.) were added and stirred at room temperature for 1 hr. The reaction solution was filtered to remove insoluble matters, and the residues obtained after concentration under reduced pressure were purified by high performance liquid chromatography to obtain the title compound (19 mg, 50%).

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.41 (1 H, d, 7.9 Hz), 8.27 (1 H, d, 8.5 Hz), 7.87 (1 s), 7.81 (1 H, s), 7.56 (1 H, d, 8.5 Hz), 7.49 (1 H, d, 7.9 Hz), 3.71 (4 H, t, 4.6 Hz), 3.68 (2 H, s), 2.51 (4 H, t, 4.6 Hz), 1.82 (6 H, s)

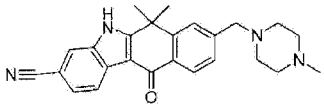
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 2.41 min (analysis condition W)

[Example 164]

Compound B3-33

6,6-Dimethyl-8-(4-methyl-piperazin-1-yl methyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0587]



[0588] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-29 and 1-methylpiperazine.

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.41 (1 H, d, 7.9 Hz), 8.26 (1 H, d, 7.9 Hz), 7.88 (1 s), 7.81 (1 H, s), 7.56 (1 H, d, 7.9 Hz), 7.48 (1 H, d, 7.9 Hz), 3.70 (2 H, s), 2.42-2.78 (8 H, m), 2.31 (3 H, s), 1.82 (6 H, s)

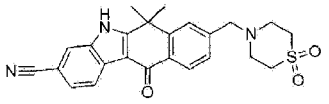
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 2.30 min (analysis condition W)

[Example 165]

Compound B3-34

8-[4-(1,1-Dioxide-4-thiomorpholinyl)methyl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0589]



[0590] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-29 and thiomorpholine 1,1-dioxide.

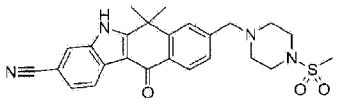
LCMS: m/z 434 $[M+H]^+$
HPLC retention time: 2.75 min (analysis condition W)

[Example 166]

Compound B3-35

8-(4-Methanesulfonyl-piperazin-1-yl methyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0591]



[0592] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-29 and 1-methanesulfonylpiperazine.

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.41 (1 H, d, 8.5 Hz), 8.28 (1 H, d, 7.9 Hz), 7.87 (1 s), 7.80 (1 H, s), 7.56 (1 H, d, 8.5 Hz), 7.50 (1 H, d, 7.9 Hz), 3.73 (2 H, s), 3.24-3.28 (4 H, m), 2.85 (3 H, s), 2.59-2.65 (4 H, m), 1.82 (6 H, s)

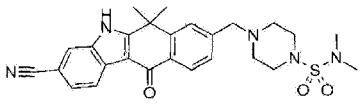
LCMS: m/z 463 $[M+H]^+$
HPLC retention time: 2.47 min (analysis condition W)

[Example 167]

Compound B3-36

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl methyl)-piperazine-1-sulfonic acid dimethylamide

[0593]



[0594] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-29 and piperazine-1-sulfonic acid dimethylamide.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.79 (1 H, s), 8.32 (1 H, d, 7.9 Hz), 8. 18 (1 H, d, 7.9 Hz), 8.00 (1 s), 7.77 (1 H, s), 7.60 (1 H, d, 7.9 Hz), 7.46 (1 H, d, 7.9 Hz), 3.67 (2 H, s), 3.18-3.23 (4 H, m), 2.76 (6 H, s), 2.45-2.50 (4 H, m), 1.77 (6 H, s)

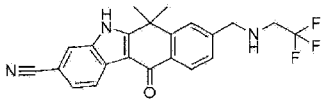
LCMS: m/z 492 $[M+H]^+$
HPLC retention time: 2.58 min (analysis condition W)

[Example 168]

Compound B3-37

6,6-Dimethyl-11-oxo-8-[(2,2,2-trifluoro-ethylamino)-methyl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0595]



[0596] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B2-29 and 2,2,2-trifluoroethylamine.

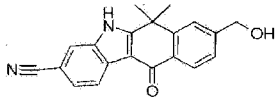
LCMS: m/z 398 $[M+H]^+$
HPLC retention time: 2.73 min (analysis condition W)

[Example 169]

Compound B3-38

8-Hydroxymethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0597]



[0598] The by-product obtained from the synthesis of Compound B3-37 was purified by high performance liquid chromatography to obtain the target compound.

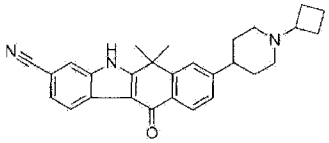
LCMS: m/z 317 $[M+H]^+$
HPLC retention time: 2.91 min (analysis condition W)

[Example 170]

Compound B4-1

8-(1-Cyclobutyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0599]



[0600] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B3-13-2 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.73 (1 H, s), 8.28-8.33 (1 H, m), 8.09-8.14 (1 H, m), 7.99 (1 H, s), 7.72 (1 H, s), 7.56-7.62 (1 H, m), 7.34-7.41 (1 H, m), 3. 52-3.64 (2 H, m), 2.85-2.95 (2 H, m), 2.56-2.75 (2 H, m), 1.91-2.04 (2 H, m), 1.56-1.84 (14 H, m)

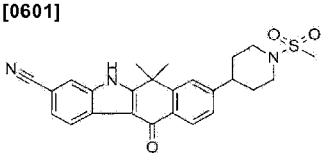
LCMS: m/z 424 $[M+H]^+$
HPLC retention time: 1.87 min (analysis condition U)

[Example 171]

Compound B4-2

8-(1-Methanesulfonyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,1-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0601]



[0602] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-13-2 and mesyl chloride.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.77 (1 H, s), 8.31 (1 H, d, 8.6 Hz), 8. 15 (1 H, d, 8.2 Hz), 8.00 (1 H, s), 7.77 (1 H, s), 7.59 (1H, d, 7.3 Hz), 7.42 (1 H, d, 8. 6 Hz), 3.74-3.70 (1 H, m), 2.93 (3 H, s), 2.86-2.77 (4H, m), 1.93-1.87 (4 H, m), 1. 77 (6.0 H, s)

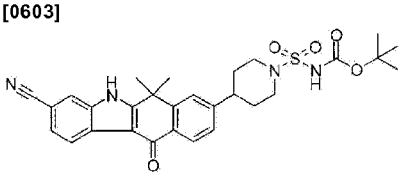
LCMS: m/z 448 $[M+H]^+$
HPLC retention time: 2.37 min (analysis condition S)

[Example 172]

Compound B4-3-1

Tert-butyl4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)piperidin-1-yl sulfonylcarbamic acid

[0603]



[0604] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-13-2 and N-(tert-butoxycarbonyl)-N-[4-(dimethylazaniumylidene)-1,4-dihydropyridine-1-yl-sulfonyl]azanide.

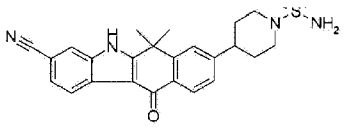
LCMS: m/z 549 $[M+H]^+$
HPLC retention time: 2.72 min (analysis condition S)

[Example 173]

Compound B4-3-2

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidine-1-sulfonic acid amide

[0605]



[0606] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B4-3-1.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.78 (1 H, s), 8.29 (1 H, d, 7.9 Hz), 8. 14 (1 H, d, 8.5 Hz), 7.97 (1 H, s), 7.76 (1 H, s), 7.55 (1 H, d, 8.5 Hz), 7.41 (1 H, d, 7. 9 Hz), 6.79 (2 H, s), 3.63 (2 H, d, 12.2 Hz), 2.80-2.73 (1 H, m), 2.70-2.64 (2 H, m), 1.96-1.93 (2 H, m), 1.87-1.81 (2 H, m), 1.77 (6 H, s)

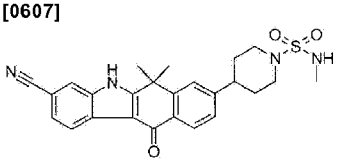
LCMS: m/z 449 $[M+H]^+$
HPLC retention time: 2.03 min (analysis condition S)

[Example 174]

Compound B4-4

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidine-1-sulfonic acid methylamide

[0607]



[0608] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-13-2 and 2-oxooxazolidine-3-sulfonic acid methylamide.

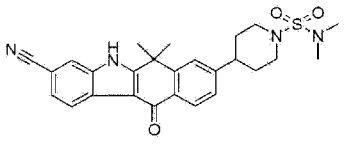
LCMS: m/z 463 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition S)

[Example 175]

Compound B4-5

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidine-1-sulfonic acid dimethylamide

[0609]



[0610] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-13-2 and dimethylsulfamoyl chloride.

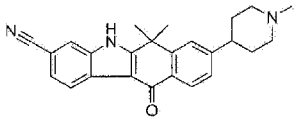
LCMS: m/z 477 $[M+H]^+$
HPLC retention time: 2.65 min (analysis condition S)

[Example 176]

Compound B4-6

6,6-Dimethyl-8-(1-methyl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0611]



[0612] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B3-13-2 and iodomethane.

LCMS: m/z 384 $[M+H]^+$

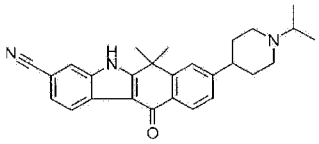
HPLC retention time: 1.50 min (analysis condition S)

[Example 177]

Compound B4-7

8-(1-Isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0613]



[0614] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B3-13-2 and acetone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.77 (1 H, s), 8. 32 (1 H, d, 7. 9 Hz), 8. 13 (1 H, d, 7. 9 Hz), 8. 01 (1 H, s), 7. 73 (1 H, s), 7. 61 (1H, d, 9. 1 Hz), 7. 39 (1 H, d, 9. 8 Hz), 2.93 (2 H, d, 11.0 Hz), 2. 77-2. 71 (1 H, m), 2. 67- 2. 62 (1 H, m), 2. 25 (2 H, t, 10. 1 Hz), 1.80-1. 73 (10 H, m), 1. 02 (6 H, d, 6. 7 Hz)

LCMS: m/z 412 $[M+H]^+$

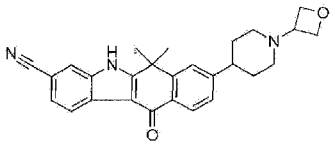
HPLC retention time: 1.60 min (analysis condition S)

[Example 178]

Compound B4-8

6,6-Dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0615]



[0616] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound B3-13-2 and oxetan-3-one.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.74 (1 H, s), 8. 32 (1 H, d, 7. 9 Hz), 8. 13 (1 H, d, 7.9 Hz), 8. 00 (1 H, s), 7. 74 (1 H, s), 7. 61 (1 H, d, 9.8 Hz), 7. 40 (1 H, d, 7. 9 Hz), 4.56 (2 H, t, 6.7 Hz), 4. 46 (2 H, t, 6. 1 Hz), 3.46-3. 39 (1 H, m), 2. 85-2. 82 (2 H, m), 2. 71-2. 64 (1 H, m), 1. 92-1. 86 (2 H, m), 1. 82-1. 79 (4 H, m), 1. 77 (6 H, s)

LCMS: m/z 426 $[M+H]^+$
HPLC retention time: 1.53 min (analysis condition S)
Sulfuric acid salt of Compound B4-8
6,6-Dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6, 1 1 -dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved at 80°C in a mixture of 5 volumes of DMA and 1.4 volumes of 2 N sulfuric acid. After cooling to room temperature, 15 volumes of acetone were added dropwise, and the precipitated solids were filtered and dried to obtain sulfuric acid salt of 6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.81 (1 H, s), 10.26 (1 H, br. s), 8. 33 (1 H, d, 8. 3 Hz), 8. 21 (1 H, d, 8. 3 Hz), 8. 04 (1 H, s), 7. 75 (1 H, s), 7.63 (1 H, d, 8. 3 Hz), 7. 41 (1 H, d, 8. 3 Hz), 4. 85-4. 70 (4 H, m), 4. 50-4. 40 (1 H, br. s), 3. 60-3. 00(6 H, br. m), 2. 20-2. 10 (2 H, m), 2. 05-1. 90 (2 H, m), 1. 79 (6 H, s)

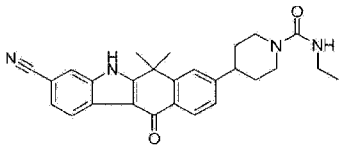
LCMS: m/z 426 $[M+H]^+$

[Example 179]

Compound B4-9

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidine-1-carboxylic acid ethylamide

[0617]



[0618] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound B-3-13-2 and ethylisocyanate.

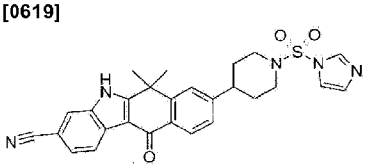
LCMS: m/z 441 $[M+H]^+$
HPLC retention time: 2.20 min (analysis condition S)

[Example 180]

Compound B4-10

8-[1-(Imidazole-1-sulfonyl)-piperidin-4-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0619]



[0620] According to the method disclosed in Journal of Organic Chemistry, 2003, page 115, 6,6-dimethyl-11-oxo-8-piperidin-4-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound B3-13-2, 10 mg, 0.027 mmol) was reacted with 3-(imidazole-1-sulfonyl)-1-methyl-3H-imidazol-1-ium (19 mg, 2 eq.). After removing the solvent, the residues were purified by liquid chromatography to obtain the

title compound (3 mg).

LCMS: m/z 500 $[M+H]^+$

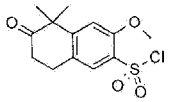
HPLC retention time: 2.80 min (analysis condition C)

[Example 181]

Compound CC1

3-Methoxy-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydro-naphthalen-2-sulfonyl chloride

[0621]



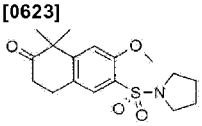
[0622] To the dichloromethane (2 ml) solution of 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 200 mg, 0.980 mmol), chlorosulfonic acid (110 µl, 1.70 eq.) was added and the mixture was stirred at room temperature for 2 hr. To the reaction solution, oxalyl chloride (297 µl, 3.0 eq.) and N,N-dimethyl formamide (45 µl, 0.6 eq.) were added in three divided portions, and the mixture was stirred at room temperature for 30 min. The reaction solution was concentrated under reduced pressure to obtain the title compound (295 mg). Since the title compound is unstable, its structure was identified in the next step.

[Example 182]

Compound CC2-1

7-Methoxy-1,1-dimethyl-6-(pyrrolidine-1-sulfonyl)-3,4-dihydro-1H-naphthalen-2-one

[0623]



[0624] The THF (4 ml) solution of 3-methoxy-5,5-dimethyl-6-oxo-5,6,7,8-tetrahydro-naphthalen-2-sulfonyl chloride (Compound CC1, 295 mg, 0.974 mmol) was cooled to 0°C, and the tetrafuran (1 ml) solution combining pyrrolidine (121 µl, 1.5 eq.) and triethylamine (272 µl, 2 eq.) was added dropwise thereto over 2 min. The mixture was stirred at 0°C until Compound CC-1 disappears. The reaction solution was added with distilled water and extracted with ethyl acetate. The organic layer was washed with 10% aqueous solution of disodium ethylenediamine tetraacetic acid. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (246 mg, 75%).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 7.76 (1 H, s), 6. 93 (1 H, s), 3. 95 (3 H, s), 3. 37-3. 46 (4H, m), 3. 09 (0. 0 H, t, J = 6.9 Hz), 2. 69 (0. 0 H, t, J = 6.9 Hz), 1. 82-1. 91 (4 H, m), 1. 47 (6 H, s)

LCMS: m/z 338 $[M+H]^+$

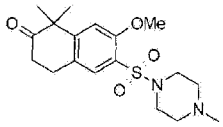
HPLC retention time: 3.21 min (analysis condition W)

[Example 183]

Compound CC2-2

7-Methoxy-1,1-dimethyl-6-(4-methyl-piperazine-1-sulfonyl)-3,4-dihydro-1H-naphthalen-2-one

[0625]



[0626] Under the same conditions as the method for synthesizing Compound CC2-1, the title compound was prepared from Compound CC1 and N-methylpiperazine.

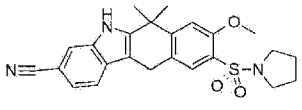
LCMS: m/z 367 $[M+H]^+$
HPLC retention time: 2.22 min (analysis condition Y)

[Example 184]

Compound CC3-1

8-Methoxy-6,6-dimethyl-9-(pyrrolidine-1-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0627]



[0628] Under the same conditions as the method for synthesizing Compound E2-1, the title compound was prepared from Compound CC2-1.

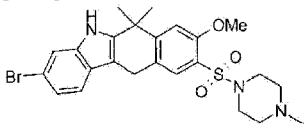
LCMS: m/z 436 $[M+H]^+$
HPLC retention time: 3.76 min (analysis condition W)

[Example 185]

Compound CC3-2

3-Bromo-8-methoxy-6,6-dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazole

[0629]



[0630] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound CC2-2.

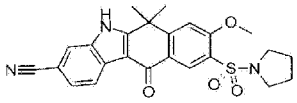
LCMS: m/z 519 $[M+H]^+$
HPLC retention time: 2.99 min (analysis condition Y)

[Example 186]

Compound CC4-1

8-Methoxy-6,6-dimethyl-11-oxo-9-(pyrrolidine-1-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0631]



[0632] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound CC3-1.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12. 86 (1 H, s), 8. 60 (1 H, s), 8. 30 (1 H, d, J = 8.5 Hz), 8. 01 (1 H, s), 7. 60 (1 H, s), 7. 59 (1 H, d, J = 8.5 Hz), 4.09 (3 H, s), 3. 21-3. 42 (4 H, m), 1. 72-1. 90 (10 H, m)

LCMS: m/z 450 $[M+H]^+$

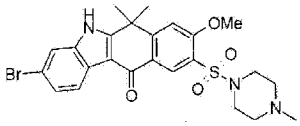
HPLC retention time: 3.40 min (analysis condition W)

[Example 187]

Compound CC4-2

3-Bromo-8-methoxy-6,6-dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-5,6-dihydro-benzo[b]carbazol-11-one

[0633]



[0634] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound CC3-2.

LCMS: m/z 532, 534 $[M+H]^+$

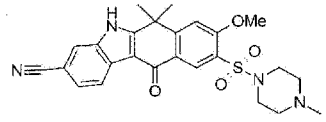
HPLC retention time: 2.18 min (analysis condition U)

[Example 188]

Compound CC-4-3

8-Methoxy-6,6-dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0635]



[0636] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound CC4-2.

LCMS: m/z 479 $[M+H]^+$

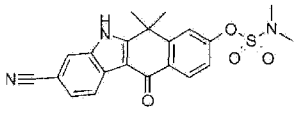
HPLC retention time: 1.93 min (analysis condition U)

[Example 189]

Compound C1-1

Dimethyl-sulfamic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0637]



[0638] 8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound A6, 50 mg, 0.165 mmol) was dissolved in DMF (1.5 mL), added with sodium hydride (13 mg, 2.0 eq.) and dimethylsulfamoyl chloride (0.02 mL, 1.2 eq.), and then stirred at room temperature for 1 hr. Water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues were concentrated under reduced pressure to obtain the target compound (yellowish white powder, 62 mg, 92%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12. 87 (1 H, s), 8. 40-8. 30 (2 H, m), 8. 05 (1 H, s), 7.82 (1 H, d, J = 1. 8 Hz), 7. 64 (1 H, d, J = 7.9 Hz), 7. 50 (1 H, dd, J = 8. 5, 2. 4 Hz), 2.96 (6 H, s), 1.81 (6 H, s)

LCMS: m/z 410 $[M+H]^+$

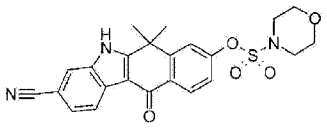
HPLC retention time: 2.38 min (analysis condition S)

[Example 190]

Compound C1-2

Morpholine-4-sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0639]



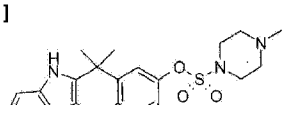
[0640] According to the same method as the method for synthesizing Compound A8-17, the title compound was prepared as a crude product from Compound A6 and Compound A8-18-0.

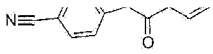
[Example 191]

Compound C1-4

4-Methyl-piperazine-1-sulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0641]





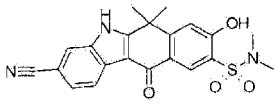
[0642] According to the same method as the method for synthesizing Compound A8-17, the title compound was prepared as a crude product from Compound A6 and Compound A8-19-0.

[Example 192]

Compound C2-1

3-Cyano-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0643]



[0644] To dimethyl-sulfamic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester (Compound C1-1, 250 mg, 0.610 mmol), aluminum chloride (1.0 M, nitromethane solution (1.8 mL, 3.0 eq.)) was added and the mixture was stirred at 160°C for 10 min under irradiation with microwave. Water was added to the reaction solution, which was then extracted with dichloromethane. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the target compound (yellowish white powder, 99 mg, 40%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12. 78 (1 H, s), 11. 72 (1 H, s), 8. 50 (1 H, s), 8. 32 (1 H, d, J = 8.5 Hz), 8. 02 (1 H, s), 7. 62 (1 H, d, J = 7.9 Hz), 7. 25 (1 H, s), 2. 80 (6 H, s), 1. 75 (6 H, s).

LCMS: m/z 410 $[M+H]^+$

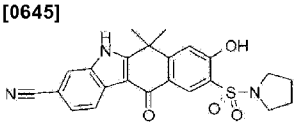
HPLC retention time: 2.00 min (analysis condition S)

[Example 193]

Compound C2-2

8-Hydroxy-6,6-dimethyl-11-oxo-9-(pyrrolidine-1-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0645]



[0646] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound CC4-1.

LCMS: m/z 436 $[M+H]^+$

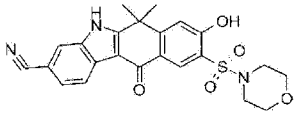
HPLC retention time: 3.32 min (analysis condition W)

[Example 194]

Compound C2-3

8-Hydroxy-6,6-dimethyl-9-(morpholine-4-sulfonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0647]



[0648] Under the same conditions as the method for synthesizing Compound C2-1, the title compound was prepared from Compound C1-2.

LCMS: m/z 452 $[M+H]^+$

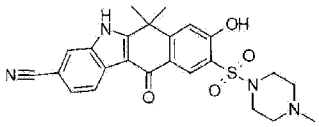
HPLC retention time: 1.89 min (analysis condition S)

[Example 195]

Compound C2-4

8-Hydroxy-6,6-dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3 -carbonitrile

[0649]



[0650] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound CC4-3.

LCMS: m/z 465 $[M+H]^+$

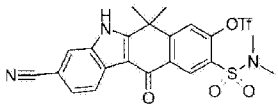
HPLC retention time: 1.87 min (analysis condition U)

[Example 196]

Compound C3-1

Trifluoro-methanesulfonic acid 3-cyano-9-dimethylsulfamoyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0651]



[0652] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound C2-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 13. 05 (1 H, s), 8. 67 (1 H, s), 8. 32 (1 H, d, J = 8. 2 Hz), 8. 06 (2 H, m), 7. 67 (1 H, dd, J = 7. 9, 1. 3 Hz), 2. 79 (6 H, s), 1. 84 (6 H, s).

LCMS: m/z 542 $[M+H]^+$

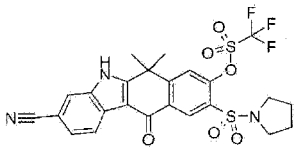
HPLC retention time: 2.67 min (analysis condition S)

[Example 197]

Compound C3-2

Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-9-(pyrrolidine-1-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0653]



[0654] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound C2-2.

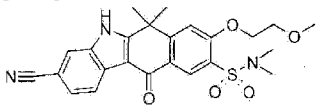
LCMS: m/z 568 $[M+H]^+$
HPLC retention time: 4.00 min (analysis condition W)

[Example 198]

Compound C4-1

3-Cyano-8-(2-methoxy-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0655]



[0656] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound C2-1 and 1-bromo-2-methoxy-ethane.

^{1}H-NMR(300 MHz, DMSO-d_6) σppm ; 12. 8(s, 1H), 8. 58 (s, 1 H), 8. 31 (d, 1 H, J=8. 4 Hz), 8. 03 (s, 1 H), 7. 62 (m, 2 H), 4.47 (m, 2H), 3. 75 (m, 2 H), 3. 32 (s, 3 H), 2. 27 (s, 6 H), 1.83 (s, 6 H)

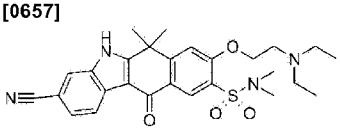
LCMS: m/z 468 $[M+H]^+$
HPLC retention time: 2.68 min (analysis condition U)

[Example 199]

Compound C4-2

3-Cyano-8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0657]



[0658] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound C2-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8. 57 (1 H, s), 8. 29 (1 H, d, J = 8. 4 Hz), 8.02 (1 H, s), 7. 70-7. 60 (2 H, m), 4. 37 (2 H, t, J = 6.3 Hz), 2.84 (2 H, m), 2.80 (6 H, s), 2. 64-2. 53 (4 H, m), 1.83 (6 H, s), 0. 98 (6 H, t, J = 7. 1 Hz).

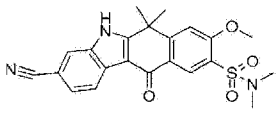
LCMS: m/z 509 $[M+H]^+$
HPLC retention time: 1.55 min (analysis condition S)

[Example 200]

Compound C4-3

3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0659]



[0660] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound C2-1 and iodomethane.

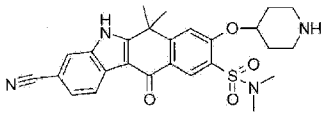
LCMS: m/z 424 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition S)

[Example 201]

Compound C4-4

3-Cyano-6,6-dimethyl-11-oxo-8-(piperidin-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0661]



[0662] Under the same conditions as the method for synthesizing Compound A7-1 and Compound A8-1, the title compound was prepared from Compound C2-1 and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester.

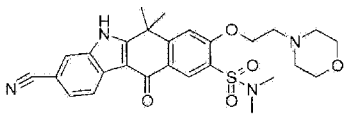
LCMS: m/z 493 $[M+H]^+$
HPLC retention time: 1.49 min (analysis condition S)

[Example 202]

Compound C4-5

3-Cyano-6,6-dimethyl-8-(2-morpholin-4-yl-ethoxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0663]



[0664] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound C2-1 and 2-morpholin-4-yl-ethanol.

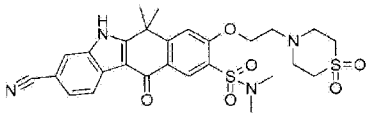
LCMS: m/z 523 $[M+H]^+$
HPLC retention time: 1.64 min (analysis condition S)

[Example 203]

Compound C4-6

3-Cyano-8-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0665]



[0666] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound C2-1 and 2-(1,1-dioxothiomorpholino)ethanol.

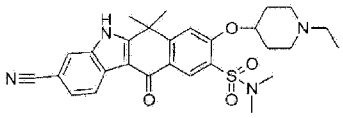
LCMS: m/z 571 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition S)

[Example 204]

Compound C4-7

3-Cyano-8-(1-ethyl-piperidin-4-yl oxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0667]



[0668] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound C2-1 and 1-ethyl-piperidin-4-ol.

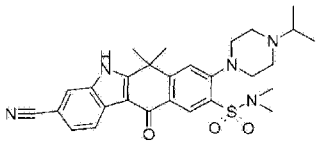
LCMS: m/z 521 $[M+H]^+$
HPLC retention time: 1.52 min (analysis condition S)

[Example 205]

Compound C4-8

3-Cyano-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0669]



[0670] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound C3-1.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.61 (1 H, s), 8. 30 (1 H, d, J = 8. 1 Hz), 8. 04 (1 H, s), 7. 87 (1 H, s), 7. 62 (1 H, dd, J = 8. 2, 1. 8 Hz), 3. 17-3. 06 (2 H, m), 2. 75-2. 70 (6 H, s), 2. 67-2. 58 (2 H, m), 1. 81 (6 H, s), 1. 02(6 H, d, J = 6. 4 Hz).

LCMS: m/z 520 $[M+H]^+$

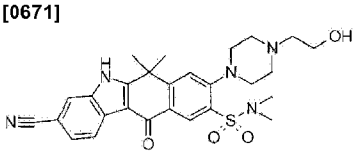
HPLC retention time: 1.52 min (analysis condition S)

[Example 206]

Compound C4-9

3-Cyano-8-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0671]



[0672] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound C3-1 and 2-piperazin-1-yl-ethanol.

LCMS: m/z 522 $[M+H]^+$

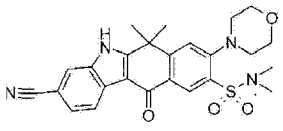
HPLC retention time: 1.40 min (analysis condition S)

[Example 207]

Compound C4-10

3-Cyano-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0673]



[0674] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound C3-1 and morpholine.

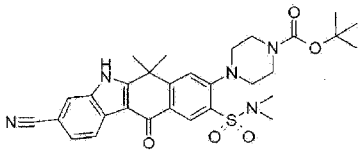
LCMS: m/z 479 $[M+H]^+$
HPLC retention time: 2.22 min (analysis condition S)

[Example 208]

Compound C4-11

4-(3-Cyano-9-dimethylsulfamoyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0675]



[0676] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound C3-1 and piperazine-1-carboxylic acid tert-butyl ester.

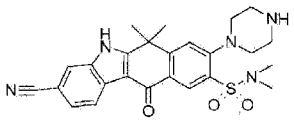
LCMS: m/z 578 $[M+H]^+$
HPLC retention time: 2.72 min (analysis condition S)

[Example 209]

Compound C4-12

3-Cyano-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0677]



[0678] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from C4-11.

^{1}H-NMR (270 MHz, CD_3OD) δ : 8.78 (1 H, s), 8.39 (1 H, dd, J = 8.2, 0.7 Hz), 7.88 (1 H, m), 7.75 (1.1 H, s), 7.55 (1 H, dd, J = 8.2, 1.5 Hz), 3.15 (4 H, m), 3. 04 (4 H, m), 2.82 (s, 6 H), 1.85 (6 H, s)

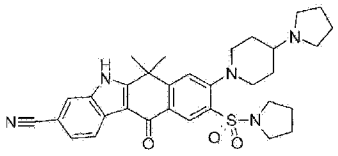
LCMS: m/z 478 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 210]

Compound C4-13

6,6-Dimethyl-11-oxo-9-(pyrrolidine-1-sulfonyl)-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0679]



[0680] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound C3-2 and 4-(1-pyrrolidyl)-piperidine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.83 (1 H, s), 8. 64 (1 H, s), 8. 32 (1 H, d, 8.2 Hz), 8. 03 (1 H, s), 7. 80 (1 H, s), 7. 63 (1 H, d, 8. 2 Hz), 2. 87-2. 94 (4 H, m), 1. 94-1. 99 (4 H, m), 1. 80 (6 H, s), 1. 58-1. 76 (10 H, m)

LCMS: m/z 572 $[M+H]^+$

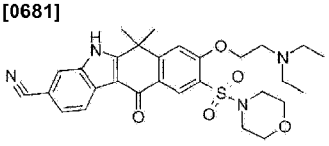
HPLC retention time: 2.81 min (analysis condition W)

[Example 211]

Compound C4-14

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-9-(morpholine-4-sulfonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0681]



[0682] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound C2-3.

LCMS: m/z 551 $[M+H]^+$

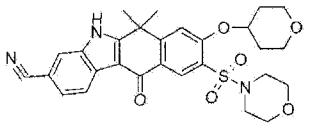
HPLC retention time: 1.46 min (analysis condition S)

[Example 212]

Compound C4-15

6,6-Dimethyl-9-(morpholine-4-sulfonyl)-11-oxo-8-(tetrahydro-pyran-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0683]



[0684] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound C2-3 and tetrahydropyran-4-ol.

LCMS: m/z 536 $[M+H]^+$

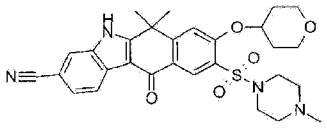
HPLC retention time: 2.05 min (analysis condition S)

[Example 213]

Compound C4-16

6,6-Dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-11-oxo-8-(tetrahydro-pyran-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0685]



[0686] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound C2-4 and tetrahydropyran-4-ol.

LCMS: m/z 549 $[M+H]^+$

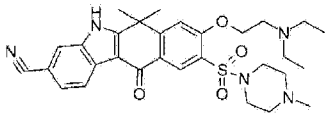
HPLC retention time: 2.03 min (analysis condition U)

[Example 214]

Compound C4-17

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-9-(4-methyl-piperazine-1-sulfonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0687]



[0688] Under the same conditions as the method for synthesizing Compound A7-1, the target compound was prepared from Compound C2-3.

LCMS: m/z 564 $[M+H]^+$

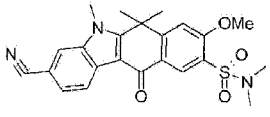
HPLC retention time: 1.20 min (analysis condition S)

[Example 215]

Compound C5

3-Cyano-8-methoxy-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0689]



[0690] The title compound was obtained as a by-product of the synthesis of Compound C4-3.

LCMS: m/z 438 $[M+H]^+$

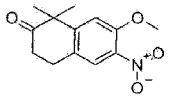
HPLC retention time: 2.29 min (analysis condition S)

[Example 216]

Compound D0-1-1

7-Methoxy-1,1-dimethyl-6-nitro-3,4-dihydro-1H-naphthalen-2-one

[0691]



[0692] Tetrabutylammonium nitrate (2.47 g, 1.07 eq.) was dissolved in dichloromethane, and added with trifluoromethanesulfonic anhydride (1.33 ml, 1.07 eq.) at 0°C. The mixture was stirred for 1 hr, added with DCM solution of 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 1.55 g, 7.59 mmol), and then stirred at 0°C for 2 hr and 30 min. The reaction solution was added to saturated aqueous solution of sodium hydrogen carbonate and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (pale yellow solid, 1.144 g, 60%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 7.79 (1 H, s), 7. 28 (1 H, s), 3. 95 (3 H, s), 3.06 (2 H, t, J = 6.9 Hz), 2. 64 (2 H, t, J = 6.9 Hz), 1.41 (6 H, s).

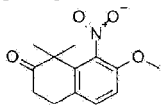
HPLC retention time: 2.03 min (analysis condition S)

[Example 217]

Compound D0-1-2

7-Methoxy-1,1-dimethyl-8-nitro-3,4-dihydro-1H-naphthalen-2-one

[0693]



[0694] The title compound was obtained as a by-product of the synthesis of Compound D0-1-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 7.44 (1 H, d, J = 8. 6 Hz), 7. 23 (1 H, d, J = 8.6 Hz), 3.84 (3 H, s), 3. 07 (2 H, t, J = 6.9 Hz), 2.65 (2 H, t, J = 6.9 Hz), 1. 35 (6 H, s)

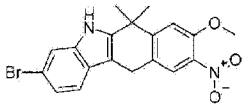
HPLC retention time: 2.15 min (analysis condition S)

[Example 218]

Compound D0-2-1

3-Bromo-8-methoxy-6,6-dimethyl-9-nitro-6,11-dihydro-5H-benzo[b]carbazole

[0695]



[0696] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound D0-1-1.

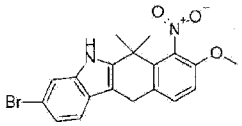
LCMS: m/z 401,403 $[M+H]^+$
HPLC retention time: 3.07 min (analysis condition S)

[Example 219]

Compound D0-2-2

3-Bromo-8-methoxy-6,6-dimethyl-7-nitro-6,11-dihydro-5H-benzo[b]carbazole

[0697]



[0698] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound D0-1-2.

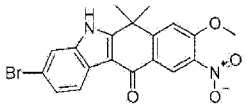
LCMS: m/z 401, 403 $[M+H]^+$
HPLC retention time: 3.10 min (analysis condition S)

[Example 220]

Compound D0-3-1

3-Bromo-8-methoxy-6,6-dimethyl-9-nitro-5,6-dihydro-benzo[b]carbazol-11-one

[0699]



[0700] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound D0-2-1.

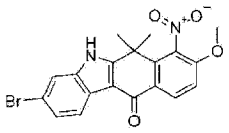
LCMS: m/z 415, 417 $[M+H]^+$
HPLC retention time: 3.07 min (analysis condition S)

[Example 221]

Compound D0-3-2

3-Bromo-8-methoxy-6,6-dimethyl-7-nitro-5,6-dihydro-benzo[b]carbazol-11-one

[0701]



[0702] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound D0-2-2.

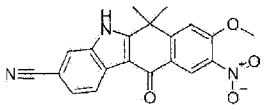
LCMS: m/z 415, 417 $[M+H]^+$
HPLC retention time: 2.72 min (analysis condition S)

[Example 222]

Compound D0-4-1

8-Methoxy-6,6-dimethyl-9-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0703]



[0704] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound D0-3-1.

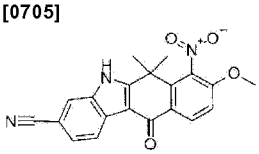
LCMS: m/z 362 $[M+H]^+$
HPLC retention time: 2.35 min (analysis condition S)

[Example 223]

Compound D0-4-2

8-Methoxy-6,6-dimethyl-7-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0705]



[0706] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound D0-3-2.

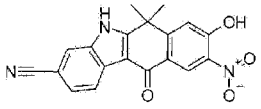
LCMS: m/z 362 $[M+H]^+$
HPLC retention time: 2.35 min (analysis condition S)

[Example 224]

Compound D0-5-1

8-Hydroxy-6,6-dimethyl-9-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0707]



[0708] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound D0-4-1.

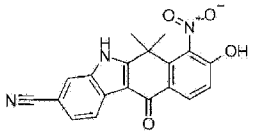
LCMS: m/z 348 $[M+H]^+$
HPLC retention time: 2.28 min (analysis condition S)

[Example 225]

Compound D0-5-2

8-Hydroxy-6,6-dimethyl-7-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0709]



[0710] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound D0-4-2.

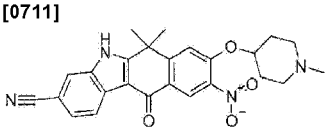
LCMS: m/z 348 $[M+H]^+$
HPLC retention time: 2.23 min (analysis condition S)

[Example 226]

Compound D1

6,6-Dimethyl-8-(1-methyl-piperidin-4-yl oxy)-9-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0711]



[0712] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound D0-5-1 and 1-methylpiperidin-4-ol.

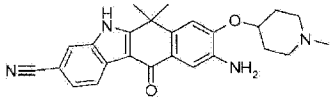
LCMS: m/z 445 $[M+H]^+$
HPLC retention time: 1.64 min (analysis condition S)

[Example 227]

Compound D2

9-Amino-6,6-dimethyl-8-(1-methyl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0713]



[0714] 6,6-Dimethyl-8-(1-methyl-piperidin-4-yl oxy)-9-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound D1, 83 mg, 0.19 mmol) was dissolved in ethanol, added with aqueous solution of ammonium acetate and aqueous solution of titanium (III) chloride, and then the mixture was stirred at room temperature for 45 min. The reaction solution was added to saturated aqueous solution of sodium hydrogen carbonate and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues were concentrated under reduced pressure to obtain the title compound (yellow solid, 60 mg, 78%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.61 (1 H, br. s), 8. 28-8. 34 (1 H, m), 7. 94-8. 00 (1 H, m), 7. 57 (1 H, dd, J = 8. 2, 1.4 Hz), 7. 46 (1 H, s), 7. 19 (1 H, s), 4.93 (1. 8 H, s), 4.65 (1. 0 H, s), 4. 06-4. 15 (1 H, m), 3. 34 (5.7 H, s), 3. 16-3. 18 (2 H, m), 2. 55-2. 67 (2 H, m), 2. 17-2. 33 (5 H, m), 1. 89-2. 07 (2H, m), 1. 65-1. 81 (8 H, m)

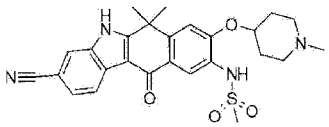
LCMS: m/z 415 $[M+H]^+$
HPLC retention time: 1.12 min (analysis condition S)

[Example 228]

Compound D3-1

N-[3-Cyano-6,6-dimethyl-8-(1-methyl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl]-methanesulfonamide

[0715]



[0716] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound D2 and methanesulfonyl chloride.

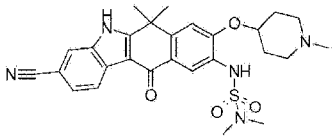
LCMS: m/z 493 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 229]

Compound D3-2

3-Cyano-6,6-dimethyl-11-oxo-8-(1-methylpiperidin-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[0717]



[0718] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound D2 and dimethylsulfamoyl chloride.

^{1}H-NMR (270 MHz, CD_3OD) δ : 8.34-8.42 (2.0H, m), 7.85 (1.0 H, s), 7. 47-7.58 (1.0 H, m), 7.32 (1.0 H, s), 4.73-4.89 (1 H, m), 2.75-2.91 (8 H, m), 2.38-2. 52 (2 H, m), 2.34 (3 H, s), 2.06-2.21 (2 H, m), 1.87-2.05 (2 H, m), 1.80 (6 H, s).

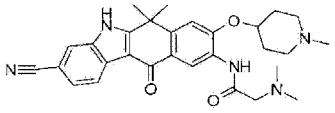
LCMS: m/z 522 $[M+H]^+$
HPLC retention time: 1.66 min (analysis condition S)

[Example 230]

Compound D3-3

N-[3-Cyano-6,6-dimethyl-8-(1-methyl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl]-2-dimethylamino-acetamide

[0719]



[0720] Under the same conditions as the method for synthesizing Compound A9-10, the title compound was prepared from Compound D2 and N,N-dimethylglycine.

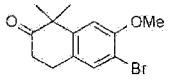
LCMS: m/z 500 $[M+H]^+$
HPLC retention time: 1.31 min (analysis condition S)

[Example 231]

Compound E1

6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[0721]



[0722] 7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 2.0 g, 9.791 mmol) was dissolved in CH3CN (40 mL), added with NBS (1.92 g, 1.1 eq.), and the mixture was stirred at room temperature for 2.5 hr. The reaction solution was added to water (40 mL), and the precipitated solid was filtered to obtain the title compound (white powder, 2.55 g, 92%).

^{1}H-NMR (270 MHz, $CDCl_3$) δ : 7.36 (1 H, s), 6. 84 (1 H, s), 3. 91 (3 H, s), 3. 02 (2 H, t, J = 6.8 Hz), 2. 66 (2 H, t, J = 6. 8 Hz), 1. 42 (6 H, s).

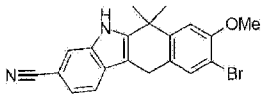
LCMS: m/z 283, 285 $[M+H]^+$
HPLC retention time: 2.67 min (analysis condition S)

[Example 232]

Compound E2-1

9-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0723]



[0724] 6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound E1, 7.89 g, 27.85 mmol) and 3-hydrazinobenzonitrile (4.45 g, 1.2 eq.) were dissolved in TFA (250 mL), and stirred at 100°C for 2 hr. TFA was removed under reduced pressure and the residues were added with saturated aqueous solution of $NaHCO_3$ (500 mL), followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with ethyl acetate. After stirring at room temperature, the precipitated solid was separated by filtration (Compound E2-2). The filtrate was concentrated under reduced pressure to obtain the title compound as a mixture with E2-2 (yellowish white powder, 2.65 g).

LCMS: m/z 381, 383 $[M+H]^+$

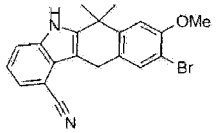
HPLC retention time: 3.03 min (analysis condition S)

[Example 233]

Compound E2-2

9-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile

[0725]



[0726] The title compound was obtained as a by-product of the synthesis of Compound E2-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 11. 70 (1 H, s), 7.69 (1 H, dd, J = 8. 1, 0. 8 Hz), 7. 55 (1 H, s), 7. 48 (1 H, dd, J = 7.4, 0. 8 Hz), 7. 27 (1 H, s), 7. 22 (1 H, dd, J = 8. 1, 7. 4 Hz), 4. 23 (2 H, s), 3. 91 (3 H, s), 1. 70 (6 H, s).

LCMS: m/z 381, 383 $[M+H]^+$

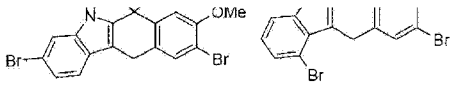
HPLC retention time: 2.92 min (analysis condition S)

[Example 234]

Compound E2-3, Compound E2-4

3,9-Dibromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole 1,9-Dibromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole

[0727]



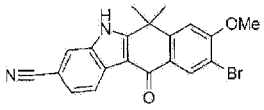
[0728] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared (as a mixture) from Compound E1.

[Example 235]

Compound E3-1-1

9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0729]



[0730] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound E2-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12. 82 (1 H, s), 8. 30 (2 H, s+d), 8. 03 (1 H, s), 7. 61 (1 H, dd, J = 8. 2, 1. 4 Hz), 7. 49 (1 H, s), 4.04 (3 H, s), 1. 81 (6 H, s).

LCMS: m/z 395, 397 $[M+H]^+$

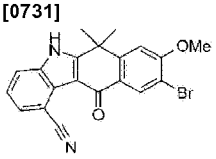
HPLC retention time: 2.77 min (analysis condition S)

[Example 236]

Compound E3-1-2

9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile

[0731]



[0732] The title compound was obtained as a by-product of the synthesis of Compound E3-1-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12. 84 (1 H, s), 8. 31 (1 H, s), 7. 86 (1 H, dd, J = 8. 2, 0. 9 Hz), 7. 70 (1 H, d, J = 7. 1 Hz), 7. 47 (1 H, s), 7. 43 (1 H, t, J = 7. 8 Hz), 4.04 (3 H, s), 1. 81 (6 H, s).

LCMS: m/z 395, 397 $[M+H]^+$

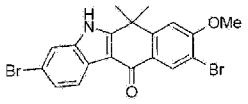
HPLC retention time: 2.42 min (analysis condition S)

[Example 237]

Compound E3-1-3

3,9-Dibromo-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[0733]



[0734] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound E2-3 and Compound E2-4 (mixture).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.42 (1 H, s), 8. 28 (1 H, s), 8. 09 (1 H, d, J = 8. 2 Hz), 7.68 (1 H, d, J = 1. 6 Hz), 7. 47 (1 H, s), 7. 39 (1 H, dd, J = 8. 3, 1. 7 Hz), 4. 03 (3 H, s), 1. 78 (6 H, s).

LCMS: m/z 448, 450, 452 $[M+H]^+$

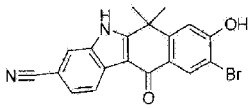
HPLC retention time: 2.93 min (analysis condition S)

[Example 238]

Compound E3-2

9-Bromo-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0735]



[0736] 9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 1.0 g, 2.53 mmol) was dissolved in NMP (10 mL), added with NaOMe (683 mg, 5 eq.) and 1-dodecanethiol (3.0 mL, 5 eq.), and stirred at 160°C for 1 hr. The reaction solution was added to 0.5 N aqueous solution of hydrochloric acid, and then extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with MeOH, and the solid remaining after dissolution was filtered to obtain the title compound (yellow powder, 1.88 g, 65%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.77 (1 H, s), 11. 13 (1 H, d, J = 2. 4 Hz), 8. 31 (1 H, dd, J = 7. 9, 2. 4 Hz), 8. 25 (1 H, d, J = 3.0 Hz), 8.01 (1 H, s), 7. 61 (1 H, d, J = 7.9 Hz), 7. 28 (1 H, d, J = 2.4 Hz), 1. 74 (6H, s).

LCMS: m/z 381, 383 $[M+H]^+$

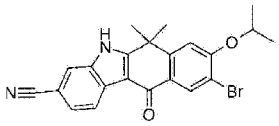
HPLC retention time: 2.40 min (analysis condition S)

[Example 239]

Compound E3-3

9-Bromo-8-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0737]



[0738] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from

Compound E3-2 and 2-bromopropane.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.77 (1 H, s), 8. 29 (2 H, s+d), 8. 01 (1 H, s), 7. 60 (1 H, d, J = 8. 1 Hz), 7. 50 (1 H, s), 5. 03 (1 H, m), 1. 79 (6 H, s), 1. 36 (6 H, d, J = 5. 9 Hz).

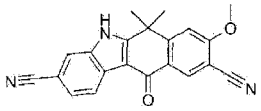
LCMS: m/z 423, 425 $[M+H]^+$
HPLC retention time: 2.98 min (analysis condition S)

[Example 240]

Compound E4-1

8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3,9-dicarbonitrile

[0739]



[0740] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound E3-1-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12. 88 (1 H, br. s), 8.43 (1 H, s), 8. 30 (1 H, d, J = 8. 2 Hz), 8. 05 (1 H, d, J = 0.5 Hz), 7. 65-7. 62 (2 H, m), 4.11 (3 H, s), 1. 84 (6 H, s).

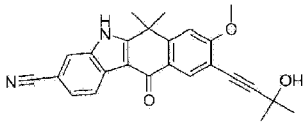
LCMS: m/z 342 $[M+H]^+$
HPLC retention time: 2.23 min (analysis condition S)

[Example 241]

Compound E4-2-1

9-(3-Hydroxy-3-methyl-but-1-ynyl)-8-methoxy-6,6-dimethyl-11-oxo-6,1 1-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0741]



[0742] 9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 50 mg, 0.13 mmol), bis (acetonitrile)dichloropalladium (II) (1.64 mg, 0.05 eq.), XPhos (9.05 mg, 0.15 eq.), cesium carbonate (185 mg, 4.5 eq.) and 3-methyl-1-butyn-1-ol (18.6 µl, 1.5 eq.) were dissolved in acetonitrile and stirred at 85°C for 2 hr. The reaction solution was added to water, and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by HPLC to obtain the title compound (brown solid, 21.3 mg, 42%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 8. 1 Hz), 8. 11 (1 H, s), 8.00 (1 H, s), 7. 57 (1 H, d, J = 8. 1 Hz), 7. 40 (1 H, s), 5. 50 (1 H, s), 3. 95 (3 H, s), 2. 54 (1 H, s), 1. 79 (6 H, s), 1. 49 (6 H, s).

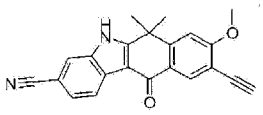
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition S)

[Example 242]

Compound E4-2-2

9-Ethynyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0743]



[0744] 9-(3-Hydroxy-3-methyl-but-1-ynyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E4-2-1, 21.3 mg, 0.05 mmol) and sodium hydride (3.2 mg, 1.5 eq.) were dissolved in THF, and the mixture was stirred overnight at 50°C. Water was added to the reaction solution and the residues obtained after concentration under reduced pressure were purified by HPLC to obtain the title compound (brown solid, 9.6 mg, 31%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.26 (1 H, d, J = 8. 2 Hz), 8. 16 (1 H, s), 7.97 (1 H, s), 7.53 (1 H, d, J = 8. 2 Hz), 7. 41 (1 H, s), 4. 32 (1 H, s), 4.00 (3 H, s), 1. 79 (6 H, s).

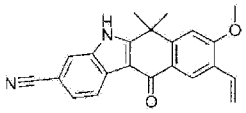
LCMS: m/z 341 $[M+H]^+$
HPLC retention time: 2.27 min (analysis condition S)

[Example 243]

Compound E4-3

8-Methoxy-6,6-dimethyl-11-oxo-9-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0745]



[0746] 9-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 50 mg, 0.13 mmol), [1,1'-bis (diphenylphosphino)ferrocene]palladium (II) dichloride dichloromethane complex (1 : 1) (10.3 mg, 0.1 eq.), TEA (53 µl, 3 eq.) and potassium vinyltrifluoroborate (51 mg, 3 eq.) were dissolved in n-propanol and the mixture was stirred at 60°C for 5 days. The reaction solution was added to water and then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (brown powder, 25 mg, 19%).

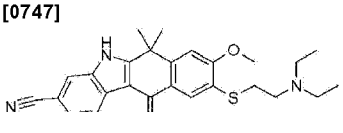
LCMS: m/z 343 $[M+H]^+$
HPLC retention time: 2.55 min (analysis condition S)

[Example 244]

Compound E4-4

9-(2-Diethylamino-ethylsulfanyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0747]



Ö

[0748] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound E3-1-1.

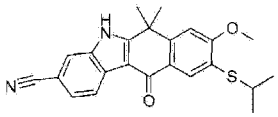
LCMS: m/z 448 $[M+H]^+$
HPLC retention time: 2.05 min (analysis condition U)

[Example 245]

Compound E4-5

9-Isopro-pylsulfanyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0749]



[0750] Under the same conditions as the method for synthesizing Compound B2-17, the title compound was prepared from Compound E3-1-1 and sodium salt of propane-2-thiol.

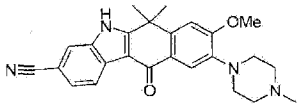
LCMS: m/z 391 $[M+H]^+$
HPLC retention time: 2.98 min (analysis condition U)

[Example 246]

Compound E4-6

8-Methoxy-6,6-dimethyl-9-(4-methylpiperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0751]



[0752] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound E3-1-1 and 1-methylpiperazine.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 8.25 (1 H, d, J = 7. 8 Hz), 7. 93 (1 H, s), 7.65 (1 H, s), 7. 50 (1 H, d, J = 6.8 Hz), 7. 25 (1 H, s), 3. 93 (3 H, s), 3. 02 (4 H, br), 2. 22 (3 H, s), 1. 73 (6 H, s).

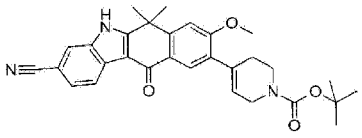
LCMS: m/z 415 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition U)

[Example 247]

Compound E4-7-1

4-(3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

[0753]



[0754] To 9-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E3-1-1, 300 mg, 0.759 mmol), 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester (282 mg, 0.911 mmol, 1.2 eq.), $Pd(PPh_3)_2Cl_2$ (26.6 mg, 0.0379 mmol, 0.05 eq.) and sodium carbonate (241 mg, 2.28 mmol, 3.0 eq.), DME (5 ml) and water (1 ml) were added. The mixture was subjected to reduced pressure under ultrasonication treatment, followed by flushing with nitrogen gas. This procedure was repeated five times and then degassed. The mixture was stirred at 80°C for 80 min under nitrogen atmosphere. $Pd(PPh_3)_2Cl_2$ (26.6 mg, 0.0379 mmol, 0.05 eq.) was added and the mixture was further stirred at 80°C for 20 min. Then, the mixture was cooled to room temperature, and added with water and ethyl acetate. The insoluble matters were filtered through Celite. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration, followed by concentration under reduced pressure to obtain the title compound as a crude product (gray powder).

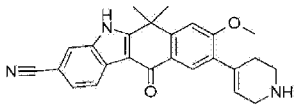
LCMS: m/z 498 $[M+H]^+$
HPLC retention time: 2.85 min (analysis condition S)

[Example 248]

Compound E4-7-2

8-Methoxy-6,6-dimethyl-11-oxo-9-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0755]



[0756] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B4-4-1.

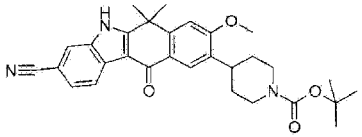
LCMS: m/z 368 $[M+H]^+$
HPLC retention time: 1.27 min (analysis condition S)

[Example 249]

Compound E4-8-1

4-(3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

[0757]



[0758] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound B4-7-1.

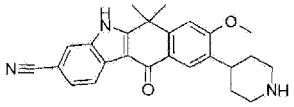
LCMS: m/z 500 $[M+H]^+$
HPLC retention time: 4.18 min (analysis condition W)

[Example 250]

Compound E4-8-2

8-Methoxy-6,6-dimethyl-11-oxo-9-piperidin-4-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0759]



[0760] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound B4-8-1.

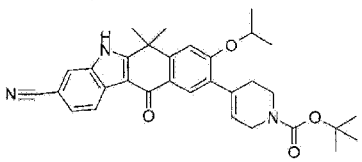
LCMS: m/z 400 $[M+H]^+$
HPLC retention time: 1.35 min (analysis condition S)

[Example 251]

Compound E4-9-1

4-(3-Cyano-8-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-3,6-dihydro--2H-pyridine-1-carboxylic acid tert-butyl ester

[0761]



[0762] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound E3-3.

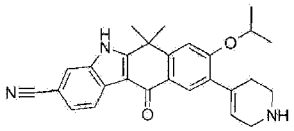
LCMS: m/z 526 $[M+H]^+$
HPLC retention time: 3.13 min (analysis condition S)

[Example 252]

Compound E4-9-2

8-Isopropoxy-6,6-dimethyl-11-oxo-9-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0763]



[0764] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound E4-9-1.

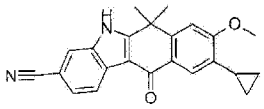
LCMS: m/z 426 $[M+H]^+$
HPLC retention time: 1.40 min (analysis condition S)

[Example 253]

Compound E4-10

9-Cyclopropyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0765]



[0766] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound E3-1-1 and potassium cyclopropyltrifluoroborate.

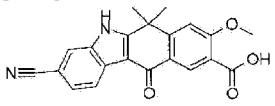
LCMS: m/z 357 $[M+H]^+$
HPLC retention time: 2.62 min (analysis condition S)

[Example 254]

Compound E4-11

3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-carboxylic acid

[0767]



[0768] Under the same conditions as the method for synthesizing Compound B2-28, the title compound was prepared from Compound E3-1-1.

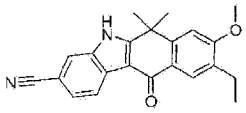
LCMS: m/z 361 $[M+H]^+$
HPLC retention time: 1.68 min (analysis condition S)

[Example 255]

Compound E5-1

9-Ethyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0769]



[0770] The ethyl acetate suspension of 8-methoxy-6,6-dimethyl-11-oxo-9-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E4-3, 25 mg, 0.07 mmol) and palladium carbon (25 mg) were stirred at room temperature for 1 hr under hydrogen atmosphere. The reaction solution was filtered through Celite. The filtrate was concentrated under reduced pressure and the resulting residues were purified by high performance liquid chromatography to obtain the title compound (white solid, 3.2 mg, 13%).

LCMS: m/z 345 $[M+H]^+$

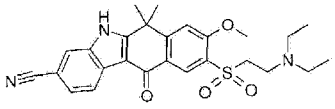
HPLC retention time: 2.62 min (analysis condition S)

[Example 256]

Compound E5-2

9-(2-Diethylamino-ethanesulfonyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0771]



[0772] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound E4-4.

LCMS: m/z 480 $[M+H]^+$

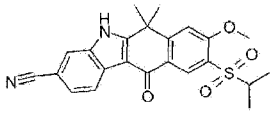
HPLC retention time: 1.97 min (analysis condition U)

[Example 257]

Compound E5-3

8-Methoxy-6,6-dimethyl-11-oxo-9-(propane-2-sulfonyl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0773]



[0774] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound E4-5.

LCMS: m/z 423 $[M+H]^+$

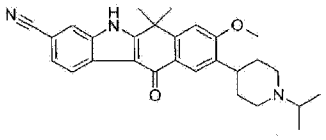
HPLC retention time: 2.40 min (analysis condition U)

[Example 258]

Compound E5-4

9-(1-Isopropyl-piperidin-4-yl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0775]



[0776] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound E4-8-2 and acetone.

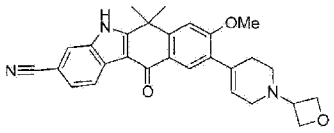
LCMS: m/z 442 $[M+H]^+$
HPLC retention time: 1.48 min (analysis condition S)

[Example 259]

Compound E5-5

8-Methoxy-6,6-dimethyl-9-(1-oxetan-3-yl-1,2,3,6-tetrahydro-pyridin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0777]



[0778] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound E4-7-2 and oxetan-3-one.

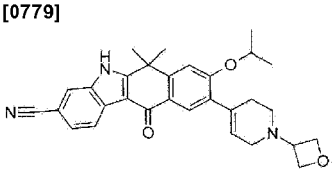
LCMS: m/z 454 $[M+H]^+$
HPLC retention time: 1.32 min (analysis condition S)

[Example 260]

Compound E5-6

8-Isopropoxy-6,6-dimethyl-9-(1-oxetan-3-yl-1,2,3,6-tetrahydro-pyridin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0779]



[0780] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from

Compound E4-9-2 and oxetan-3-one.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.71 (1 H, s), 8. 31 (1 H, d, J = 8. 2 Hz), 7.99 (1 H, s), 7. 94 (1 H, s), 7. 58 (1 H, d, J = 7. 6 Hz), 7. 33 (1 H, s), 5. 84 (1. 0 H, m), 4.95 (1 H, m), 4.56 (4 H, dt, J = 17. 4, 6. 3 Hz), 3. 56 (1 H, m), 3. 01 (2 H, br), 1. 78 (6 H, s), 1.34 (6 H, d, J = 5.9 Hz).

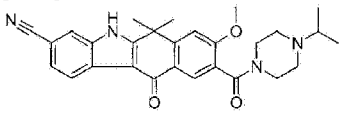
LCMS: m/z 482 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 261]

Compound E5-7

9-(4-Isopropyl-piperazin-1-carbonyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0781]



[0782] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound E4-11 and 1-isopropylpiperazine.

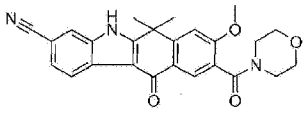
LCMS: m/z 471 $[M+H]^+$
HPLC retention time: 1.18 min (analysis condition S)

[Example 262]

Compound E5-8

8-Methoxy-6,6-dimethyl-9-(morpholine-4-carbonyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0783]



[0784] Under the same conditions as the method for synthesizing Compound B3-15, the title compound was prepared from Compound E4-11 and morpholine.

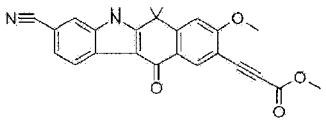
LCMS: m/z 430 $[M+H]^+$
HPLC retention time: 1.68 min (analysis condition S)

[Example 263]

Compound E6-1

(3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-propionic acid methyl ester

[0785]



[0786] To the mixture of 9-ethynyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E4-2, 27 mg, 0.079 mmol), palladium (II) chloride (2.0 mg, 0.14 eq.), copper (II) chloride (25.0 mg, 2.2 eq.), and sodium acetate (14.1 mg, 2.13 eq.), methanol (1.5 mL) was added, and then the mixture was stirred at room temperature for 2 days under carbon monoxide atmosphere. The mixture was extracted with water and ethyl acetate and the insoluble matters were filtered off. The organic layer was washed with brine and dried over magnesium sulfate. The residues obtained after filtration and concentration under reduced pressure were washed with dichloromethane to obtain the title compound (13.9 mg, 44%).

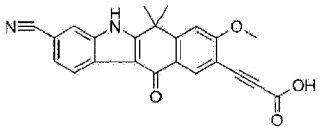
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 2.81 min (analysis condition F)

[Example 264]

Compound E6-2

(3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-propynoic acid

[0787]



[0788] (3-Cyano-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-propynoic acid methyl ester (Compound E6-1, 15.2 mg, 0.038 mmol) was dissolved in a mixture solvent of methanol (1.5 mL) and THF (0.5 mL), added with 2 N aqueous solution of potassium hydroxide (5 drops), and then stirred at room temperature overnight. 0.5 N Hydrochloric acid was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The solids obtained after filtration and concentration under reduced pressure were washed with dichloromethane and purified by HPLC to obtain the title compound (white solid, 9.6 mg, 66%).

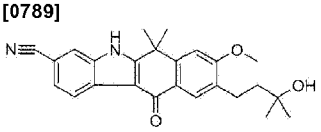
LCMS: m/z 385 $[M+H]^+$
HPLC retention time: 2.35 min (analysis condition F)

[Example 265]

Compound E6-3

9-(3-Hydroxy-3-methyl-butyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0789]



[0790] 9-(3-Hydroxy-3-methyl-but-1-ynyl)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound E4-2-1, 21.0 mg, 0.0527 mmol) was dissolved in ethanol (15 mL) and N,N-dimethylacetamide (2 mL), added with 10% Pd/C (6.7 mg), and then stirred at room temperature overnight under hydrogen atmosphere. The reaction solution was filtered and concentrated under reduced pressure. The resulting residues were diluted with ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting solid was washed with dichloromethane to obtain

the title compound (yellow powder, 16.9 mg, 80%).

LCMS: m/z 403 $[M+H]^+$

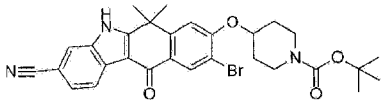
HPLC retention time: 5.39 min (analysis condition H)

[Example 266]

Compound F1-1

4-(9-Bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yloxy)-piperidine-1-carboxylic acid tert-butyl ester

[0791]



[0792] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound E3-2 and 4-trifluoromethanesulfonyloxy-piperidine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 564, 566 $[M+H]^+$

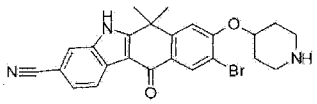
HPLC retention time: 3.30 min (analysis condition S)

[Example 267]

Compound F1-2

9-Bromo-6,6-dimethyl-11-oxo-8-(piperidin-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0793]



[0794] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound F1-1.

LCMS: m/z 464, 466 $[M+H]^+$

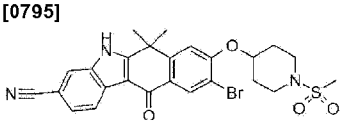
HPLC retention time: 1.52 min (analysis condition S)

[Example 268]

Compound F1-3

9-Bromo-8-(1-methanesulfonyl-piperidin-4-yl oxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3 -carbonitrile

[0795]



[0796] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound F1-2 and methanesulfonyl chloride.

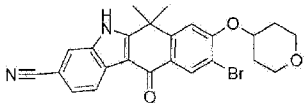
LCMS: m/z 542, 544 $[M+H]^+$
HPLC retention time: 2.57 min (analysis condition S)

[Example 269]

Compound F1-4

9-Bromo-6,6-dimethyl-11-oxo-8-(tetrahydro-pyran-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0797]



[0798] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound E3-2 and tetrahydropyran-4-ol.

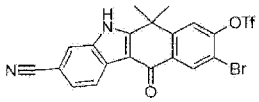
LCMS: m/z 465, 467 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition S)

[Example 270]

Compound F2

Trifluoro-methanesulfonic acid 9-bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[0799]



[0800] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound E3-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.99 (1 H, s), 8. 51 (1 H, s), 8. 31 (1 H, dd, J = 8.2, 0.7 Hz), 8.17 (1 H, s), 8. 07 (1 H, s), 7. 67 (1 H, dd, J = 8. 2, 1.4 Hz), 1. 81 (6 H, s).

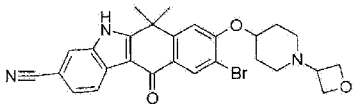
LCMS: m/z 513, 515 $[M+H]^+$
HPLC retention time: 3.13 min (analysis condition S)

[Example 271]

Compound F3-1

9-Bromo-6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0801]



[0802] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F1-2 and oxetan-3-one.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.29(1 H, d, 8 Hz), 8. 29(1 H, s), 8. 01(1 H, s), 7. 60(1 H, d, 8 Hz), 7. 55(1 H, s), 5. 00-4. 95(1 H, m), 4. 55(2 H, dd, 8, 8 Hz), 4. 44(2 H, dd, 8, 8 Hz), 2. 52-2. 46(1 H, m), 2. 33-2. 29(2 H, m), 1. 96-1. 94(2 H, m), 1. 79(8 H, br. s)

LCMS: m/z 519, 521 $[M+H]^+$

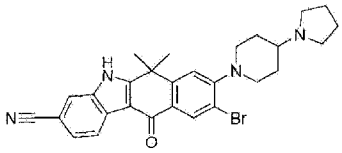
HPLC retention time: 2.78 min (analysis condition W)

[Example 272]

Compound F3-2

9-Bromo-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0803]



[0804] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and 4-pyrrolidin-1-yl-piperidine.

LCMS: m/z 517, 519 $[M+H]^+$

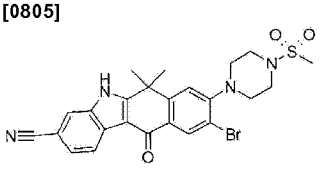
HPLC retention time: 1.70 min (analysis condition S)

[Example 273]

Compound F3-3

9-Bromo-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0805]



[0806] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and 1-methanesulfonylpiperazine.

LCMS: m/z 527, 529 $[M+H]^+$

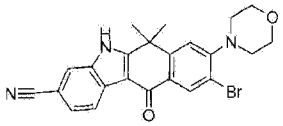
HPLC retention time: 2.48 min (analysis condition S)

[Example 274]

Compound F3-4

9-Bromo-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0807]



[0808] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and morpholine.

LCMS: m/z 450, 452 $[M+H]^+$

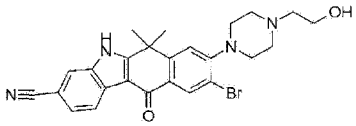
HPLC retention time: 2.65 min (analysis condition S)

[Example 275]

Compound F3-5

9-Bromo-8-[4-(2-hydroxy-ethyl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0809]



[0810] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and 2-piperazin-1-yl ethanol.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.26 (2.0 H, s+d), 7.97 (1 H, s), 7.54 (1 H, d, J = 8.7 Hz), 7.43 (1 H, s), 4.45 (1 H, t, J = 5.4 Hz), 3.55 (2 H, q, J = 5.8 Hz), 3. 17 (4 H, br), 2.66 (2 H, br), 1.76 (6 H, s).

LCMS: m/z 493, 495 $[M+H]^+$

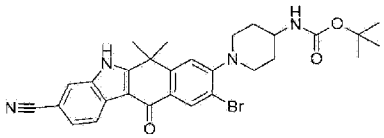
HPLC retention time: 1.43 min (analysis condition S)

[Example 276]

Compound F3-6-1

[1-(9-Bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester

[0811]



[0812] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and piperidin-4-yl-carbamic acid tert-butyl ester.

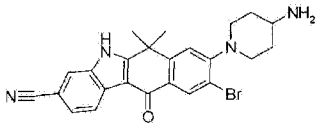
LCMS: m/z 563, 565 $[M+H]^+$
HPLC retention time: 3.05 min (analysis condition S)

[Example 277]

Compound F3-6-2

8-(4-Amino-piperidin-1-yl)-9-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0813]



[0814] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound F3-6-1.

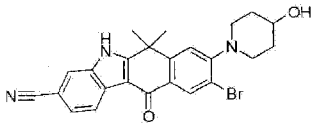
LCMS: m/z 463, 465 $[M+H]^+$
HPLC retention time: 1.47 min (analysis condition S)

[Example 278]

Compound F3-7

9-Bromo-8-(4-hydroxy-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0815]



[0816] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and piperidin-4-ol.

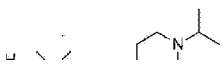
LCMS: m/z 464, 466 $[M+H]^+$
HPLC retention time: 2.25 min (analysis condition S)

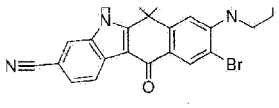
[Example 279]

Compound F3-8

9-Bromo-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0817]





[0818] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and 1-isopropylpiperazine.

LCMS: m/z 491, 493 $[M+H]^+$

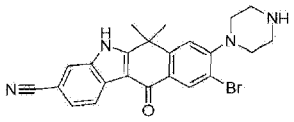
HPLC retention time: 1.58 min (analysis condition S)

[Example 280]

Compound F3-9

9-Bromo-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0819]



[0820] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and piperazine.

^{1}H-NMR (DMSO-d_6) δ : 8.30-8.24 (2 H, m), 8.00 (1 H, s), 7.63-7.58 (1 H, m), 7.37 (1 H, s), 3.10-3.01 (4 H, m), 2.91-2.85 (4 H, m), 1.76 (6 H, s)

LCMS: m/z 449, 451 $[M+H]^+$

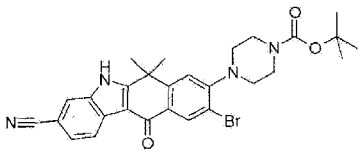
HPLC retention time: 1.45 min (analysis condition S)

[Example 281]

Compound F3-10

4-(9-Bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0821]



[0822] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and piperazine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 549, 551 $[M+H]^+$

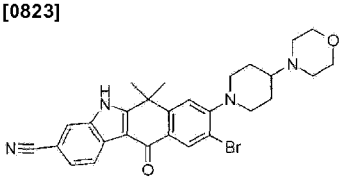
HPLC retention time: 4.61 min (analysis condition W)

[Example 282]

Compound F3-11

9-Bromo-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0823]



[0824] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound F2 and 4-piperidin-4-yl morpholine.

^{1}H-NMR (DMSO-d_6) δ : 8.30-8. 24 (2 H, m), 8.00 (1 H, s), 7.59 (1 H, d, J = 8.2 Hz), 7.42 (1 H, s), 3.66-3.45 (6 H, m), 2.80 (2 H, t, J = 11.1 Hz), 2.38-2.28 (1 H, m), 1.96-1.87 (2 H, m), 1.75 (6 H, s), 1.66-1.56 (2 H, m)

LCMS: m/z 533, 535 $[M+H]^+$

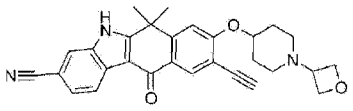
HPLC retention time: 1.53 min (analysis condition S)

[Example 283]

Compound F4-1-1

9-Ethynyl-6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0825]



[0826] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F3-1.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.30(1 H, d, 8 Hz), 8.17(1 H, s), 8.01(1 H, s), 7.60(1 H, d, 8 Hz), 7.50(1 H, s), 4.87-4.83(1 H, m), 4.55(2 H, dd, 4, 4 Hz), 4. 45(2 H, dd, 4, 4 Hz), 3.44(1 H, ddd, 4, 4, 4 Hz), 2.33-2.24(2 H, m), 1.99-1.91(2 H, m), 1.78(8 H, br. s)

LCMS: m/z 466 $[M+H]^+$

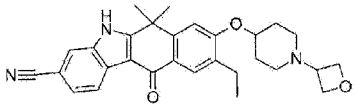
HPLC retention time: 2.67 min (analysis condition W)

[Example 284]

Compound F4-1-2

9-Ethyl-6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0827]



[0828] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from

Compound F4-1-1.

LCMS: m/z 470 $[M+H]^+$

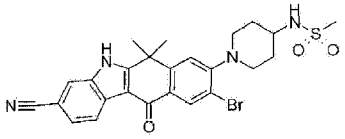
HPLC retention time: 2.74 min (analysis condition W)

[Example 285]

Compound F4-2

N-[1-(9-Bromo-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-pipendin-4-yl]-methanesulfonamide

[0829]



[0830] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound F3-6-2 and methanesulfonyl chloride.

LCMS: m/z 541, 543 $[M+H]^+$

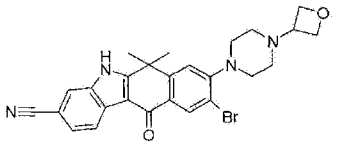
HPLC retention time: 2.37 min (analysis condition S)

[Example 286]

Compound F4-3

9-Bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0831]



[0832] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F3-9 and 1-oxetan-3-one.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.83 (1 H, br. s), 8.31-8.32 (1 H, m), 8. 27-8.29 (1 H, m), 8.01-8.04 (1 H, m), 7.59-7.64 (1 H, m), 7.48 (1 H, s), 4.59 (2 H, dd, J = 6.3, 6.3 Hz), 4.48 (2 H, dd, J = 6.3, 6.3 Hz), 3.52 (1 H, t, J = 6.3 Hz), 3.12-3. 25 (4 H, m), 2.44-2.54 (4 H, m), 1.78 (6 H, s).

LCMS: m/z 505, 507 $[M+H]^+$

HPLC retention time: 1.45 min (analysis condition S)

Hydrochloric acid salt of Compound F4-3

9-Bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with DMSO and 6 N hydrochloric acid (1.05 eq.) and dissolved therein. After freeze-drying, crystallization was performed by using ethanol comprising 25% water to obtain monohydrochloric acid salt of 9-bromo-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.91 (1 H, br.s), 11.70(1 H, br. s), 8.32-8.29(2 H, m), 8.04(1 H, s), 7.64-7.62(1 H, m), 7.52(1 H, s), 4.89-4.62(4 H, br. m), 3. 66-3.39(1 H, m), 3.31-3.05(8 H, br. m), 1.81 (6 H, s)

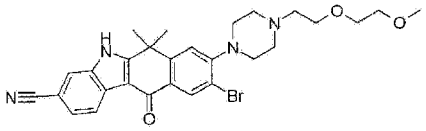
LCMS: m/z 505, 507 $[M+H]^+$

[Example 287]

Compound F4-4

9-Bromo-8-{4-[2-(2-methoxy-ethoxy)-ethyl]-piperazin-1-yl}-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0833]



[0834] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound F3-9 and 1-bromo-2-(2-methoxyethoxy)ethane.

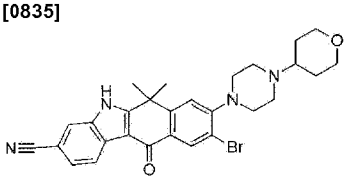
LCMS: m/z 551, 553 $[M+H]^+$
HPLC retention time: 2.80 min (analysis condition W)

[Example 288]

Compound F4-5

9-Bromo-6,6-dimethyl-11-oxo-8-[4-(tetrahydro-pyran-4-yl)-piperazin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0835]



[0836] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F3-9 and tetrahydropyran-4-one.

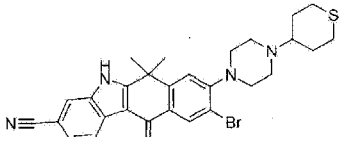
LCMS: m/z 533, 535 $[M+H]^+$
HPLC retention time: 2.67 min (analysis condition W)

[Example 289]

Compound F4-6

9-Bromo-6,6-dimethyl-11-oxo-8-[4-(tetrahydro-thiopyran-4-yl)-piperazin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0837]



O

[0838] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F3-9 and tetrahydrothiopyran-4-one.

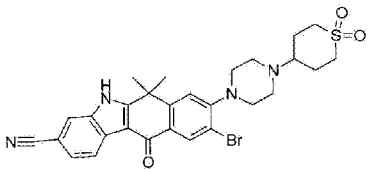
LCMS: m/z 549, 551 $[M+H]^+$
HPLC retention time: 2.86 min (analysis condition W)

[Example 290]

Compound F4-7

9-Bromo-8-[4-(1,1-dioxo-hexahydro-1λ6-thiopyran-4-yl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0839]



[0840] Under the same conditions as the method for synthesizing Compound B3-8, the title compound was prepared from Compound F4-6.

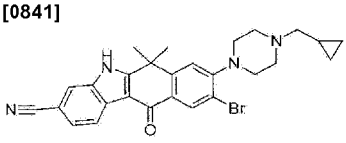
LCMS: m/z 581, 583 $[M+H]^+$
HPLC retention time: 2.66 min (analysis condition W)

[Example 291]

Compound F4-8

9-Bromo-8-(4-cyclopropylmethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0841]



[0842] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound F3-9 and bromomethylcyclopropane.

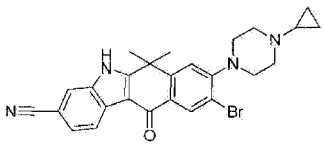
LCMS: m/z 503, 505 $[M+H]^+$
HPLC retention time: 2.81 min (analysis condition W)

[Example 292]

Compound F4-9

9-Bromo-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0843]



[0844] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F3-9 and (1-ethoxy-cyclopropoxy)-trimethyl-silane.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.22-8.30 (2 H, m), 8.00 (1 H, s), 7.56 (1 H, d, J = 7.9 Hz), 7.43 (1 H, s), 3.30(1 H, d, J = 5.8 Hz), 3.11 (4 H, s), 2.75 (4 H, s), 1.75 (6H, s), 0.47 (2 H, d, J = 5.8 Hz), 0.34 (2H, d, J = 5.8 Hz)

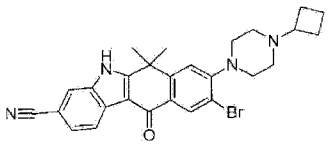
LCMS: m/z 489, 491 $[M+H]^+$
HPLC retention time: 1.68 min (analysis condition S)

[Example 293]

Compound F4-10

9-Bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0845]



[0846] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F3-9 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.23-8.29 (2 H, m), 8.00 (1 H, s), 7.55 (1 H, d, 7.9 Hz), 7.45 (1 H, s), 4.04-4.15 (1 H, m), 3.10-3.20 (4 H, m), 2.39-2.48 (4 H, m), 1.97-2.06 (2 H, m), 1.78-1.88 (2 H, m), 1.77 (6 H, s), 1.61-1.72 (2 H, m)

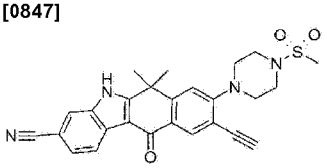
LCMS: m/z 503, 505 $[M+H]^+$
HPLC retention time: 2.78 min (analysis condition W)

[Example 294]

Compound F5-1

9-Ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0847]



[0848] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F3-3.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.78 (1 H, s), 8.31 (1 H, dd, J = 8.1, 0. 7 Hz), 8.19 (1 H, s), 8.02 (1 H, dd, J = 1.4, 0.7 Hz), 7.61 (1 H, dd, J = 8.2, 1.4 Hz), 7.33 (1 H, s), 4.55 (1 H, s), 3.43 (4 H, br), 2.98 (3 H, s), 1.79 (6 H, s).

LCMS: m/z 473 $[M+H]^+$

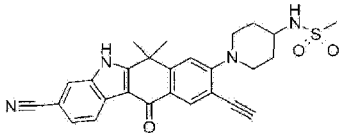
HPLC retention time: 2.27 min (analysis condition S)

[Example 295]

Compound F5-2

N-[1-(3-Cyano-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)piperidin-4-yl]-methanesulfonamide

[0849]



[0850] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F4-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.98 (1 H, s), 8.30 (1 H, d, J = 8.1 Hz), 8.15 (1 H, s), 8.02 (1 H, s), 7.61 (1 H, d, J = 7.9 Hz), 7.23 (2 H, s+d), 4. 55 (1 H, s), 3. 79 (2 H, brd), 2.95 (4 H, br), 1.96 (2 H, brd), 1.78 (3 H, s), 1.65 (2 H, brd).

LCMS: m/z 487 $[M+H]^+$

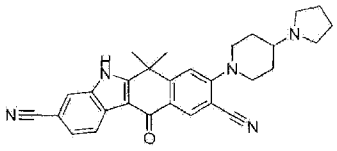
HPLC retention time: 2.15 min (analysis condition S)

[Example 296]

Compound F5-3

6,6-Dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3,9-dicarbonitrile

[0851]



[0852] Under the same conditions as the method for synthesizing Compound A5-2, the target compound was prepared from Compound F3-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.33 (1 H, d, J = 1.3 Hz), 8.27 (1 H, dd, J = 7.7, 1.3 Hz), 8.00 (1 H, s), 7.57 (1 H, d, J = 7.7 Hz), 7.40 (1 H, s), 3.74 (2 H, m), 3.19-3.33 (1 H, m), 2.98-3.12 (2 H, m), 2.35-2.62 (2 H, m), 2.11-2.29 (2 H, m), 1. 89-2.06 (2 H, m), 1.78 (6 H, s), 1.54-1.70 (6 H, m).

LCMS: m/z 464 $[M+H]^+$

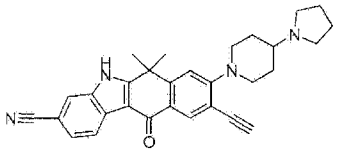
HPLC retention time: 1.55 min (analysis condition S)

[Example 297]

Compound F5-4

9-Ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0853]



[0854] Under the same conditions as the method for synthesizing Compound E4-2-1 and Compound E4-2-2, the title compound was prepared from Compound F3-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 8.2 Hz), 8.14 (1 H, s), 8.00 (1 H, s), 7.58 (1 H, dd, J = 8.1, 1.3 Hz), 7.24 (1H, s), 4.50 (1 H, s), 3.70-3.83 (2 H, m), 3.34-3.48 (1 H, m), 2.83-2.98 (2 H, m), 2.45-2.58 (2 H, m), 2.10-2.23 (2 H, m), 1.90-2.03 (2 H, m), 1.76 (6 H, s), 1.51-1.74 (6 H, m).

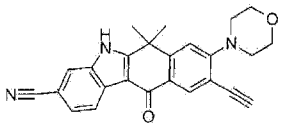
LCMS: m/z 463 $[M+H]^+$
HPLC retention time: 1.60 min (analysis condition S)

[Example 298]

Compound F5-5

9-Ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0855]



[0856] Under the same conditions as the method for synthesizing Compound E4-2-1 and Compound E4-2-2, the title compound was prepared from Compound F3-4.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.82 (1 H, s), 8.31 (1 H, d, J = 7.9 Hz), 8.18 (1 H, s), 8.02 (1 H, s), 7.61 (1 H, d, J = 7.9 Hz), 7.28 (1 H, s), 4.53 (1 H, s), 3. 80 (4 H, s), 3.36 (4 H, s), 1.79 (6 H, s).

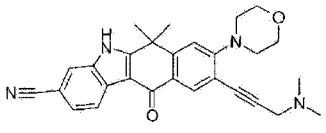
LCMS: m/z 396 $[M+H]^+$
HPLC retention time: 2.32 min (analysis condition S)

[Example 299]

Compound F5-6

9-(3-Dimethylamino-prop-1-ynyl)-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0857]



[0858] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F3-4 and 3-dimethylaminopropyne.

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.52 (1 H, d, J = 7.8 Hz), 8.47 (1 H, s), 7.76 (1 H, s), 7.56 (1 H, d, J = 7.8 Hz), 7.03 (1 H, s), 3.92 (4 H, m), 3.55 (2 H, s), 3.39 (4 H, m), 2.37 (6H, s), 1.83 (6 H, s)

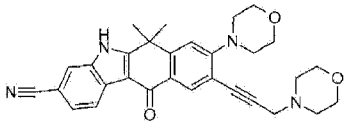
LCMS: m/z 453 $[M+H]^+$

[Example 300]

Compound F5-7

6,6-Dimethyl-8-morpholin-4-yl-9-(3-morpholin-4-yl-prop-1-ynyl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0859]



[0860] To 9-bromo-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound F3-4, 30 mg, 0.067 mmol), 3-bromopropyne (0.01 ml, 0.13 mmol), morpholine (0.029 ml, 0.33 mmol), X-Phos (4.8 mg, 15% mol), $PdCl_2(CH_3CN)_2$ (0.9 mg, 5% mol) and cesium carbonate (87 mg, 0.27 mmol), acetonitrile (2 ml) was added and the mixture was stirred at 80°C for 2 hr. The reaction solution was added to water, and then extracted with dichloromethane. The organic layer was dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the target compound (pale brown solid, 18 mg, 64%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 7.8 Hz), 8.14 (1 H, s), 8. 00 (1 H, s), 7.59 (1 H, d, J = 7.8 Hz), 7.27 (1 H, s), 3.79 (4 H, m), 3.64 (4 H, m), 3. 61 (2 H, s), 3.33 (4 H, m), 2.56 (4 H, m), 1.77 (6 H, s)

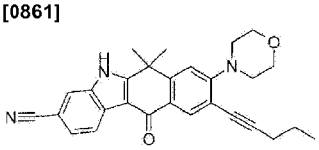
LCMS: m/z 495 $[M+H]^+$ [0497]

[Example 301]

Compound F5-8

6,6-Dimethyl-8-morpholin-4-yl-11-oxo-9-pent-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0861]



[0862] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F3-4 and 1-pentyne.

LCMS: m/z 438 $[M+H]^+$

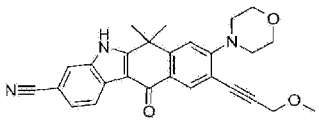
HPLC retention time: 2.88 min (analysis condition S)

[Example 302]

Compound F5-9

9-(3-Methoxy-prop-1-ynyl)-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0863]



[0864] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F3-4 and 3-methoxypropyne.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, J = 7.8 Hz), 8.15 (1 H, s), 8. 01 (1 H, s), 7.60 (1 H, d, J = 7.8 Hz), 7.28 (1 H, s), 4.41 (2 H, s), 3.79 (4 H, m), 3.37 (3 H, s), 3.34 (4 H, m), 1.78 (6 H, s)

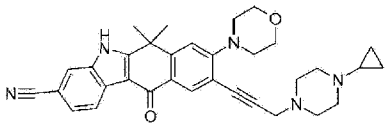
LCMS: m/z 440 $[M+H]^+$

[Example 303]

Compound F5-10

9-[3-(4-Cyclopropyl-piperazin-1-yl)-prop-1-ynyl]-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0865]



[0866] Under the same conditions as the method for synthesizing Compound F5-7, the title compound was prepared from Compound F3-4 and 3-bromopropyne and 4-cyclopropylpiperazine.

LCMS: m/z 534 $[M+H]^+$

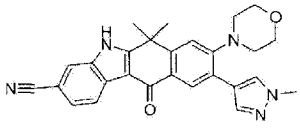
HPLC retention time: 1.40 min (analysis condition S)

[Example 304]

Compound F5-11

6,6-Dimethyl-9-(1-methyl-1H-pyrazol-4-yl)-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0867]



[0868] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F3-4 and 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 7.8 Hz), 8.22 (1 H, s), 8.09 (1 H, s), 7.99(1 H, s), 7.95(1 H, s), 7.56-7.61(1 H, m),

7.36(1 H, s), 3.90(3 H, s), 3.73(4 H, s), 2.95(4 H, s), 1.77 (6 H, s).

LCMS: m/z 452 $[M+H]^+$

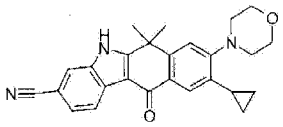
HPLC retention time: 2.18 min (analysis condition U)

[Example 305]

Compound F5-12

9-Cyclopropyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0869]



[0870] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F3-4 and potassium cyclopropyltrifluoroborate.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.45 (1 H, d, J = 7.8 Hz), 7.83(2 H, m), 7.54 (1 H, d, J = 7.8 Hz), 7.20 (1 H, s), 3.96 (4 H, m), 3.24 (4 H, m), 2.25 (1 H, m), 1.80 (6 H, s), 1.09 (2 H, m), 0.93 (2 H, m)

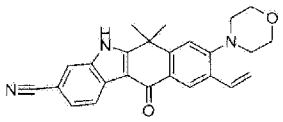
LCMS: m/z 412 $[M+H]^+$

[Example 306]

Compound F5-13

6,6-Dimethyl-8-morpholin-4-yl-11-oxo-9-vinyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0871]



[0872] Under the same conditions as the method for synthesizing Compound B2-24, the title compound was prepared from Compound F3-4 and potassium vinyltrifluoroborate.

LCMS: m/z 398 $[M+H]^+$

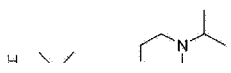
HPLC retention time: 2.67 min (analysis condition U)

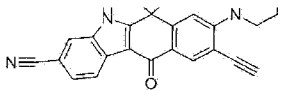
[Example 307]

Compound F5-14

9-Ethynyl-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0873]





[0874] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F3-8.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.73 (1 H, s), 8.31 (1 H, d, J = 9.1 Hz), 8.16 (1 H, d, J = 1.2 Hz), 8.00 (1 H, s), 7.60 (1 H, d, J = 7.9 Hz), 7.25 (1 H, s), 4.50 (1 H, d, J = 1.8 Hz), 2.72 (1 H, m), 2.65 (4 H, s), 1.78 (6 H, s), 1.04 (6 H, d, J = 5.5 Hz).

LCMS: m/z 437 $[M+H]^+$

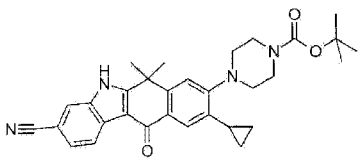
HPLC retention time: 1.48 min (analysis condition S)

[Example 308]

Compound F5-15-1

4-(3-Cyano-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperazine-1-carboxylic acid tert-butyl ester

[0875]



[0876] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F3-10 and potassium cyclopropyltri fluoroborate.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.55(1 H, s), 8.28-8.25(1 H, m), 7.98-7. 95(1 H, m), 7.62(1 H, s), 7.32(1 H, s), 3.56-3.53(4 h, m), 3.09-3.07(4 H, m), 2.22-2. 18(1 H, m), 1.73(6 H, br s), 1.44(9 H, s), 1.08-1.05(2 H, m), 0.77-0.76(2 H, m)

LCMS: m/z 511 $[M+H]^+$

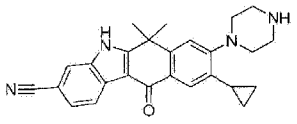
HPLC retention time: 4.50 min (analysis condition W)

[Example 309]

Compound F5-15-2

9-Cyclopropyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0877]



[0878] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound F5-15-1.

LCMS: m/z 411 $[M+H]^+$

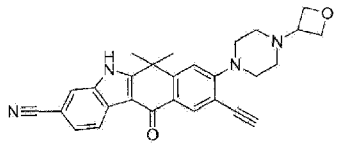
HPLC retention time: 2.67 min (analysis condition W)

[Example 310]

Compound F5-16

9-Ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0879]



[0880] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F4-3.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.77 (1 H, br. s), 8.31 (1 H, d, J = 8.2 Hz), 8.16 (1 H, s), 8.02 (1 H, s), 7.61 (1 H, dd, J = 8.2, 1.3 Hz), 7.27 (1 H, s), 4.59 (2 H, dd, J = 6.6, 6.6 Hz), 4.51 (1 H, s), 4.49 (2 H, dd, J = 6.6, 6.6 Hz), 3.51 (1 H, t, J = 6.6 Hz), 3.35-3.43 (4 H, m), 2.43-2.50 (4H, s), 1.78 (6 H, s).

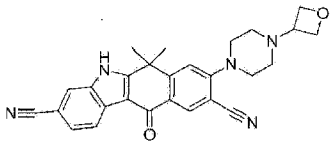
LCMS: m/z 451 $[M+H]^+$
HPLC retention time: 1.40 min (analysis condition S)

[Example 311]

Compound F5-17

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3,9-dicarbonitrile

[0881]



[0882] According to the same method as the method for synthesizing Compound A5-2, the title compound was prepared from Compound F4-3.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.84 (1 H, br. s), 8.36 (1 H, s), 8.32-8. 29 (1 H, d, 8.08 Hz), 8.04 (1 H, s), 7.65-7.62 (1 H, d, 8.08 Hz), 7.44 (1 H, s), 4. 62-4.57 (2 H, m), 4.52-4.47 (2 H, m), 3.81-3.78 (2 H, t, 4.61 Hz), 3.57-3.50 (1 H, m), 3.43 (4 H, m) 2.51 (4 H, m), 1.80 (6 H, s)

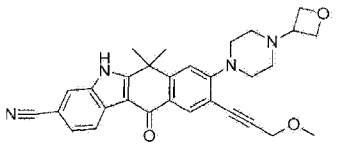
LCMS: m/z 452 $[M+H]^+$

[Example 312]

Compound F5-18

9-(3-Methoxy-prop-1-ynyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0883]



[0884] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 3-methoxypropyne.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.77 (1 H, br. s), 8.32-8.29 (1 H, d, 8. 08 Hz), 8.13 (1 H, s), 8.01 (1 H, s), 7.62-7.59 (1 H, d, 8.08 Hz), 7.27 (1 H, s), 4. 62-4.57 (2 H, m), 4.52-4.47 (2 H, m), 4.39 (2 H, s), 3.53-3.47 (1 H, m), 3.38 (4 H, m), 3.36 (3 H, s), 2.51 (4 H, m), 1.77 (6 H, s)

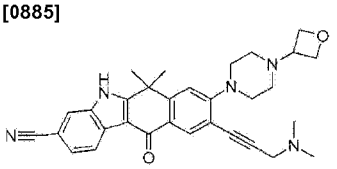
LCMS: m/z 495 $[M+H]^+$

[Example 313]

Compound F5-19

9-(3-Dimethylamino-prop-1-ynyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0885]



[0886] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and dimethyl-prop-2-ynylamine.

LCMS: m/z 508 $[M+H]^+$

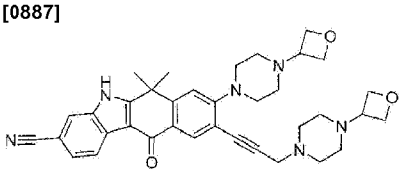
HPLC retention time: 1.07 min (analysis condition S)

[Example 314]

Compound F5-20

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-9-[3-(4-oxetan-3-yl-piperazin-1-yl)-prop-1-ynyl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0887]



[0888] Under the same conditions as the method for synthesizing Compound F5-7, the title compound was prepared from Compound F4-3, 3-bromopropyne and 4-oxetan-3-yl-piperazine.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.30 (1 H, d, J = 7.8 Hz), 8.12 (1 H, s), 8. 00 (1 H, s), 7.59 (1 H, d, J = 7.8 Hz), 7.26 (1 H, s), 4.60-4.42 (8 H, m), 3.61 (2 H, s), 3.60-3.30 (6 H, m), 2.60-2.30 (12 H, m), 1.77 (6 H, s)

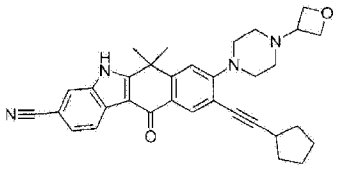
LCMS: m/z 605 $[M+H]^+$

[Example 315]

Compound F5-21

9-Cyclopentylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0889]



[0890] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and cyclopentylacetylene.

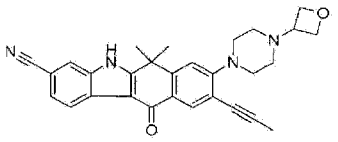
LCMS: m/z 519 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition S)

[Example 316]

Compound F5-22

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0891]



[0892] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and propyne.

^{1}H-NMR(400 MHz, CD_3OD) δ : 8.37 (1 H, d, J = 8.2 Hz), 8.18 (1 H, s), 7. 84 (1 H, s), 7.53 (1 H, d, J = 8.2 Hz), 7.19 (1 H, s), 4.70-4.77 (2 H, m), 4.62-4.68 (2 H, m), 3.57-3.63 (1 H, m), 3.38-3.45 (4 H, m), 2.54-2.61 (4 H, m), 2.10 (3 H, s), 1. 79 (6 H, s)

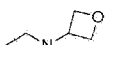
LCMS: m/z 465 $[M+H]^+$
HPLC retention time: 1.90 min (analysis condition U)

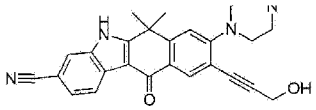
[Example 317]

Compound F5-23

9-(3-Hydroxy-prop-1-ynyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0893]





[0894] Under the same conditions as the method for synthesizing Compound E4-2-1, the TMS complex of the title compound was prepared from Compound F4-3 and trimethylprop-2-ynyloxysilane. By treating the resulting TMS complex with tetrabutylammonium fluoride, the title compound was obtained.

LCMS: m/z 481 $[M+H]^+$

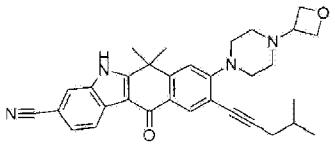
HPLC retention time: 1.30 min (analysis condition S)

[Example 318]

Compound F5-24

6,6-Dimethyl-9-(4-methyl-pent-1-ynyl)-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0895]



[0896] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 4-methylpent-1-yne.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.75 (1 H, br. s), 8.32-8.29 (1 H, d, 8. 08 Hz), 8.08 (1 H, s), 8.01 (1 H, s), 7.62-7.59 (1 H, m), 7.23 (1 H, s), 4.61-4.57 (2 H, m), 4.51-4.46 (2 H, m), 3.51-3.47 (1 H, m), 3.37 (4 H, m), 2.46 (4 H, m), 2.41-2. 39 (2 H, d, 5.94 Hz), 1.92-1.80 (1 H, m), 1.77 (6 H, s), 1.04 (3 H, s), 1.01 (3 H, s)

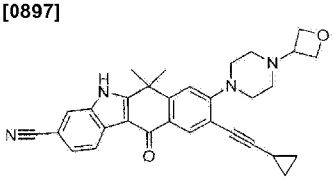
LCMS: m/z 507 $[M+H]^+$

[Example 319]

Compound F5-25

9-Cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0897]



[0898] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and ethynylcyclopropane.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.74 (1 H, br. s), 8.32-8.29 (1 H, d, 8. 08 Hz), 8.05 (1 H, s), 8.00 (1 H, s), 7.62-7.58 (1 H, m), 7.21 (1 H, s), 4.62-4.57 (2 H, m), 4.51-4.47 (2 H, m), 3.53-3.48 (1 H, m), 3.34 (4 H, m), 2.46 (4 H, m), 1.76 (6 H, s), 1.64-1.58 (1 H, m), 0.97-0.89 (2 H, m), 0.76-0.70 (2 H, m)

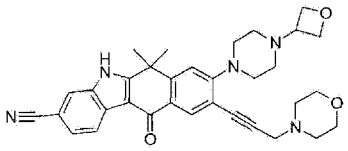
LCMS: m/z 491 $[M+H]^+$

[Example 320]

Compound F5-26

6,6-Dimethyl-9-(3-morpholin-4-yl-prop-1-ynyl)-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0899]



[0900] Under the same conditions as the method for synthesizing Compound F5-7, the title compound was prepared from Compound F4-3, 3-bromopropyne and morpholine.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 7.8 Hz), 8.13 (1 H, s), 8. 02 (1 H, s), 7.59 (1 H, d, J = 7.8 Hz), 7.25 (1 H, s), 4.61-4.48 (4 H, m), 3.64-3.32 (11 H, m), 2.60-2.40 (8 H, m), 1.78 (6 H, s)

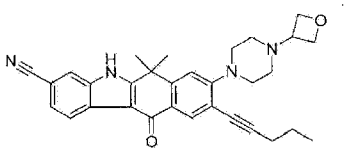
LCMS: m/z 550 $[M+H]^+$

[Example 321]

Compound F5-27

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-pent-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0901]



[0902] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 1-pentyne.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.72 (1 H, br. s), 8.28 (1 H, d, 8.1 Hz), 8.06 (1 H, s), 7.98 (1 H, s), 7.58 (1 H, d, 8.1 Hz), 7.21 (1 H, s), 4.60-4.43 (4 H, m), 3. 53-3.44 (1 H, m), 3.39-3.32 (2 H, m), 1.75 (6 H, s), 1.60-1.53 (4 H, m), 1.01 (3 H, t, 7.3 Hz)

LCMS: m/z 493 $[M+H]^+$

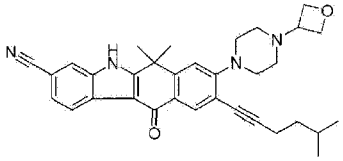
HPLC retention time: 2.17 min (analysis condition U)

[Example 322]

Compound F5-28

6,6-Dimethyl-9-(5-methyl-hex-1-ynyl)-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0903]



[0904] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 5-methylhex-1-yne.

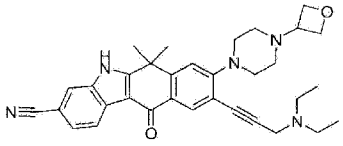
LCMS: m/z 521 $[M+H]^+$
HPLC retention time: 2.37 min (analysis condition U)

[Example 323]

Compound F5-29

9-(3-Diethylamino-prop-1-ynyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0905]



[0906] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 3-diethylaminopropyne.

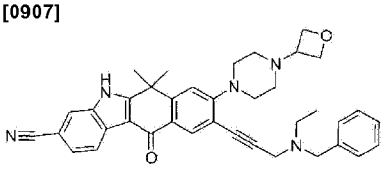
LCMS: m/z 536 $[M+H]^+$
HPLC retention time: 1.13 min (analysis condition S)

[Example 324]

Compound F5-30

9-[3-(Benzyl-ethyl-amino)-prop-1-ynyl]6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0907]



[0908] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 3-benzyl-3-ethylaminopropyne.

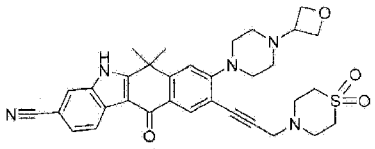
LCMS: m/z 584 $[M+H]^+$
HPLC retention time: 1.32 min (analysis condition S)

[Example 325]

Compound F5-31

9-[3-(1,1-Dioxo-1λ6-thiomorpholin-4-yl)-prop-1-ynyl]-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0909]



[0910] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-3 and 3-(1,1-dioxo-1λ6-thiomorpholin-4-yl)-propyne.

LCMS: m/z 598 $[M+H]^+$

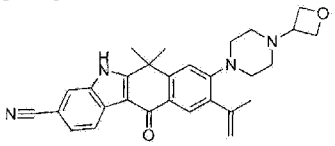
HPLC retention time: 1.35 min (analysis condition S)

[Example 326]

Compound F5-32

9-Isopropenyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0911]



[0912] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-3 and 2-isopropenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.44 (1H, d, J = 7.8 Hz), 8.09 (1 H, s), 7.83 (1 H, s), 7.54 (1 H, d, J = 7.8 Hz), 7.18 (1 H, s), 5.24-5.20 (2 H, m), 4.81-4. 68 (4 H, m), 3.66 (1 H, m), 3.30 (4 H, m), 2.57 (4 H, m), 2.21 (3 H, s), 1.82 (6 H, s)

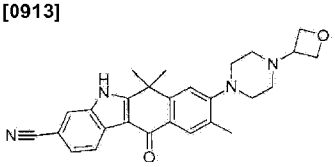
LCMS: m/z 467 $[M+H]^+$

[Example 327]

Compound F5-33

6,6,9-Trimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0913]



[0914] Under the same conditions as the method for synthesizing Compound F5-47, the title compound was prepared from Compound F4-3.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.71 (1 H, br. s), 8.33-8.31 (1 H, d, 8. 08 Hz), 8.01 (1 H, s), 7.97 (1 H, s), 7.62-7.59 (1 H, m), 7.32 (1 H, s), 4.61-4.57 (2 H, m), 4.51-4.47 (2 H, m), 3.55-3.49 (1 H, m), 3.05 (4 H, m), 2.47 (4 H, m), 2. 33 (3 H, s), 1.76 (6 H, s)

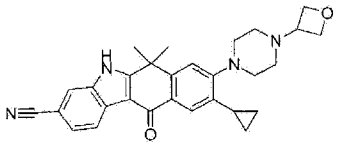
LCMS: m/z 441 $[M+H]^+$

[Example 328]

Compound F5-34

9-Cyclopropyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0915]



[0916] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F5-15-2 and oxetan-3-one.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.32-8.29(1 H, m), 8.00-7.99(1 H, m), 7. 62-7.58(2 H, m), 7.32-7.31(1 H, m), 4.61-4.57(2 H, m), 4.52-4.49(2 H, m), 3.53(1 H, br. s), 3.18(4 H, br. s), 1.75(6 H, s), 1.25-1.23(1 H, m), 1.09-1.04(2 H, m), 0.79-0. 75(2 H, m)

LCMS: m/z 467 $[M+H]^+$

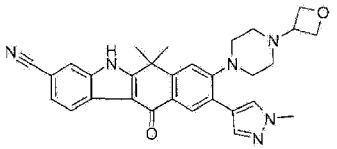
HPLC retention time: 2.74 min (analysis condition W)

[Example 329]

Compound F5-35

6,6-Dimethyl-9-(1-methyl-1H-pyrazol-4-yl)-8-(4-oxetan-3-yl-piperazin-1-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0917]



[0918] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-3 and 1-methyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-1H-pyrazole.

LCMS: m/z 507 $[M+H]^+$

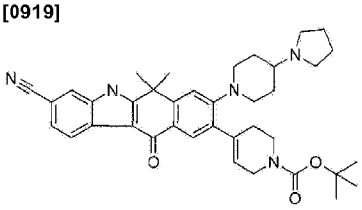
HPLC retention time: 1.75 min (analysis condition U)

[Example 330]

Compound F5-36-1

4-[3-Cyano-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazol-9-yl]-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

[0919]



[0920] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F3-2.

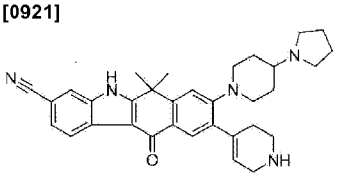
LCMS: m/z 621 $[M+H]^+$
HPLC retention time: 2.58 min (analysis condition U)

[Example 331]

Compound F5-36-2

6,6-Dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-9-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0921]



[0922] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound F5-36-1.

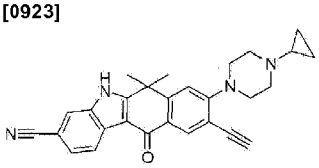
LCMS: m/z 520 $[M+H]^+$
HPLC retention time: 1.82 min (analysis condition U)

[Example 332]

Compound F5-37

8-(4-Cyclopropyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0923]



[0924] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F4-9.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.76 (1 H, br. s), 8.31 (1 H, d, J = 8.1 Hz), 8.15 (1 H, s), 8.01 (1 H, s), 7.61 (1 H, dd, J = 8.1, 1.5 Hz), 7.24 (1 H, s), 4.52 (1 H, s), 3.28-3.36 (4 H, m), 3.17 (1 H, d, J = 5.3 Hz), 2.70-2.77 (4 H, m), 1.76 (6 H, s), 0.47 (2 H, d, J = 5.3 Hz), 0.36 (2 H, d, J = 5.3 Hz).

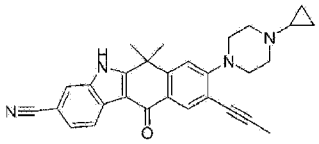
LCMS: m/z 435 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition S)

[Example 333]

Compound F5-38

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0925]



[0926] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-9 and propyne.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.76 (1 H, br. s), 8.31-8.28 (1 H, d, 8. 08 Hz), 8.06 (1 H, s), 8.00 (1 H, s), 7.60-7.57 (1 H, m), 7.19 (1 H, s), 3.29 (4 H, m), 2.74 (4 H, m), 2.55 (1 H, m), 2.13 (3 H, s), 1.75 (6 H, s), 0.51-0.43 (2 H, m), 0. 38-0.32 (2 H, m)

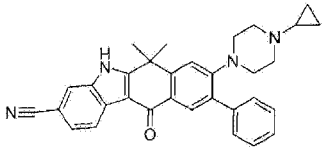
LCMS: m/z 449 $[M+H]^+$

[Example 334]

Compound F5-39

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-phenyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0927]



[0928] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-9 and phenylboric acid.

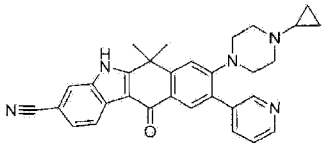
LCMS: m/z 487 $[M+H]^+$
HPLC retention time: 2.15 min (analysis condition U)

[Example 335]

Compound F5-40

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-pyridin-3-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0929]



[0930] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-9 and pyridine-3-boric acid.

LCMS: m/z 488 $[M+H]^+$

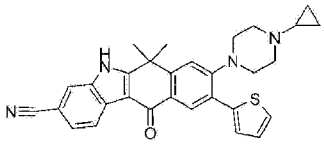
HPLC retention time: 1.53 min (analysis condition U)

[Example 336]

Compound F5-41

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-thiophene-2-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0931]



[0932] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-9 and thiophene-2-boric acid.

LCMS: m/z 493 $[M+H]^+$

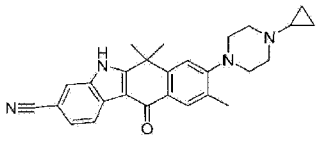
HPLC retention time: 2.13 min (analysis condition U)

[Example 337]

Compound F5-42

8-(4-Cyclopropyl-piperazin-1-yl)-6,6,9-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0933]



[0934] Under the same conditions as the method for synthesizing Compound F5-47, the title compound was prepared from Compound F4-9.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.71 (1 H, br. s), 8.33-8.30 (1 H, d, 8. 08 Hz), 8.00 (1 H, s), 7.96 (1 H, s), 7.61-7.58 (1 H, m), 7.29 (1 H, s), 2.97 (4 H, m), 2.73 (4 H, m), 2.56 (1 H, m), 2.34 (3 H, s), 1.76 (6 H, s), 1.64-1.58 (1 H, m), 0. 50-0.44 (2 H, m), 0.37-0.32 (2 H, m)

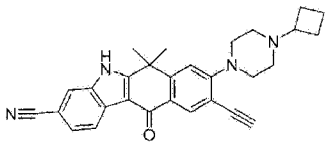
LCMS: m/z 425 $[M+H]^+$

[Example 338]

Compound F5-43

8-(4-Cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0935]



[0936] Under nitrogen atmosphere, to the MeCN (8 ml) suspension of 9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound F4-10, 200 mg, 0.397 mmol), ethynyltriisopropylsilane (268 mg, 3.0 eq.), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (Xphos) (39 mg, 0.2 eq.), $Pd(CH_3CN)_2Cl_2$ (11 mg, 0.1 eq.) and cesium carbonate (518 mg, 4.0 eq.) were added and the mixture was stirred and heated under reflux condition until the reaction is completed. Upon the completion of the reaction, distilled water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/methanol) to obtain 8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-[(triisopropylsilanyl)-ethynyl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (179 mg, 74%).

[0937] To the THF (6 ml) solution of the obtained compound (179 mg, 0.295 mmol), 1 M THF solution (710 µl) of tetrabutylammonium fluoride was added and the mixture was stirred until the reaction is completed. Upon the completion of the reaction, ethyl acetate was added to the reaction solution, which was then washed with distilled water and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were washed with a mixture solvent of ethanol and distilled water to obtain the title compound (67 mg, 92%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.85 (1 H,s), 8.31 (1 H, d, 7.9 Hz), 8. 20 (1 H, s), 8.03 (1 H, s), 7.62 (1 H, d, 7.9 Hz), 7.35 (1 H, s), 4.62 (1 H, s), 3.94-4. 03 (2 H, m), 3.79-3.89 (1 H, m), 3.48-3.54 (2 H, m), 3.27-3.38 (2 H, m), 2.96-3.16 (2 H, m), 2.30-2.41 (2 H, m), 2.16-2.26 (2 H, m), 1.72-1.85 (8 H, m)

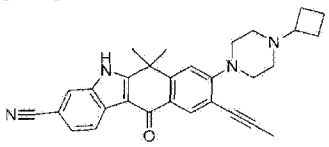
LCMS: m/z 449 $[M+H]^+$
HPLC retention time: 2.69 min (analysis condition W)

[Example 339]

Compound F5-44

8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0938]



[0939] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-10 under propyne gas atmosphere.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.71 (1 H, s), 8.30 (1 H, d, 7.9 Hz), 8. 06 (1 H, s), 8.00 (1 H, s), 7.59 (1 H, d, 7.9 Hz), 7.20 (1 H, s),

2.75-2.83 (1 H, m), 2. 40-2.48 (4 H, m), 2.11 (3 H, s), 1.97-2.06 (2 H, m), 1.76 (6 H, s), 1.62-1.71 (2 H, m)

LCMS: m/z 463 $[M+H]^+$

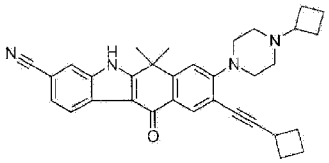
HPLC retention time: 2.80 min (analysis condition W)

[Example 340]

Compound F5-45

9-Cyclobutylethynyl-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0940]



[0941] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F4-10 and ethynylcyclobutane.

LCMS: m/z 503 $[M+H]^+$

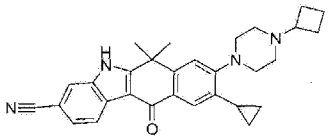
HPLC retention time: 1.85 min (analysis condition S)

[Example 341]

Compound F5-46

8-(4-Cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0942]



[0943] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F5-15-2 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.23(1 H, d, 8 Hz), 7.92(1 H, br. s), 7. 59(1 H, s), 7.47(1 H, br. d, 8 Hz), 7.28(1 H, s), 3.12(4 H, br. s), 2.80(1 H, dddd, 8, 8, 8, 8 Hz), 2.20-2.13(1 H, m), 2.01(2 H, br. s), 1.86-1.68(10 H, m), 1.05(2 H, d, 8 Hz), 0.76(2 H, d, 4 Hz)

LCMS: m/z 465 $[M+H]^+$

HPLC retention time: 2.79 min (analysis condition W)

Hydrochloric acid salt of Compound F5-46

8-(4-Cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with DMSO and 6 N hydrochloric acid (1.05 eq.) and dissolved therein. After freeze-drying, crystallization was performed by using ethanol comprising 25% water to obtain monohydrochloric acid salt of 8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.81(1 H, s), 10.64(1 H, br. s), 8.32-8. 29(1 H, m), 8.01(1 H, s), 7.67(1 H, s), 7.61-7.60(1 H, m), 7.33(1 H, s),4.00-3.39(6 H, m), 3.28-3.02(3 H, m), 2.45-2.05(5 H, m), 1.83-1.77(8 H, m), 1.09-1.07(2 H, m),0.81-0.80(2 H, m)

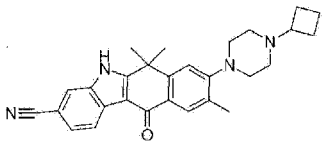
LCMS: m/z 465 $[M+H]^+$

[Example 342]

Compound F5-47

8-(4-Cyclobutyl-piperazin-1-yl)-6,6,9-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0944]



[0945] Under nitrogen atmosphere, to the N,N-dimethyl formamide (1.5 ml) solution of 9-bromo-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound F4-10, 50 mg, 0.099 mmol), trimethyl boroxine (12 mg, 0.1 eq.), tetrakis triphenylphosphine palladium (39 mg, 0.2 eq.), and potassium carbonate (41 mg, 3.0 eq.) were added, and the mixture was stirred at 100°C for 24 hr. Upon the completion of the reaction, distilled water was added to the reaction solution, which was then extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/methanol) to obtain the title compound (25 mg, 58%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.67 (1 H,s), 8.31 (1 H, d, 7.9 Hz), 7. 98 (1 H, s), 7.95 (1 H, s), 7.59 (1 H, d, 7.9 Hz), 7.30 (1 H, s), 2.96-3.04 (4 H, m), 2. 76-2.84 (1 H, m), 2.39-2.48 (4 H, m), 2.32 (3 H, s), 1.78-1.87 (2 H, m), 1.75 (6 H, s), 1.63-1.71 (2 H, m)

LCMS: m/z 439 $[M+H]^+$

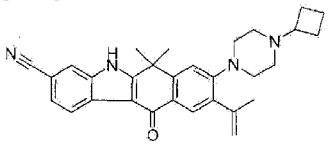
HPLC retention time: 2.66 min (analysis condition W)

[Example 343]

Compound F5-48

8-(4-Cyclobutyl-piperazin-1-yl)-9-isopropenyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0946]



[0947] Under the same conditions as the method for synthesizing Compound E4-7-1, the title compound was prepared from Compound F4-10 and 2-isopropenyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane.

LCMS: m/z 465 $[M+H]^+$

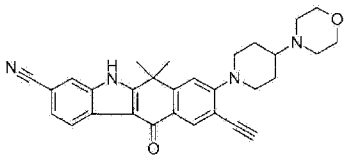
HPLC retention time: 1.63 min (analysis condition S)

[Example 344]

Compound F5-49

9-Ethynyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0948]



[0949] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound F3-11.

LCMS: m/z 479 $[M+H]^+$

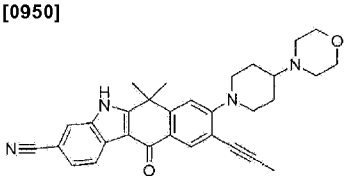
HPLC retention time: 1.90 min (analysis condition U)

[Example 345]

Compound F5-50

6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0950]



[0951] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound F3-11 and propyne gas.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.40 (1 H, d, J = 7.8 Hz), 8.24 (1 H, s), 7.84 (1 H, s), 7.54 (1 H, d, J = 7.8 Hz), 7.14 (1 H, s), 4.01-3.96 (2 H, m), 3.78 (4 H, m), 2.88-2.84 (2 H, m), 2.68 (4 H, m), 2.16-1.73 (5 H, m), 2.16 (3 H, s), 1.80 (6 H, s)

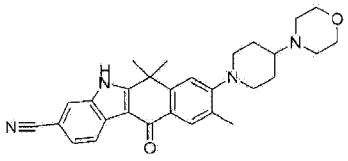
LCMS: m/z 493 $[M+H]^+$

[Example 346]

Compound F5-51

6,6,9-Trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0952]



[0953] Under the same conditions as the method for synthesizing Compound F5-47, the title compound was prepared from Compound F3-11

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.70 (1 H, br. s), 8.33-8.30 (1 H, d, 8. 08 Hz), 8.00 (1 H, s), 7.95 (1 H, s), 7.61-7.58 (1 H, m), 7.28 (1 H, s),, 3.60 (4 H, m), 3.32-3.26 (2 H, m), 2.79-2.69 (2 H, m), 2.32 (3 H, s), 1.95-1.90 (2 H, m), 1.74 (6 H, s), 1.65-1.52 (2 H, m),

LCMS: m/z 469 $[M+H]^+$

Methanesulfonic acid salt of Compound F5-51

6,6,9-Trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with DMSO

and 2 N methanesulfonic acid (1.05 eq.) and dissolved therein. After freeze-drying, crystallization was performed with ethanol to obtain methanesulfonic acid salt of 6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.72(1 H, br.s), 9.60(1 H, br. s), 8.33-8. 31(1 H, d, 9.8 Hz), 8.01(1 H, s), 7.99(1 H, s), 7.61-7.59(1 H, m), 7.31 (1 H, s), 4. 07-4.04 (2 H, m), 3.73-3.67(2 H, m), 3.55-3.40(8 H, m), 3.32-3.26(1 H, m), 2.70-2. 60(2 H, m), 2.34(3 H, s), 2.30(3 H, s), 1.95-1.90 (2 H, m), 1.75(6 H, s)

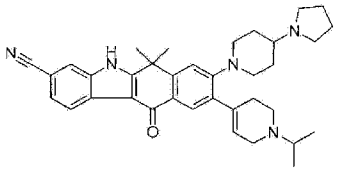
LCMS: m/z 469 $[M+H]^+$

[Example 347]

Compound F6-1

9-(1-Isopropyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0954]



[0955] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound F5-36-2 and acetone.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.68 (1 H, br. s), 8.30 (1 H, d, 8.1 Hz), 7.98 (1 H, s), 7.82 (1 H, s), 7.58 (1 H, d, 8.1 Hz), 7.20 (1 H, s), 5.85 (1 H, s), 3.56-3. 44 (2 H, m), 3.21-3.14 (2 H, m), 2.77-2.66 (5 H, m), 2.12-2.09 (1 H, m), 1.98-1.88 (2 H, m), 1.74 (6 H, s), 1.70-1.63 (1 H, m), 1.58-1.45(2 H, m), 1.09-1.00 (6 H, m)

LCMS: m/z 563 $[M+H]^+$

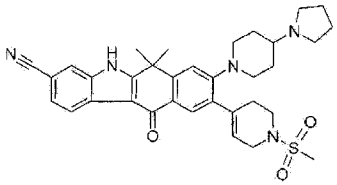
HPLC retention time: 1.90 min (analysis condition U)

[Example 348]

Compound F6-2

9-(1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0956]



[0957] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound F5-36-2.

LCMS: m/z 598 $[M+H]^+$

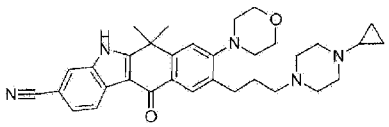
HPLC retention time: 1.52 min (analysis condition S)

[Example 349]

Compound F6-3

9-[3-(4-Cyclopropyl-piperazin-1-yl)-propyl]-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0958]



[0959] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-10.

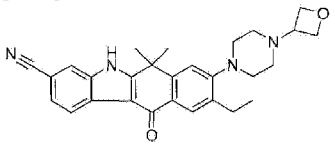
LCMS: m/z 538 $[M+H]^+$
HPLC retention time: 1.32 min (analysis condition S)

[Example 350]

Compound F6-4

9-Ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0960]



[0961] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-16.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.70 (1 H, br. s), 8.29 (1 H, d, 8.0 Hz), 8.03-7.94 (2H, m), 7.59-7.55 (1 H, m), 7.38 (1 H, s), 4.59-4.47 (4 H, m), 3.53-5.47 (1 H, m), 3.03-2.97 (2 H, m), 2.73-2.62 (2 H, m), 1.74 (6 H, s), 1.29-1.98 (3 H, m)

LCMS: m/z 455 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition U)
Hydrochloric acid salt of Compound F6-4
9-Ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was added with DMSO and 6 N hydrochloric acid (1.05 eq.) and dissolved therein. After freeze-drying, crystallization was performed with ethanol comprising 25% water to obtain monohydrochloric acid salt of 9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.83 (1 H, br.s), 11.59(1 H, br. s), 8.33-8.31(1 H, m), 8.09(1H, s), 8.02(1 H, s), 7.63-7.61(1 H, m), 7.39(1 H,s), 4.91-4.60(4 H, br. m), 3.58-3.40(1 H, m), 3.31-3.05(8 H, br. m), 2.73(2 H, q,, J = 7.3), 1.81(6 H, s), 1.29(3 H, t, J = 7.3)

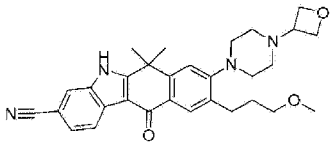
LCMS: m/z 455 $[M+H]^+$

[Example 351]

Compound F6-5

9-(3-Methoxy-propyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0962]



[0963] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-18.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.73 (1 H, br. s), 8.33-8.30 (1 H, d, 8. 08 Hz), 8.01 (1 H, s), 8.00 (1 H, s), 7.62-7.59 (1 H, d, 8.08 Hz), 7.42 (1 H, s), 4. 61-4.56 (2 H, m), 4.51-4.46 (2 H, m), 3.53-3.47 (1 H, m), 3.42-3.37 (2 H, m), 3.02 (4 H, m), 2.75-2.68 (2 H, m), 2.51 (4 H, m), 1.93-1.82 (2 H, m), 1.76 (6 H, s)

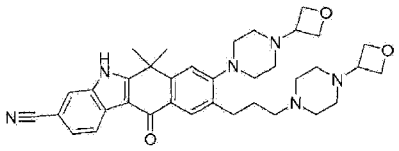
LCMS: m/z 499 $[M+H]^+$

[Example 352]

Compound F6-6

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-9-[3-(4-oxetan-3-yl-piperazin-1-yl)-propyl]-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0964]



[0965] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-20.

LCMS: m/z 609 $[M+H]^+$

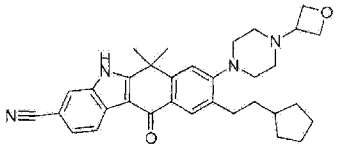
HPLC retention time: 1.00 min (analysis condition S)

[Example 353]

Compound F6-7

9-(2-Cyclopentyl-ethyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0966]



[0967] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-21.

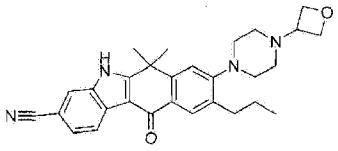
LCMS: m/z 523 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition S)

[Example 354]

Compound F6-8

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0968]



[0969] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-22.

^{1}H-NMR (270 mHz DMSO-d_6) δ : 12.75 (1 H, s), 8.30 (1 H, d, J = 8.2 Hz), 8.01-7.97 (2H, m), 7.59 (1 H, d, J = 7.1 Hz), 7.38 (1H, s), 4.51 (4 H, dt, J = 27.7, 6. 3 Hz), 3.55-3.49 (1 H, m), 3.02-2.96 (4 H, m), 2.63 (2 H, t, J = 7.3 Hz), 2.47-2.41 (4 H, m), 1.73 (6 H, s), 1.70-1.61 (2 H, m), 0.94 (3 H, t, J = 7.4 Hz).

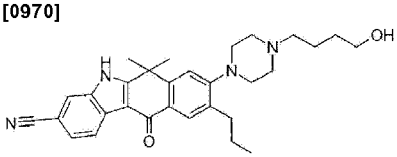
LCMS: m/z 469 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition S)

[Example 355]

Compound F6-9

8-[4-(4-Hydroxy-butyl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0970]



[0971] The title compound was obtained as a by-product of the synthesis of Compound F6-8.

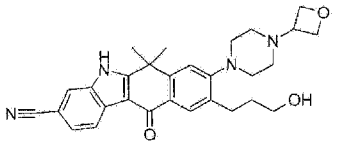
LCMS: m/z 485 $[M+H]^+$
HPLC retention time: 1.61 min (analysis condition S)

[Example 356]

Compound F6-10

9-(3-Hydroxy-propyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0972]



[0973] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-23.

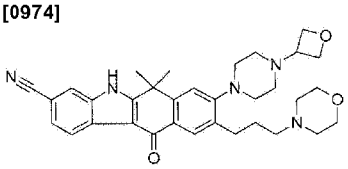
LCMS: m/z 499 $[M+H]^+$
HPLC retention time: 1.42 min (analysis condition S)

[Example 357]

Compound F6-11

6,6-Dimethyl-9-(3-morpholin-4-yl-propyl)-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0974]



[0975] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-26.

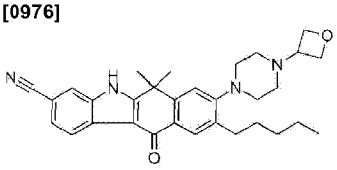
LCMS: m/z 554 $[M+H]^+$
HPLC retention time: 1.50 min (analysis condition U)

[Example 358]

Compound F6-12

6,6-Dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-pentyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0976]



[0977] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-27.

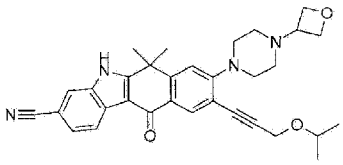
LCMS: m/z 497 $[M+H]^+$
HPLC retention time: 2.25 min (analysis condition U)

[Example 359]

Compound F6-13

9-(3-Isopropoxy-prop-1-ynyl)-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0978]



[0979] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound F5-23 and 2-bromopropane.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.40 (1 H, d, J = 7.8 Hz), 8.32 (1 H, s), 7.84 (1 H, s), 7.53 (1 H, d, J = 7.8 Hz), 7.18 (1 H, s), 4.80-4.68 (4 H, m), 4.46 (2 H, s), 3.95 (1 H, m), 3.64 (1 H, m), 3.46 (4 H, m), 2.62 (4H, m), 1.82 (6 H, s), 1.24 (6 H, d, J = 7.0 Hz)

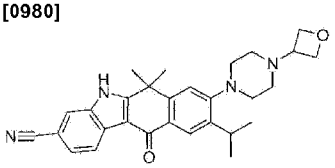
LCMS: m/z 523 $[M+H]^+$

[Example 360]

Compound F6-14

9-Isopropyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0980]



[0981] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-32.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.44 (1 H, d, J = 7.8 Hz), 8.27 (1 H, s), 7.84 (1 H, s), 7.54 (1 H, d, J = 7.8 Hz), 7.36 (1 H, s), 4.82-4.70 (4 H, m), 3.68 (1 H, m), 3.45 (1 H, m), 3.13-3.09 (4 H, m), 2.64-2.62 (4 H, m), 1.81 (6 H, s), 1.31 (6 H, d, J = 7.0 Hz)

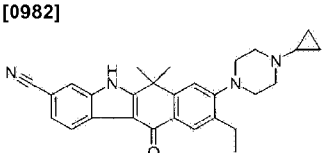
LCMS: m/z 469 $[M+H]^+$

[Example 361]

Compound F6-15

8-(4-Cyclopropyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0982]



[0983] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-37.

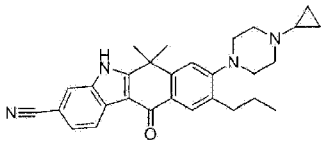
LCMS: m/z 439 $[M+H]^+$
HPLC retention time: 1.98 min (analysis condition U)

[Example 362]

Compound F6-16

8-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0984]



[0985] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-38.

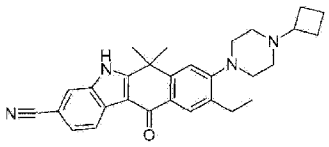
LCMS: m/z 453 $[M+H]^+$
HPLC retention time: 1.63 min (analysis condition S)

[Example 363]

Compound F6-17

8-(4-Cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0986]



[0987] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-43.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.80 (1 H, s), 8.32 (1 H, d, 7.9 Hz), 8. 10 (1 H, s), 8.02 (1 H, s), 7.62 (1 H, d, 7.9 Hz), 7.38 (1 H, s), 3.78-3.88 (1 H, m), 3. 79-3.89 (1 H, m), 3.48-3.54 (2 H, m), 3.40-3.47 (2 H, m), 3.30-3.39 (2 H, m), 3.02-3.24 (4 H, m), 2.73 (2 H, q, 7.3 Hz), 2.30-2.41 (2 H, m), 2.17-2.26 (2 H, m), 1.71-1. 86 (8 H, m), 1.29 (3 H, t, 7.3 Hz)

LCMS: m/z 453 $[M+H]^+$
HPLC retention time: 2.76 min (analysis condition W)
Methanesulfonic acid salt of Compound F6-17
8-(4-Cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved in 6 volumes of DMF at room temperature and added dropwise with aqueous solution of methanesulfonic acid (2 M, 1.05 eq.). The resulting solution was added dropwise to 60 volumes of acetonitrile, and the precipitated solid was filtered and dried to obtain monomethanesulfonic acid salt of 8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile.

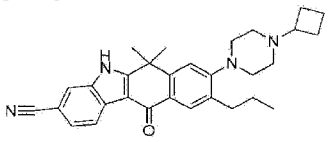
^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.75(1 H, s), 8.31(1 H, J = 8.4 Hz), 8. 07(1 H, s), 8.01(1 H, s), 7.59(1 H, d, J = 7.9 Hz), 7.38(1 H, s), 3.58-2.84(10 H, m), 2. 71(2 H, q, J = 7.5 Hz), 2.34(3 H, s), 2.20-2.04(4 H, m), 1.76-1.68(8 H, m), 1.26(3 H, t, J = 7.5 Hz)
FABMS: m/z 453 $[M+H]^+$

[Example 364]

Compound F6-18

8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0988]



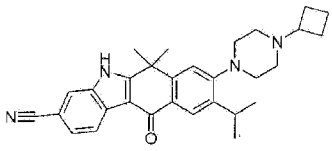
[0989] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-44.
^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.69 (1 H,s), 8.31 (1 H, d, 7.9 Hz), 8. 01 (1 H, s), 7.99 (1 H, s), 7.60 (1 H, d, 7.9 Hz), 7.39 (1 H, s), 2.92-3.02 (4 H, m), 2. 75-2.84 (1 H, m), 2.65 (2 H, t, 7.3 Hz), 2.38-2.48 (4 H, m), 1.96-2.06 (2 H, m), 1. 78-1.87 (2 H, m), 1.75 (6 H, s), 1.62-1.73 (4 H, m), 0.97 (3 H, t, 7.3 Hz)
LCMS: m/z 467 $[M+H]^+$
HPLC retention time: 2.96 min (analysis condition W)

[Example 365]

Compound F6-19

8-(4-Cyclobutyl-piperazin-1-yl)-9-isopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0990]



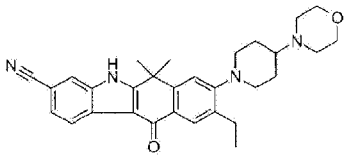
[0991] Under the same conditions as the method for synthesizing Compound B3-13, the title compound was prepared from Compound F5-48.
LCMS: m/z 467 $[M+H]^+$
HPLC retention time: 1.67 min (analysis condition S)

[Example 366]

Compound F6-20

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0992]



[0993] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-49.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.70 (1 H, s), 8.32 (1 H, d, J = 7.9 Hz), 8.04 (1 H, s), 8.00 (1 H, s), 7.61 (1 H, d, J = 8.5 Hz), 7.34 (1 H, s), 3.64-3.57 (4 H, m), 3.27-3.18(2 H, m), 2.82-2.66 (4 H, m), 2.39-2.28 (1 H, m), 1.96-1.87 (2 H, m), 1.76 (6 H, s), 1.69-1.53 (2 H, m), 1.29 (3 H, t, J = 7.3 Hz)

LCMS: m/z 483 $[M+H]^+$

HPLC retention time: 1.98 min (analysis condition U)

Hydrochloric acid salt of Compound F6-20

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile was dissolved in a mixture solution of methylethyl ketone (10 volumes), water (4 volumes) and acetic acid (3 volumes) at 60°C. To the dissolved solution, hydrochloric acid (2 N) was added dropwise (1 volume). After stirring at 60°C for 30 min, ethanol (25 volume) was added dropwise. The precipitated solid was filtered and dried to obtain monohydrochloric acid salt of 9-ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo [b]carbazole-3-carbonitrile.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.78(1 H, s), 10.57(1 H, br. s), 8.30(1 H, J = 8.4 Hz),8.05(1 H, s), 7.99(1 H, s), 7.59(1 H, d, J = 7.9 Hz), 7.36(1 H, s), 4. 02-3.99(2 H, m), 3.84-3.78(2 H, m), 3.51-3.48(2 H, m), 3.15-3.13(1 H, s), 2.83-2. 73(2 H, s), 2.71-2.67(2 H, s), 2.23-2.20(2 H, m), 1.94-1.83(2 H, m), 1.75(6 H, s), 1. 27(3H, t, J = 7.5 Hz)

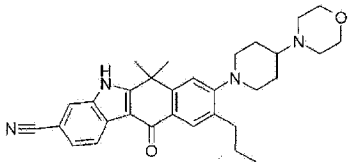
FABMS: m/z 483 $[M+H]^+$

[Example 367]

Compound F6-21

6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[0994]



[0995] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound F5-50.

^{1}H-NMR(270 MHz, CD_3OD+$CDCl_3$) δ : 8.41 (1 H, d, J = 7.8 Hz), 8.14 (1 H, s), 7.84 (1 H, s), 7.53 (1 H, d, J = 7.8 Hz), 7.31 (1 H, s), 3.77 (4 H, m), 3.32 (2 H, m), 2.86-2.66 (8 H, m), 2.43-2.05 (3 H, m), 1.79 (6 H, s), 1.79-1.66 (4 H, m), 1.02 (3 H, t, J = 7.3 Hz)

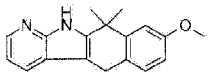
LCMS: m/z 497 $[M+H]^+$

[Example 368]

Compound G2

8-Methoxy-10,10-dimethyl-10,11-dihydro-5H-1,11-diaza-benzo[B]fluorene

[0996]



[0997] 2-Hydrazinopyridine (1.3 g, 11.8 mmol) and 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 2.4 g, 11.8 mmol) were dissolved in NMP (60 mL), and stirred at 190°C for 48 hr. The reaction solution was diluted with ethyl acetate, washed with water and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane/ethyl acetate) to obtain the target compound (white solid, 101 mg, 3%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 11.53 (1 H, s), 8.16 - 8.12 (1 H, m), 7. 84 (1 H, d, J = 7.8 Hz), 7.23 (1 H, d, J = 8.4 Hz), 7.11 (1 H, s), 7.03-6.98 (1 H, m), 6. 85-6.81 (1 H, m), 3.96 (2 H, s), 3.77 (3 H, s), 1.64 (6 H, s)

LCMS: m/z 279 $[M+H]^+$

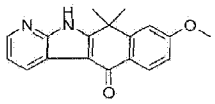
HPLC retention time: 2.08 min (analysis condition U)

[Example 369]

Compound G3

8-Methoxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one

[0998]



[0999] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound G2.

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 12.95 (1 H, br. s), 8.78 (1 H, d, J = 7.8 Hz), 8.52 (1 H, d, J = 4.9 Hz), 8.41 (1 H, d, J = 8.8 Hz), 7.37 (1 H, dd, J = 7.7, 5.0 Hz), 7. 15 (1 H, s), 7.04-7.00 (1 H, m), 3.94 (3 H, s), 1.98 (6 H, s)

LCMS: m/z 293 $[M+H]^+$

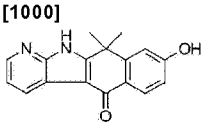
HPLC retention time: 2.13 min (analysis condition U)

[Example 370]

Compound G4

8-Hydroxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one

[1000]



[1001] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound G3.

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.66 (1 H, d, J = 7.7 Hz), 8.29 (1 H, d, J = 4. 9 Hz), 8.23 (1 H, d, J = 13.8 Hz), 7.29 (1 H, dd, J = 7.7, 5.0 Hz), 7.12 (1 H, s), 6.93 (1 H, d, J = 8.6 Hz), 1.71 (6 H, s)

LCMS: m/z 279 $[M+H]^+$

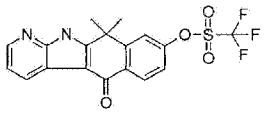
HPLC retention time: 1.72 min (analysis condition U)

[Example 371]

Compound G5

Trifluoro-methanesulfonic acid 10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester

[1002]



[1003] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound G4.

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 8.81 (1 H, d, J = 7.8 Hz), 8.60-8.52 (2 H, m), 7.55 (1 H, s), 7.46-7.40 (2 H, m), 2.01 (6 H, s)

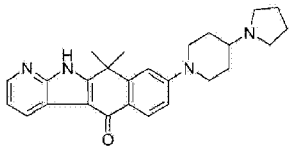
LCMS: m/z 411 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition U)

[Example 372]

Compound G6

10,10-Dimethyl-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one

[1004]



[1005] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound G5 and 4-pyrrolidin-1-yl-piperidine.

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 13.12(1 H, s), 8.78 (1 H, d, J = 7.8 Hz), 8. 49 (1 H, d, J = 4.9 Hz), 8.29 (1 H, d, J = 8.8 Hz), 7.34 (1 H, dd, J = 7.7, 5. 0 Hz), 7. 06-6.98 (2 H, m), 3.96-3.88 (2 H, m), 3.02-3.92 (2H, m), 2.69-2.60 (4 H, m), 2.32-2.23 (1 H, m), 2.09-2.00 (4 H, m), 1.92 (6 H, s), 1.26-1.19 (4 H, m)

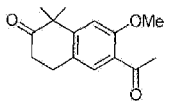
LCMS: m/z 415 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition U)

[Example 373]

Compound H1

6-Acetyl-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1006]



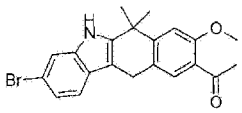
[1007] To the dichloromethane (70 ml) solution of 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 3 g, 14.7 mmol), acetic anhydride (1.7 ml, 1.2 eq.) and aluminum chloride - nitrobenzene solution (1 M, 44 ml, 3 eq.) was added at 0°C, and stirred for 3 hr. Thereafter, the reaction solution was added with saturated aqueous solution of sodium hydrogen carbonate and extracted twice with dichloromethane. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound as a crude product.

[Example 374]

Compound H2-1

1-(3-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-ethanone

[1008]



[1009] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound H1 and (3-bromo-phenyl)-hydrazine.

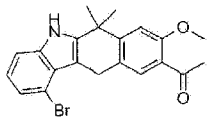
LCMS: m/z 398 $[M+H]^+$
HPLC retention time: 3.97 min (analysis condition Y)

[Example 375]

Compound H2-2

1-(1-Bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-ethanone

[1010]



[1011] The title compound was obtained as a by-product of the synthesis of Compound H2-1.

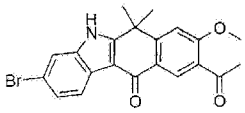
LCMS: m/z 398 $[M+H]^+$
HPLC retention time: 3.97 min (analysis condition Y)

[Example 376]

Compound H3

9-Acetyl-3-bromo-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1012]



[1013] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound H2.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.80 (6 H, s), 2.58 (3 H, s), 4.06 (3 H, s), 7.38 (1 H, dd, 8.39 Hz, 1.91 Hz), 7.51 (1 H, s), 7.67 (1 H, bs, 1.53 Hz), 8.10 (1 H, d, 8.39 Hz), 8.41 (1 H, s), 12.3 (1 H, s)

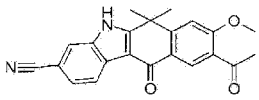
LCMS: m/z 412, 414 $[M+H]^+$
HPLC retention time: 2.73 min (analysis condition U)

[Example 377]

Compound H4

9-Acetyl-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1014]



[1015] According to the same method as the method for synthesizing Compound A5-2, the title compound was prepared from Compound H3.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.83 (6 H, s), 2.58 (3 H, s), 4.07 (3 H, s), 7.53 (1 H, s), 7.61 (1 H, d, 8.01 Hz), 8.03 (1 H, s), 8.31 (1 H, d, 8.77 Hz), 8.42 (1 H, s), 12.8 (1 H, s).

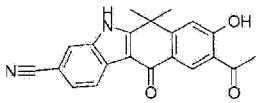
LCMS: m/z 359 $[M+H]^+$
HPLC retention time: 2.47 min (analysis condition U)

[Example 378]

Compound H5

9-Acetyl-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1016]



[1017] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound H4.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.77 (6 H, s), 2.75 (3 H, s), 7.43 (1 H, s), 7.63 (1 H, d, 8.01 Hz), 8.02 (1 H, s), 8.32 (1 H, d, 8.01 Hz), 8.67 (1 H, s), 12.2 (1 H, s), 12.8 (1 H, s).

LCMS: m/z 345 $[M+H]^+$

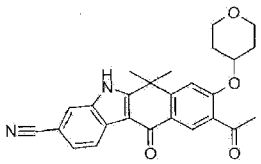
HPLC retention time: 2.27 min (analysis condition S)

[Example 379]

Compound H6-1

9-Acetyl-6,6-dimethyl-11-oxo-8-(tetrahydro-pyran-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1018]



[1019] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound H5 and tetrahydropyran-4-ol.

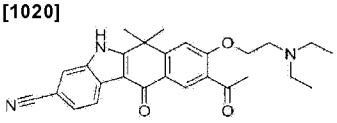
LCMS: m/z 429 $[M+H]^+$
HPLC retention time: 2.48 min (analysis condition U)

[Example 380]

Compound H6-2

9-Acetyl-8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1020]



[1021] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound H5.

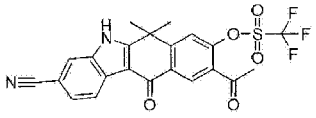
LCMS: m/z 444 $[M+H]^+$
HPLC retention time: 2.05 min (analysis condition U)

[Example 381]

Compound H7

Trifluoro-methanesulfonic acid 9-acetyl-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[1022]



[1023] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound H5.

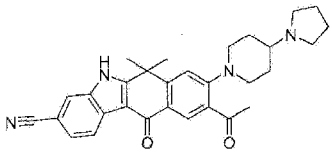
^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.83 (6 H, s), 2. 74 (3 H, s), 7.68 (1 H, dd, 8.01 Hz, 1.53 Hz), 8.08 (2 H, s), 8.33 (1 H, d, 8.77 Hz), 8.79 (1 H, s), 12.9 (1 H, s).

[Example 382]

Compound H8-1

9-Acetyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1024]



[1025] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound H7 and 4-pyrrolidin-1-yl-piperidine.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.65 (2 H, m), 1.69 (4 H, s), 1.79 (6 H, s), 1.95 (2 H, m), 2.18 (1 H, m), 2.54 (4 H, s), 2.59 (3 H, s), 2.93 (2 H, t, 11.8 Hz), 3. 37 (2 H, m), 7.36 (1 H, s), 7.60 (1 H, d, 8.01), 8. 01 (1 H, s), 8.13 (1 H, s), 8.30 (1 H, d, 8.39), 12.7 (1 H, s).

LCMS: m/z 481 $[M+H]^+$

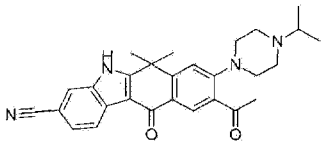
HPLC retention time: 2.03 min (analysis condition U)

[Example 383]

Compound H8-2

9-Acetyl-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1026]



[1027] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound H7.

LCMS: m/z 455 $[M+H]^+$

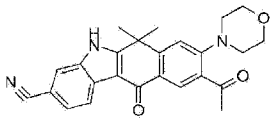
HPLC retention time: 2.02 min (analysis condition U)

[Example 384]

Compound H8-3

9-Acetyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1028]



[1029] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound H7 and morpholine.

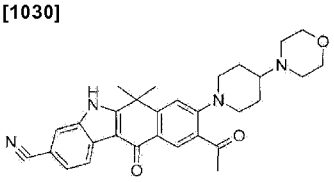
LCMS: m/z 414 $[M+H]^+$
HPLC retention time: 2.11 min (analysis condition S)

[Example 385]

Compound H8-4

9-Acetyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1030]



[1031] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound H7 and 4-piperidin-4-yl-morpholine.

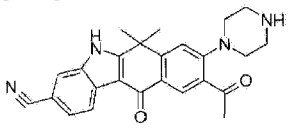
LCMS: m/z 497 $[M+H]^+$
HPLC retention time: 1.45 min (analysis condition S)

[Example 386]

Compound H8-5

9-Acetyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1032]



[1033] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound H7 and piperazine.

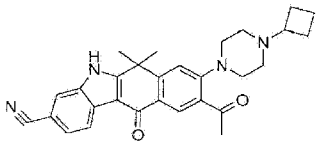
LCMS: m/z 413 $[M+H]^+$
HPLC retention time: 1.71 min (analysis condition U)

[Example 387]

Compound H9-1

9-Acetyl-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1034]



[1035] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound H8-5 and cyclobutanone.

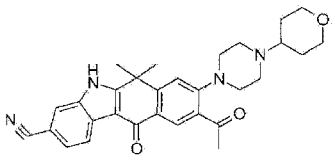
LCMS: m/z 467 $[M+H]^+$
HPLC retention time: 1.82 min (analysis condition U)

[Example 388]

Compound H9-2

9-Acetyl-6,6-dimethyl-11-oxo-8-[4-(tetrahydro-pyran-4-yl)-piperazin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1036]



[1037] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound H8-5 and tetrahydropyran-4-one.

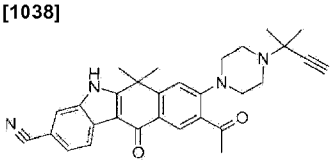
LCMS: m/z 497 $[M+H]^+$
HPLC retention time: 1.76 min (analysis condition U)

[Example 389]

Compound H9-3

9-Acetyl-8-[4-(1,1-dimethyl-prop-2-ynyl)-piperazin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1038]



[1039] To the anhydrous THF solution (0.5 mL) of 9-acetyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-

3-carbonitrile (Compound H8-5, 25 mg, 0.06 mmol), 3-chloro-3-methyl-but-1-yne (0.013 mL, 0.12 mmol), copper (I) chloride (0.6 mg, 0.006 mmol) and triethylamine (0.017 mL, 0.12 mmol) were added at room temperature. After stirring for 30 min, the mixture was added with water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by amino silica gel column chromatography (dichloromethane/methanol) to obtain the title compound (white solid, 9.8 mg, 35%).

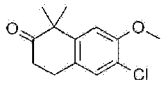
LCMS: m/z 479 $[M+H]^+$
HPLC retention time: 1.88 min (analysis condition U)

[Example 390]

Compound I1-1

6-Chloro-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1040]



[1041] 7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 3.37 g, 16.5 mmol) was dissolved in CH_3CN (82 mL), added with NCS (2.42 g, 1.1 eq.) and stirred at 90°C for 1.5 hr. The reaction solution was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed and the target compound was obtained after concentration under reduced pressure (yellow oily substance, 4.45 g).

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 7.16 (1 H, s), 6.85 (1 H, s), 3.90 (3 H, s), 3. 00 (2 H, t, J = 6.8 Hz), 2.65 (2 H, t, J = 6.8 Hz), 1.42 (6 H, s).

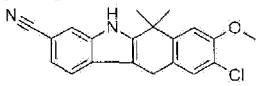
LCMS: m/z 239 $[M+H]^+$
HPLC retention time: 2.80 min (analysis condition U)

[Example 391]

Compound I1-2

9-Chloro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1042]



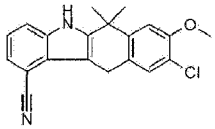
[1043] 6-Chloro-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound I1-1, 4.45 g, 16.5 mmol) and 3-hydrazinobenzonitrile (2.63 g, 1.2 eq.) were dissolved in TFA (91 mL), and stirred at 90°C for 3 hr. According to the concentration under reduced pressure, TFA was removed and the residues were added with saturated aqueous solution of $NaHCO_3$, followed by extraction with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were added with ethyl acetate. After stirring at room temperature, the precipitated solid was separated by filtration. The filtrate was concentrated under reduced pressure to obtain the title compound as a mixture with I1-3 (red powder, 6.46 g).

[Example 392]

Compound I1-3

9-Chloro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile

[1044]



[1045] The title compound was obtained as a by-product of the synthesis of Compound I1-2.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 11.66 (1 H, s), 7.65-7.69 (1 H, m), 7.44-7.48 (1 H, m), 7.39 (1 H, s), 7.29 (1 H, s), 7.17-7.23 (1 H, m), 4.21 (2 H, s), 3.91 (3 H, s), 1.69 (6 H, s).

LCMS: m/z 337 $[M+H]^+$

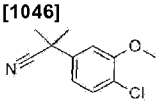
HPLC retention time: 3.15 min (analysis condition U)

[Example 393]

Compound I2-1

2-(4-Chloro-3-methoxy-phenyl)-2-methyl-propionitrile

[1046]



[1047] 1-Chloro-4-fluoro-2-methoxy-benzene (4.3 g, 26.78 mmol) and isobutyronitrile (9.61 mL, 4.0 eq.) were dissolved in toluene (9.0 mL), added with KHMDS (80 mL, 0.5 M toluene solution) and stirred at 65°C for 2 hr. The reaction solution was cooled to room temperature, added with aqueous solution of 1 N hydrochloric acid and then extracted with MTBE. The organic layer was washed with saturated brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane/ethyl acetate) to obtain the title compound (1.72 g, 31%).

^{1}H-NMR (270 MHz, $CDCl_3$) δ : 7.37 (1 H, d, J = 8.4 Hz), 7.05 (1 H, d, J = 2. 1 Hz), 6.97 (1 H, dd, J = 8.2, 2.1 Hz), 3.95 (3 H, s), 1.73 (6 H, s).

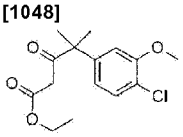
HPLC retention time: 2.33 min (analysis condition S)

[Example 394]

Compound I2-2

4-(4-Chloro-3-methoxy-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1048]



[1049] Under the same conditions as the method for synthesizing Compound K3, the title compound was prepared from Compound 12-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 7.42 (1 H, d, J = 8.1 Hz), 6.92 (1 H, d, J = 2.1 Hz), 6.86 (1 H, dd, J = 8.2, 2.3 Hz), 4.01 (2 H, q, J = 7.1 Hz), 3.87 (3 H, s), 3. 43 (2 H, s), 1.44 (6 H, s), 1.12 (3 H, t, J = 7.2 Hz).

LCMS: m/z 299, 301 $[M+H]^+$

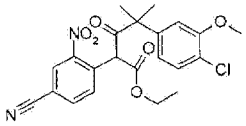
HPLC retention time: 2.52, 3.05 min (analysis condition S)

[Example 395]

Compound I2-3

4-(4-Chloro-3-methoxy-phenyl)-2-(4-cyano-2-nitro-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1050]



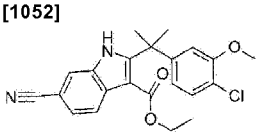
[1051] Under the same conditions as the method for synthesizing Compound K4, the title compound was obtained as a crude product from Compound 12-2.

[Example 396]

Compound I2-4

2-[1-(4-Chloro-3-methoxy-phenyl)-1-methyl-ethyl]-6-cyano-1H-indole-3-carboxylic acid ethyl ester

[1052]



[1053] Under the same conditions as the method for synthesizing Compound K5, the title compound was obtained from Compound 12-3.

LCMS: m/z 397, 399 $[M+H]^+$

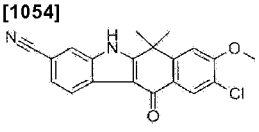
HPLC retention time: 2.83 min (analysis condition S)

[Example 397]

Compound I3

9-Chloro-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1054]



[1055] (Method 1) Under the same conditions as the method for synthesizing Compound A4, the title compound was obtained from Compound I1-2.

[1056] (Method 2) Under the same conditions as the method for synthesizing Compound L8-1, the title compound was obtained from Compound I2-4.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.79 (1 H, s), 8.27-8.31 (1 H, m), 8.12 (1 H, s), 8.00-8.02 (1 H, m), 7.58-7.63 (1 H, m), 7.51 (1 H, s), 4.03 (3 H, s), 1.80 (6 H, s).

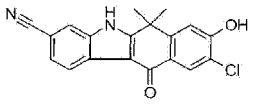
LCMS: m/z 351 $[M+H]^+$
HPLC retention time: 2.87 min (analysis condition U)

[Example 398]

Compound I4

9-Chloro-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1057]



[1058] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound 13.

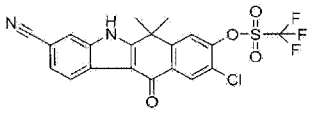
LCMS: m/z 337 $[M+H]^+$
HPLC retention time: 2.47 min (analysis condition U)

[Example 399]

Compound I5

Trifluoro-methanesulfonic acid 9-chloro-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[1059]



[1060] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound I4.

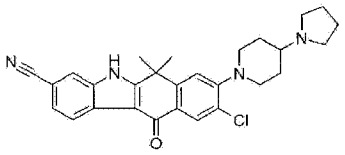
LCMS: m/z 469 $[M+H]^+$
HPLC retention time: 3.40 min (analysis condition U)

[Example 400]

Compound I6-1

9-Chloro-6,6-dimethyl-11-oxo-8-(4-pyrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1061]



[1062] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound I5 and 4-pyrrolidin-1-yl-piperidine.

LCMS: m/z 473 $[M+H]^+$

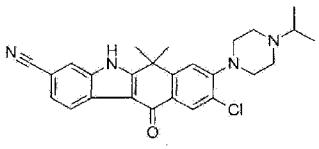
HPLC retention time: 2.25 min (analysis condition U)

[Example 401]

Compound I6-2

9-Chloro-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1063]



[1064] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound 15.

LCMS: m/z 447 $[M+H]^+$

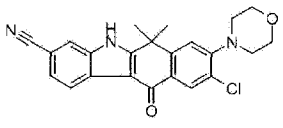
HPLC retention time: 2.30 min (analysis condition U)

[Example 402]

Compound I6-3

9-Chloro-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1065]



[1066] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from 15 and morpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.79 (1 H, s), 8.28 (1 H, d, 8.0 Hz), 8. 09 (1 H, s), 8.00 (1 H, s), 7.59 (1 H, d, 8.0 Hz), 7.45 (1 H, s), 3.75-3.81 (4 H, m), 3. 13-3.19 (4 H, m), 1.76 (6 H, s)

LCMS: m/z 406 $[M+H]^+$

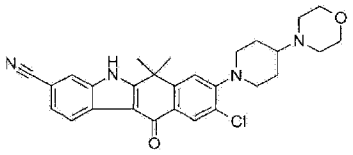
HPLC retention time: 2.88 min (analysis condition U)

[Example 403]

Compound I6-4

9-Chloro-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1067]



[1068] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound 15 and 4-piperidin-4-yl-morpholine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.75 (1 H, s), 8.28 (1 H, d, 8.0 Hz), 8. 07 (1 H, s), 8.00 (1 H, s), 7.59 (1 H, d, 8.0 Hz), 7.41 (1 H, s), 3.55-3.62 (4 H, m), 3. 47-3.56 (4H, m), 2.75-2.86 (2 H, m), 2.45-2.55 (4 H, m), 2.28-2.39 (1 H, m), 1.86-1.96 (2 H, m), 1.76 (6 H, s), 1.52-1.66 (2 H, m)

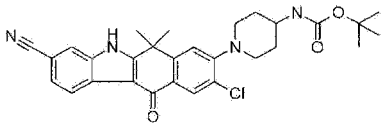
LCMS: m/z 489 $[M+H]^+$
HPLC retention time: 1.97 min (analysis condition U)

[Example 404]

Compound I6-5-1

[1-(9-Chloro-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidin-4-yl]-carbamic acid tert-butyl ester

[1069]



[1070] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound 15 and piperidin-4-yl-carbamic acid tert-butyl ester.

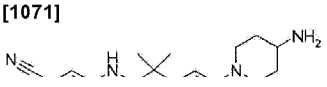
LCMS: m/z 519 $[M+H]^+$
HPLC retention time: 3.27 min (analysis condition U)

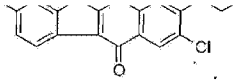
[Example 405]

Compound I6-5-2

8-(4-Amino-piperidin-1-yl)-9-chloro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1071]





[1072] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound I6-5-1.

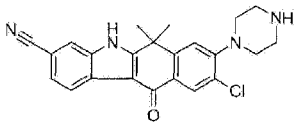
LCMS: m/z 419 $[M+H]^+$
HPLC retention time: 2.12 min (analysis condition U)

[Example 406]

Compound I6-6

9-Chloro-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1073]



[1074] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound 15 and piperazine.

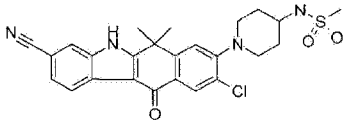
LCMS: m/z 405 $[M+H]^+$
HPLC retention time: 1.87 min (analysis condition U)

[Example 407]

Compound I7-1

N-[1-(9-Chloro-3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-piperidin-4-yl]-methanesulfonamide

[1075]



[1076] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound I6-5-2.

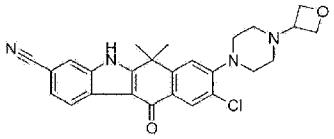
LCMS: m/z 497 $[M+H]^+$
HPLC retention time: 2.62 min (analysis condition U)

[Example 408]

Compound I7-2

9-Chloro-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1077]



[1078] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound I5 and 1-oxetan-3-yl-piperazine.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.78 (1 H, s), 8.27-8.31 (1 H, m), 8.07-8.09 (1 H, s), 7.99-8.02 (1 H, m), 7.59-7.62 (1 H, m), 7.44-7.46 (1 H, s), 4.54-4.60 (2 H, m), 4.44-4.51 (2 H, m), 3.47-3.55 (1 H, m), 3.16-3.24 (4 H, m), 2.40-2.55 (4 H, m), 1.77 (6H, s)

LCMS: m/z 461 $[M+H]^+$

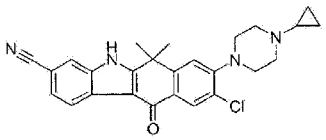
HPLC retention time: 2.13 min (analysis condition U)

[Example 409]

Compound I7-3

9-Chloro-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1079]



[1080] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound I5 and 1-cyclopropylpiperazine.

LCMS: m/z 445 $[M+H]^+$

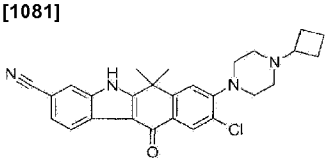
HPLC retention time: 1.97 min (analysis condition U)

[Example 410]

Compound I7-4

9-Chloro-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1081]



[1082] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound I6-6 and cyclobutanone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.78 (1 H, s), 8.29 (1 H, d, 8.5 Hz), 8. 08 (1 H, s), 8.01 (1 H, s), 7.60 (1 H, d, 8.5 Hz), 7.44 (1 H, s), 3.17-3.15 (4 H, m), 2. 83-2.76 (1 H, m), 2.47-2.44 (4 H, m), 2.04-1.97 (2 H, m), 1.82 (2 H, t, 9.8 Hz), 1. 77 (6 H, s), 1.70-1.63 (2 H, m)

LCMS: m/z 459, 461 $[M+H]^+$

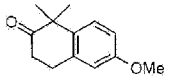
HPLC retention time: 1.63 min (analysis condition S)

[Example 411]

Compound J2

6-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1083]



[1084] Under the same conditions as the method for synthesizing Compound A2, the title compound was prepared from 6-methoxy-3,4-dihydro-1H-naphthalen-2-one and iodomethane.

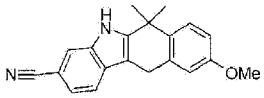
LCMS: m/z 205 $[M+H]^+$
HPLC retention time: 1.54 min (analysis condition S)

[Example 412]

Compound J3-1

9-Methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1085]



[1086] Under the same conditions as the method for synthesizing Compound E2-1, the title compound was prepared from Compound J2 and 3-hydrazino-benzonitrile.

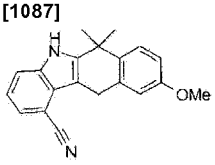
LCMS: m/z 303 $[M+H]^+$
HPLC retention time: 2.73 min (analysis condition S)

[Example 413]

Compound J3-2

9-Methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-1-carbonitrile

[1087]



[1088] Compound J3-2 was obtained as a by-product of the synthesis of Compound J3-1.

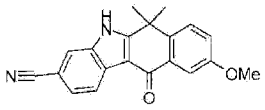
LCMS: m/z 303 $[M+H]^+$
HPLC retention time: 2.67 min (analysis condition S)

[Example 414]

Compound J4

9-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1089]



[1090] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound J3-1 and Compound J3-2 (mixture).

^{1}H-NMR (DMSO-d_6) δ : 12.79 (1 H, s), 8.33 (1 H, d, J = 8.2 Hz), 8.02 (1 H, s), 7.81 (1 H, d, J = 8.6 Hz), 7.69 (1 H, d, J = 3.0 Hz), 7.63 (1 H, dd, J = 8.3, 1.4 Hz), 7.28 (1 H, dd, J = 8.7, 3.0 Hz), 3.87 (3 H, s), 1.74 (6 H, s).

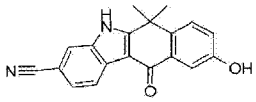
LCMS: m/z 317 $[M+H]^+$
HPLC retention time: 2.25 min (analysis condition S)

[Example 415]

Compound J5

9-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1091]



[1092] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound J4.

^{1}H-NMR (DMSO-d_6) δ : 12.75 (1 H, s), 9.77 (1 H, s), 8.32 (1 H, dd, J = 8.2, 0.7 Hz), 8.01 (1 H, s), 7.68 (1 H, d, J = 8.6 Hz), 7.62 (1 H, dd, J = 8.2, 1.4 Hz), 7. 58 (1H, d, J = 2.8 Hz), 7.10 (1 H, dd, J = 8.6, 2.8 Hz), 1.72 (6 H, s).

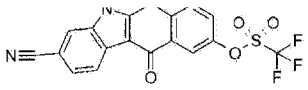
LCMS: m/z 303 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition S)

[Example 416]

Compound J6

Trifluoro-methanesulfonic acid 3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl ester

[1093]



[1094] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound J5.

^{1}H-NMR (DMSO-d_6) δ : 12.95 (1 H, s), 8.31 (1 H, d, J = 8.2 Hz), 8.15 (2 H, m), 8.05 (1 H, s), 7.87 (1 H, dd, J = 9.0, 2.7 Hz), 7.65 (1 H, d, J = 8.2 Hz), 1.80 (6 H, s).

LCMS: m/z 435 $[M+H]^+$

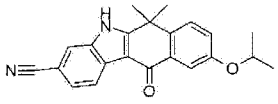
HPLC retention time: 2.75 min (analysis condition S)

[Example 417]

Compound J7-1

9-Isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1095]



[1096] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound J4 and isopropanol.

LCMS: m/z 345 $[M+H]^+$

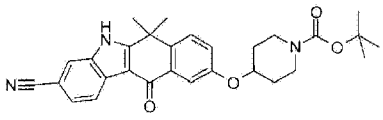
HPLC retention time: 3.87 min (analysis condition W)

[Example 418]

Compound J7-2-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1097]



[1098] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound J5.

LCMS: m/z 486 $[M+H]^+$

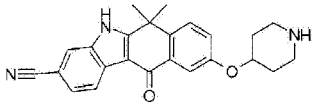
HPLC retention time: 4.15 min (analysis condition W)

[Example 419]

Compound J7-2-2

6,6-Dimethyl-11-oxo-9-(piperidin-4-yl oxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1099]



[1100] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound J7-2-1.

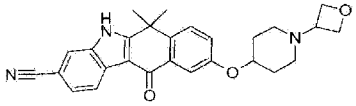
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 2.48 min (analysis condition W)

[Example 420]

Compound J7-2-3

6,6-Dimethyl-9-(1-oxetan-3-yl-piperidin-4-yl oxy)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1101]



[1102] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-2-2 and oxetan-3-one.

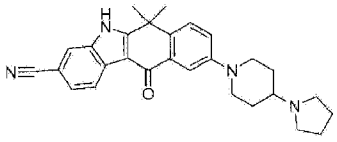
LCMS: m/z 442 $[M+H]^+$
HPLC retention time: 2.61 min (analysis condition W)

[Example 421]

Compound J7-3

6,6-Dimethyl-11-oxo-9-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1103]



[1104] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound J6 and 4-pyrrolidin-1-yl-piperidine.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 13.12 (1 H, s), 8.32 (1 H, d, J = 8.1 Hz), 8.01 (1 H, s), 7.72 (1 H, d, J = 8.7 Hz), 7.68 (1 H, d, J = 2.6 Hz), 7.62 (1 H, dd, J = 8. 2, 1.2 Hz), 7.38 (1 H, dd, J = 9.1, 2.8 Hz), 3.90 (2 H, d, J = 11.5 Hz), 2.76 (2 H, t, J = 12.2 Hz), 2.14 (2 H, d, J = 10.9 Hz), 1.91 (4 H, br), 1.74 (6 H, s).

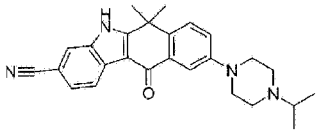
LCMS: m/z 439 $[M+H]^+$
HPLC retention time: 1.35 min (analysis condition S)

[Example 422]

Compound J7-4

9-(4-Isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1105]



[1106] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound J6 and 1-isopropyl-piperazine.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.80 (1 H, s), 8.33 (1 H, d, J = 7.6 Hz), 8.02 (1 H, s), 7.66 (3 H, m), 7.33 (1 H, d, J = 8.2 Hz), 3.21 (4 H, br), 2.66 (5 H, m), 1.72 (6 H, s), 1.02 (6 H, d, J = 6.3 Hz).

LCMS: m/z 413 $[M+H]^+$

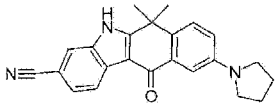
HPLC retention time: 1.38 min (analysis condition S)

[Example 423]

Compound J7-5

6,6-Dimethyl-11-oxo-9-pyrrolidin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1107]



[1108] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound J6 and pyrrolidine.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.24 (1 H, d, J = 8.1 Hz), 7.91 (1 H, s), 7.59 (1 H, d, J = 8.6 Hz), 7.45 (1 H, d, J = 7.9 Hz), 7.30 (1 H, d, J = 2.6 Hz), 6.85 (1 H, dd, J = 8.6, 2.8 Hz), 3.31 (4 H, t, J = 6.3 Hz), 1.99 (4 H, t, J = 6.2 Hz), 1.67 (6 H, s).

LCMS: m/z 356 $[M+H]^+$

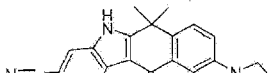
HPLC retention time: 2.38 min (analysis condition S)

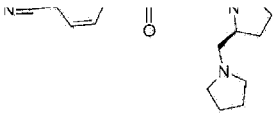
[Example 424]

Compound J7-6

6,6-Dimethyl-11-oxo-9-((S)-2-pyrrolidin-1-ylmethyl-pyrrolidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1109]





[1110] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound J6 and (S)-2-pyrrolidin-1-yl methyl-pyrrolidine.

LCMS: m/z 439 $[M+H]^+$

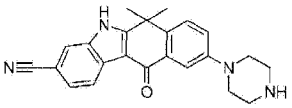
HPLC retention time: 1.50 min (analysis condition S)

[Example 425]

Compound J7-7

6,6-Dimethyl-11-oxo-9-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1111]



[1112] Under the same conditions as the method for synthesizing Compound B2-10, the title compound was prepared from Compound J6 and piperazine.

LCMS: m/z 371 $[M+H]^+$

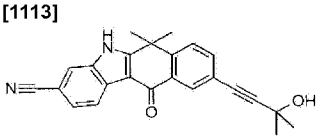
HPLC retention time: 1.31 min (analysis condition S)

[Example 426]

Compound J7-8

9-(3-Hydroxy-3-methyl-but-1-ynyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1113]



[1114] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound J6.

LCMS: m/z 369 $[M+H]^+$

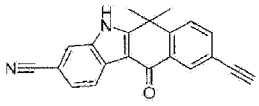
HPLC retention time: 2.16 min (analysis condition S)

[Example 427]

Compound J7-9

9-Ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1115]



[1116] Under the same conditions as the method for synthesizing Compound E4-2-2, the title compound was prepared from Compound J7-8.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.31 (1 H, d, J = 8.1 Hz), 8.23 (1 H, d, J = 1.8 Hz), 8.02 (1 H, d, J = 1.3 Hz), 7.93 (1 H, d, J = 8.2 Hz), 7.78 (1 H, dd, J = 8.2, 1.8 Hz), 7.61 (1 H, dd, J = 8.1, 1.3 Hz), 4.31 (1 H, s), 1.77 (6 H, s).

LCMS: m/z 311 $[M+H]^+$

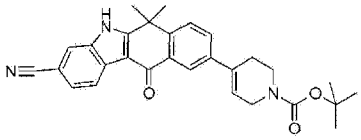
HPLC retention time: 2.40 min (analysis condition S)

[Example 428]

Compound J7-10-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

[1117]



[1118] Under the same conditions as the method for synthesizing Compound B2-22-1, the title compound was prepared from Compound J6.

LCMS: m/z 468 $[M+H]^+$

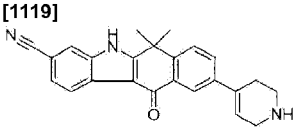
HPLC retention time: 2.90 min (analysis condition S)

[Example 429]

Compound J7-10-2

6,6-Dimethyl-11-oxo-9-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1119]



[1120] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound J7-10-1.

LCMS: m/z 368 $[M+H]^+$

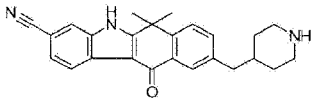
HPLC retention time: 1.27 min (analysis condition S)

[Example 430]

Compound J7-11-1

9-(Piperidin-4-ylmethyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1121]



[1122] Under the same conditions as the method for synthesizing Compound B2-25-1 and Compound B2-25-2, the title compound was prepared from Compound J6.

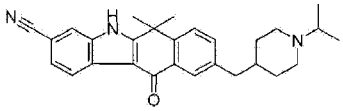
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 1.42 min (analysis condition S)

[Example 431]

Compound J7-11-2

9-(1-Isopropyl-piperidin-4-ylmethyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1123]



[1124] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-11-1 and acetone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.79 (1 H, s), 8.33 (1 H, d, 7.9 Hz), 8. 01 (1 H, s), 7.98 (1 H, d, 1.8 Hz), 7.79 (1 H, d, 7.9 Hz), 7.61 (1 H, d, 7.9 Hz), 7.51-7.49 (1 H, m), 2.74 (2 H, d, 11.0 Hz), 2.64-2.60 (3 H, m), 2.04 (2 H, t, 10.7 Hz), 1. 77 (6 H, s), 1.60-1.51 (3 H, m), 1.23-1.14 (2 H, m), 0.94 (6 H, d, 6.7 Hz)

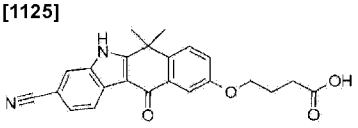
LCMS: m/z 426 $[M+H]^+$

[Example 432]

Compound J7-12

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-butyric acid

[1125]



[1126] 9-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound J5, 30 mg, 0.099 mmol), 4-bromo-butyric acid methyl ester (24.9 µl, 0.198 mmol) and cesium carbonate (64.5 mg, 0.198 mmol) were dissolved in DMA (0.20 ml)

and stirred at room temperature for 4 hr. Water was added to the reaction solution, which was then extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The yellow solid obtained after concentration under reduced pressure was purified by silica gel column chromatography (methylene chloride/MeOH) to obtain 4-(3-cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-butyric acid methyl ester as an intermediate.

[1127] The intermediate was dissolved in MeOH (0.50 ml), added with aqueous solution of sodium hydroxide (6 mol/l) and stirred at room temperature for 30 min. The reaction solution was added with hydrochloric acid (3 mol/l), extracted with diethyl ether. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. After concentration under reduced pressure, white solid was obtained, which was then washed with methylene chloride to obtain the title compound (19.0 mg, 70%).

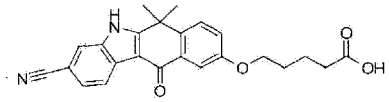
LCMS: m/z 389 $[M+H]^+$
HPLC retention time: 2.39 min (analysis condition F)

[Example 433]

Compound J7-13

5-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-pentanoic acid

[1128]



[1129] Under the same conditions as the method for synthesizing Compound J7-12, Compound J5 and 5-bromo-pentanoic acid methyl ester were reacted to obtain the target compound (19.5 mg, 64%).

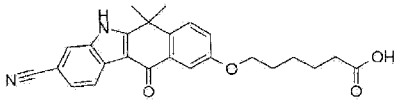
LCMS: m/z 403 $[M+H]^+$
HPLC retention time: 2.49 min (analysis condition F)

[Example 434]

Compound J7-14

6-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-hexanoic acid

[1130]



[1131] Under the same conditions as the method for synthesizing Compound J7-12, Compound J5 and 6-bromo-hexanoic acid ethyl ester were reacted to obtain the target compound (19.6 mg, 66%).

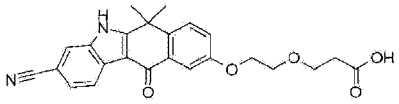
LCMS: m/z 417 $[M+H]^+$
HPLC retention time: 2.61 min (analysis condition F)

[Example 435]

Compound J7-15

3-[2-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-ethoxy]-propionic acid

[1132]



[1133] Under the same conditions as the method for synthesizing Compound A7-1, Compound JJ2 and 3-(2-hydroxy-ethoxy)-propionic acid tert-butyl ester were reacted to obtain 3-[2-(3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-ethoxy]-propionic acid tert-butyl ester.

[1134] The resultant was dissolved in DMA (0.30 ml), added with copper cyanide (25.5 mg, 0.285 mmol), and stirred at 200°C for 1 hr under irradiation with microwave. The reaction solution was diluted with ethyl acetate, washed with saturated brine and dried over anhydrous magnesium sulfate. The residues obtained after concentration under reduced pressure were dissolved in methylene chloride (0.75 ml). The solution was added with TFA (250 µl) and stirred at room temperature for 5 min. Thereafter, the residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (methylene chloride/MeOH) to obtain the title compound (5.6 mg, 14%).

LCMS: m/z 419 $[M+H]^+$

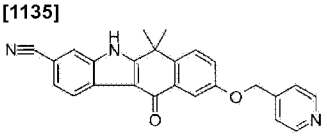
HPLC retention time: 2.31 min (analysis condition F)

[Example 436]

Compound J7-16

6,6-Dimethyl-11-oxo-9-(pyridin-4-ylmethoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1135]



[1136] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound J5 and pyridin-4-yl-methanol (pale yellow solid, 6.1 mg, 31%).

LCMS: m/z 394 $[M+H]^+$

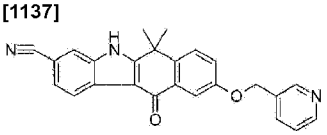
HPLC retention time: 1.97 min (analysis condition F)

[Example 437]

Compound J7-17

6,6-Dimethyl-11-oxo-9-(pyridin-3-ylmethoxy)-6,11-dihydro-5H-benzo[b]]carbazole-3-carbonitrile

[1137]



[1138] Under the same conditions as the method for synthesizing Compound JJ3-1, the title compound was prepared from Compound J5 and pyridin-3-yl-methanol (pale yellow solid, 7.9 mg, 38%).

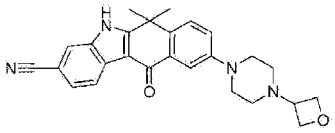
LCMS: m/z 394 $[M+H]^+$
HPLC retention time: 1.99 min (analysis condition F)

[Example 438]

Compound J8-1

6,6-Dimethyl-9-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1139]



[1140] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-7 and oxetan-3-one.

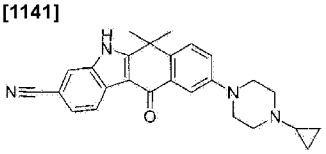
LCMS: m/z 427 $[M+H]^+$
HPLC retention time: 1.31 min (analysis condition S)

[Example 439]

Compound J8-2

9-(4-Cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1141]



[1142] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-7 and (1-ethoxycyclopropoxy)trimethylsilane.

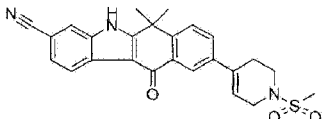
LCMS: m/z 411 $[M+H]^+$
HPLC retention time: 1.39 min (analysis condition S)

[Example 440]

Compound J8-3

9-[1-Methanesulfonyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1143]



[1144] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound J7-10-2.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.81 (1 H, s), 8.33 (1 H, d, 7.9 Hz), 8. 26 (1 H, d, 2.4 Hz), 8.01 (1 H, s), 7.88-7.81 (2 H, m), 7.61 (1 H, d, 7.9 Hz), 6.36 (1 H, s), 3.93 (2 H, d, 3.0 Hz), 3.45 (2 H, t, 5.8 Hz), 2.97 (3 H, s), 2.73-2. 70 (2 H, m), 1.78 (6 H, s)

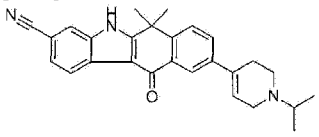
LCMS: m/z 446 $[M+H]^+$
HPLC retention time: 2.15 min (analysis condition S)

[Example 441]

Compound J8-4

9-(1-Isopropyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3 -carbonitrile

[1145]



[1146] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-10-2 and acetone.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.82 (1 H, s), 8.33 (1 H, d, 7.9 Hz), 8. 22 (1 H, d, 1.8 Hz), 8.02 (1 H, s), 7.84 (1 H, d, 8.5 Hz), 7.78 (1 H, dd, 8.2, 2.1 Hz), 7.62 (1 H, d, 7.9 Hz), 6.32 (1 H, t, 3.7 Hz), 3.23-3.20 (2 H, m), 2.83-2.76 (1 H, m), 2.72 (2 H, t, 5.5 Hz), 2.56-2.54 (2 H, m), 1.78 (6 H, s), 1.06 (6 H, d, 6.7 Hz)

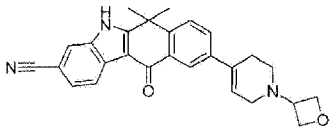
LCMS: m/z 410 $[M+H]^+$
HPLC retention time: 1.38 min (analysis condition S)

[Example 442]

Compound J8-5

6,6-Dimethyl-9-(1-oxetan-3-yl-1,2,3,6-tetrahydro-pyridin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1147]



[1148] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-10-2 and oxetan-3-one.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.81 (1 H, br. s), 8.34 (1 H, d, J = 8.2 Hz), 8.22 (1 H, d, J = 1.8 Hz), 8.03 (1 H, s), 7.76-7.90 (2 H, m), 7.64 (1 H, dd, J = 8. 2, 1.8 Hz), 6.25-6.34 (1 H, m), 4.60 (2 H, dd, J = 6.6, 6.0 Hz), 4.52 (2 H, dd, J = 6. 6, 6.0 Hz), 3.57 (1 H, t, J = 6.0 Hz), 3.03 (2 H, m), 2.55 (4 H, m), 1.77 (6 H, s).

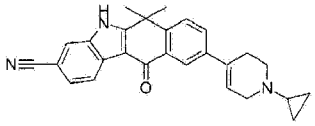
LCMS: m/z 424 $[M+H]^+$
HPLC retention time: 1.34 min (analysis condition S)

[Example 443]

Compound J8-6

9-(1-Cyclopropyl-1,2,3,6-tetrahydro-pyridin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1149]



[1150] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound J7-10-2 and (1-ethoxycyclopropoxy)trimethylsilane.

LCMS: m/z 408 $[M+H]^+$

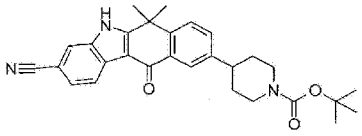
HPLC retention time: 1.36 min (analysis condition S)

[Example 444]

Compound J9-1

4-(3-Cyano-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl)-piperidine-1-carboxylic acid tert-butyl ester

[1151]



[1152] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound J7-10-1.

LCMS: m/z 414, 470 $[M+H]^+$

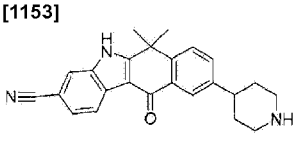
HPLC retention time: 2.83 min (analysis condition S)

[Example 445]

Compound J9-2

6,6-Dimethyl-11-oxo-9-piperidin-4-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1153]



[1154] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound J9-1.

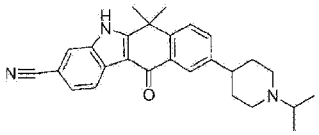
LCMS: m/z 370 $[M+H]^+$
HPLC retention time: 1.30 min (analysis condition S)

[Example 446]

Compound J9-3

9-(1-Isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1155]



[1156] Under the same conditions as the method for synthesizing Compound A9-1, the title compound was prepared from Compound J9-2 and 2-bromopropane.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.83 (1 H, s), 8.34 (2 H, d, J = 8.1 Hz), 8.05 (2 H, m), 7.82 (1 H, d, J = 8.1 Hz), 7.61 (2 H, m), 3.02 (2 H, br), 2.42 (2 H, br), 1.76 (6 H, s), 1.06 (6 H, d, J = 6.4 Hz).

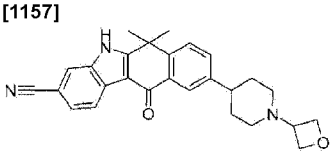
LCMS: m/z 412 $[M+H]^+$
HPLC retention time: 1.45 min (analysis condition S)

[Example 447]

Compound J9-4

6,6-Dimethyl-9-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1157]



[1158] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound J8-5.

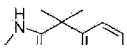
LCMS: m/z 426 $[M+H]^+$
HPLC retention time: 1.26 min (analysis condition S)

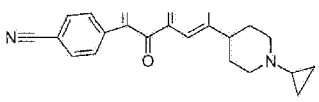
[Example 448]

Compound J9-5

9-(1-Cyclopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1159]





[1160] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound J8-6.

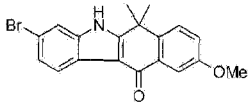
LCMS: m/z 410 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 449]

Compound JJ1

3-Bromo-9-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1161]



[1162] 6-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound J2, 2.15 g, 10.5 mmol) and 3-bromophenylhydrazine hydrochloric acid salt (3.11 g, 1.3 eq.) were dissolved in acetic acid (12 mL), and stirred at 100°C for 2.5 hr under nitrogen atmosphere. After cooling, the reaction solution was added with ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate, and saturated brine, and dried over magnesium sulfate. After the filtration, it was concentrated under reduced pressure. The resulting residues were dissolved in THF (30 mL) and water (3 mL), added with DDQ (5.96 g, 2.5 eq.) at 0°C, and then stirred at room temperature overnight. The reaction solution was added with MTBE, washed with 0.5 N aqueous solution of sodium hydroxide and saturated brine, and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting residues were washed with MTBE to obtain the title compound (brown solid, 1.80 g, 46%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.4 (1 H, s), 8.12 (1 H, d, J = 8.6 Hz), 7. 79 (1 H, d, J = 8.9 Hz), 7.67-7.68 (2 H, m), 7.40 (1 H, dd, J = 1.7, 8. 6 Hz), 7.26 (1 H, dd, J = 2.6, 8.9 Hz), 3.86 (3 H, s), 1.72 (6 H, s),

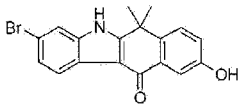
LCMS: m/z 370 $[M+H]^+$
HPLC retention time: 6.45 min (analysis condition H)

[Example 450]

Compound JJ2

3-Bromo-9-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1163]



[1164] 3-Bromo-9-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ1, 1.50 g, 4.05 mmol) and pyridinium chloride (15.2 g, 32.5 eq.) were stirred at 160°C for 12 hr under nitrogen atmosphere. After cooling, water and ethyl acetate were added and the resulting suspension was filtered. The organic layer was washed with water and saturated brine and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting residues were washed with MTBE to obtain the title compound (brown solid, 1.47 g, 100%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.4 (1 H, s), 9.71 (1 H, s), 8.11 (1 H, d, J = 8.2 Hz), 7.64-7.68 (2 H, m), 7.57 (1 H, d, J = 3.0 Hz),

7.38 (1 H, dd, J = 1.7, 8. 2 Hz), 7.07 (1 H, dd, J = 3.0, 8.6 Hz), 1.69 (6 H, s),

LCMS: m/z 356 $[M+H]^+$

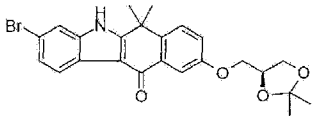
HPLC retention time: 2.52 min (analysis condition F)

[Example 451]

Compound JJ3-1

3-Bromo-9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1165]



[1166] Under nitrogen atmosphere, 3-bromo-9-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ2, 356 mg, 1.00 mmol) and triphenylphosphine (317 mg, 1.2 eq.) were added with THF (3 ml), followed by dropwise addition of ((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (148 µl, 1.2 eq.) and diisopropyl azodicarboxylic acid (252 µl, 1.3 eq.). The mixture was then stirred at 50°C for 2 hr. After cooling, the reaction solution was added with ethyl acetate, washed with brine and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting residues were purified by silica gel column chromatography (ethyl acetate/dichloromethane) to yield the solid, which was then washed with dichloromethane to obtain the title compound (white powder, 241.6 mg, 51%).

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.4 (1 H, s), 8.12 (1 H, d, J = 8.2 Hz), 7. 79 (1 H, d, J = 8.9 Hz), 7.67-7.69 (2 H, m), 7.40 (1 H, dd, J = 1.8, 8.2 Hz), 7.28 (1 H, dd, J = 3.0, 8.9 Hz), 4.41-4.48 (1 H, m), 4.06-4.17 (2 H, m), 3.79-3.85 (1 H, m), 1.72 (3 H, s), 1.38 (3 H, s), 1.33 (3 H, s),

LCMS: m/z 470 $[M+H]^+$

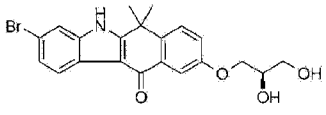
HPLC retention time: 3.08 min (analysis condition F)

[Example 452]

Compound JJ3-2

3-Bromo-9-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1167]



[1168] 3-Bromo-9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ3-1, 18.7 mg, 0.0398 mmol) was dissolved in methanol (1 mL) and THF (0.3 mL), added with 1 N hydrochloric acid (5 drops) and stirred at 50°C for 1 hr. After cooling, the reaction solution was concentrated under reduced pressure, and the resulting residues were added with dichloromethane, and the solid was separated by filtration to obtain the title compound (yellow powder, 16.8 mg, 98%).

[1169] ^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.43(1 H, s), 8.12 (1 H, d, J = 8.6 Hz), 7.78 (1 H, d, J = 8.9 Hz), 7.67-7.70 (2 H, m), 7.40 (2 H, dd, J = 1.8, 8.6 Hz), 7.27 (2 H, dd, J = 2.8, 8.9 Hz), 4.43 (2 H, brs), 4.12 (1 H, dd, J = 9.9, 4.3 Hz), 3.96 (1 H, dd, J = 9.7, 6.1 Hz), 3.85 (1 H, dd, J = 9.9, 5.6 Hz), 3.48 (2 H, d, J = 5.6 Hz), 1.72 (6 H, s),

LCMS: m/z 430 $[M+H]^+$

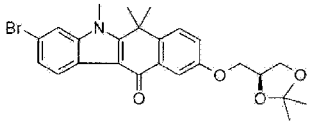
HPLC retention time: 2.02 min (analysis condition F)

[Example 453]

Compound JJ4-1

3-Bromo-9-((S)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1170]



[1171] To the mixture of 3-bromo-9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ3-1, 33.2 mg, 0.0706 mmol) and sodium hydride (60% in oil, 6.4 mg, 2.3 eq.), DMA (0.55 mL) and methyl iodide (0.015 mL, 3.4 eq.) were added under nitrogen atmosphere at 0°C, and the mixture was stirred at room temperature overnight. The reaction solution was added with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting solid was washed with MTBE to obtain the title compound (white solid, 31.2 mg, 91%).

LCMS: m/z 484 $[M+H]^+$

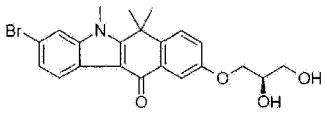
HPLC retention time: 3.34 min (analysis condition F)

[Example 454]

Compound JJ4-2

3-Bromo-9-((R)-2,3-dihydroxy-propoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1172]



[1173] Under the same conditions as the method for synthesizing Compound JJ3-2, the title compound was prepared from Compound JJ4-1 (yellow solid, 13.3 mg, 83%).

LCMS: m/z 444 $[M+H]^+$

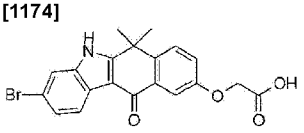
HPLC retention time: 2.47 min (analysis condition F)

[Example 455]

Compound JJ5

(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-acetic acid

[1174]



[1175] Under the same conditions as the method for synthesizing Compound A7-1, (3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-acetic acid methyl ester was prepared from Compound JJ2 and hydroxy-acetic acid methyl ester. The resultant was dissolved in MeOH (0.35 ml), added with aqueous solution of sodium hydroxide (6 mol/l), and stirred at room temperature for 10 min. The reaction solution was added with hydrochloric acid (3 mol/l), extracted with diethyl ether and dried over anhydrous magnesium sulfate. After the concentration under reduced pressure, white solid was obtained, which was then washed with methylene chloride to obtain the title compound (11.2 mg, 48%).

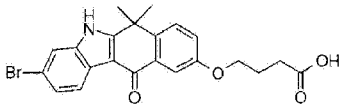
LCMS: m/z 414 $[M+H]^+$
HPLC retention time: 2.50 min (analysis condition F)

[Example 456]

Compound JJ6

4-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-butyric acid

[1176]



[1177] 3-Bromo-9-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ2, 20 mg, 0.056 mmol), 4-bromo-butyric acid methyl ester (7.0 µl, 0.056 mmol) and cesium carbonate (36.6 mg, 0.112 mmol) were dissolved in DMA (0.09 ml), and then stirred at room temperature for 1 hr. Thereafter, 4-bromo-butyric acid methyl ester (7.0 µl, 0.056 mmol) was added thereto and the mixture was stirred at room temperature for 3 hr, followed by further stirring at 45°C for 30 min. The reaction solution was added with water, extracted with diethyl ether and dried over anhydrous magnesium sulfate. After the concentration under reduced pressure, the resulting residues were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 4-(3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-9-yl oxy)-butyric acid methyl ester. This compound was dissolved in MeOH (0.50 ml), added with aqueous solution of sodium hydroxide (6 mol/l), and then stirred at room temperature for 10 min. The reaction solution was added with hydrochloric acid (3 mol/l), extracted with diethyl ether, and dried over anhydrous magnesium sulfate and concentrated under reduced pressure to obtain white solid. This white solid was washed with methylene chloride to obtain the title compound (6.1 mg, 25%).

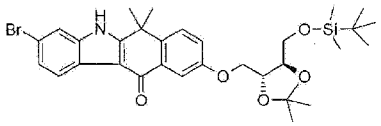
LCMS: m/z 442 $[M+H]^+$
HPLC retention time: 2.65 min (analysis condition F)

[Example 457]

Compound JJ7-1

3-Bromo-9-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-5,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1178]



[1179] Under the same conditions as the method for synthesizing Compound A7-1, the title compound (white solid, 111.5 mg, 65%) was prepared from Compound JJ2 and [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol.

LCMS: m/z 614 $[M+H]^+$

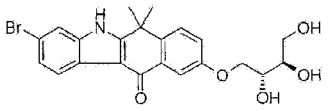
HPLC retention time: 4.04 min (analysis condition F)

[Example 458]

Compound JJ7-2

3-Bromo-6,6-dimethyl-9-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1180]



[1181] 3-Bromo-9-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ7-1, 13.7 mg, 0.0223 mmol) was dissolved in THF (0.15 mL) and methanol (0.1 mL), added with 0.5 M sulfuric acid (0.05 mL), and then stirred at 60°C for 3 hr. After cooling, the reaction solution was added with saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting solid was washed with dichloromethane to obtain the title compound (white solid, 8.4 mg, 82%).

LCMS: m/z 460 $[M+H]^+$

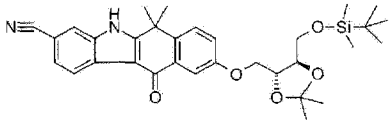
HPLC retention time: 2.18 min (analysis condition F)

[Example 459]

Compound JJ8-1

9-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4yl methoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1182]



[1183] According to the same method as the method for synthesizing Compound A5-2, the title compound (11.1 mg, 50%) was prepared from Compound JJ7-1 and [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol.

LCMS: m/z 561 $[M+H]^+$

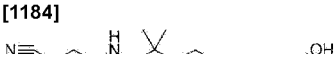
HPLC retention time: 3.84 min (analysis condition F)

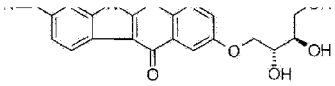
[Example 460]

Compound JJ8-2

6,6-Dimethyl-11-oxo-9-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1184]





[1185] Under the same conditions as the method for synthesizing Compound JJ7-2, the title compound was prepared from 9-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound JJ8-1) (white solid, 7.8 mg, 97%).

LCMS: m/z 407 $[M+H]^+$

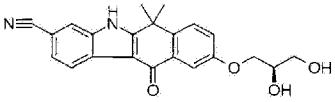
HPLC retention time: 1.92 min (analysis condition F)

[Example 461]

Compound JJ9-1

9-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6.11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1186]



[1187] 3-Bromo-9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound JJ3-1, 49.5 mg, 0.105 mmol) and copper cyanide (90%, 35.3 mg, 3.4 eq.) were added with DMA (0.5 mL), and the mixture was irradiated with microwave at 200°C for 1 hr under nitrogen atmosphere. After cooling, the reaction solution was added with water and extracted with ethyl acetate. The insoluble matters were separated off by filtration, and the organic layer was washed with brine and dried over magnesium sulfate. After filtration and the concentration under reduced pressure, the resulting residues were purified by preparative TLC (methanol/dichloromethane) to obtain the title compound (white solid, 8.5 mg, 22%).

LCMS: m/z 377 $[M+H]^+$

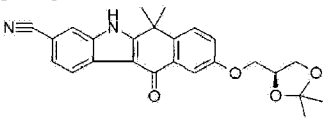
HPLC retention time: 2.02 min (analysis condition F)

[Example 462]

Compound JJ9-2

9-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1188]



[1189] The title compound was obtained as a by-product of the synthesis of Compound JJ9-1 (white solid, 24.8 mg, 57%).

LCMS: m/z 417 $[M+H]^+$

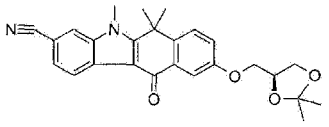
HPLC retention time: 2.81 min (analysis condition F)

[Example 463]

Compound JJ9-3

9-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1190]



[1191] Under the same conditions as the method for synthesizing Compound JJ4-1, the title compound was prepared from 9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound JJ9-2) (17.0 mg, 84%).

LCMS: m/z 431 $[M+H]^+$

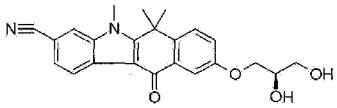
HPLC retention time: 3.00 min (analysis condition F)

[Example 464]

Compound JJ9-4

9-((R)-2,3-Dihydroxy-propoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1192]



[1193] Under the same conditions as the method for synthesizing Compound JJ3-2, the title compound was prepared from 9-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (JJ9-3) (white solid, 12.1 mg, 90%).

LCMS: m/z 391 $[M+H]^+$

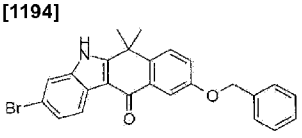
HPLC retention time: 2.13 min (analysis condition F)

[Example 465]

Compound JJ10-1

9-Benzyloxy-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1194]



[1195] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound JJ2 and benzyl bromide (18.2 mg, 61%).

LCMS: m/z 446 $[M+H]^+$

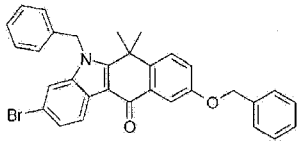
HPLC retention time: 2.68 min (analysis condition D)

[Example 466]

Compound JJ10-2

5-Benzyl-9-benzyloxy-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11 -one

[1196]



[1197] The title compound was obtained as a by-product of the synthesis of Compound JJ10-1 (5.3 mg, 21%).

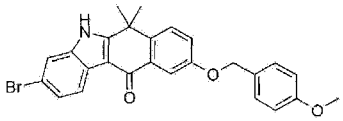
LCMS: m/z 536 $[M+H]^+$
HPLC retention time: 3.17 min (analysis condition D)

[Example 467]

Compound JJ10-3

3-Bromo-9-(4-methoxy-benzyloxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1198]



[1199] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared by reacting Compound JJ2 and (4-methoxyphenyl)-methanol (7.5 mg, 28%).

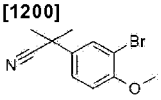
LCMS: m/z 476 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition D)

[Example 468]

Compound K2

2-(3-Bromo-4-methoxy-phenyl)-2-methyl-propionitrile

[1200]



[1201] To the THF suspension of potassium tert-butoxide (15.35 g, 3 eq.), (3-bromo-4-methoxyphenyl)acetonitrile (Compound K1, 10 g, 0.044 mmol) was added, and then stirred at 0°C for 1 hr. Then, iodomethane (8.26 ml, 3 eq.) was added and the mixture was stirred at room temperature for 1 hr. To the reaction solution, saturated aqueous solution of ammonium chloride and water were added

followed by extraction with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (colorless oily substance, 11.24 g, 100%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 7.69 (1 H, d, J = 2. 5 Hz), 7.50 (1 H, dd, J = 8.6, 2.5 Hz), 7.16 (1 H, d, J = 8.6 Hz), 3.86 (3 H, s), 1.67 (6 H, s).

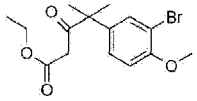
HPLC retention time: 2.30 min (analysis condition S)

[Example 469]

Compound K3

4-(3-Bromo-4-methoxy-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1202]



[1203] To the THF suspension of zinc (5.72 g, 2 eq.), methanesulfonic acid (25.6 µl, 0.01 eq.) was added, and then stirred at 80°C for 10 min. Then, the THF solution of 2-(3-bromo-4-methoxy-phenyl)-2-methyl-propionitrile (10 g, 39.35 mmol) was added , followed by addition of bromoethyl acetate (11.07 ml, 1.6 eq.) over 1 hr. The mixture was further stirred for 30 min. To the reaction solution, 4 M hydrochloric acid was added, and stirred at room temperature overnight. After extraction with ethyl acetate, the organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (orange oily substance, 9.74 g, 72%).

^{1}H-NMR (270 MHz, $CDCl_3$) δ : 7.46 (1 H, d, J = 2.5 Hz), 7.16 (1 H, dd, J = 8.6, 2.5 Hz), 6.89 (1 H, d, J = 8.6 Hz), 4.17-4.08 (2 H, m), 3.90 (3 H, s), 3.26 (2 H, s), 1.49 (6 H, s), 1.23 (3 H, t, J = 7.2 Hz).

LCMS: m/z 343, 345 $[M+H]^+$

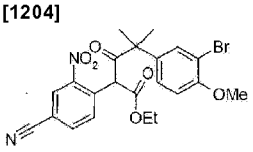
HPLC retention time: 2.64 min (analysis condition S)

[Example 470]

Compound K4

4-(3-Bromo-4-methoxy-phenyl)-2-(4-cyano-2-nitro-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1204]



[1205] 4-(3-Bromo-4-methoxy-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester (Compound K3, 10.3 g, 30.01 mmol) was dissolved in DMF (80 mL), added with cesium carbonate (24.4 g, 2.5 eq.) and 4-chloro-3-nitro-benzonitrile (7.12 g, 1.3 eq.), and then stirred at 45°C for 4 hr. The reaction solution was added to 1 N aqueous solution of hydrochloric acid, and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration, and after concentration under reduced pressure the title compound was obtained as a crude product (yellow oily substance).

LCMS: m/z 489, 491 $[M+H]^+$

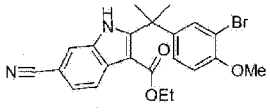
HPLC retention time: 2.85, 3.20 min (analysis condition S)

[Example 471]

Compound K5

2-[1-(3-Bromo-4-methoxy-phenyl)-1-methyl-ethyl]-6-cyano-1H-indole-3-carboxylic acid ethyl ester

[1206]



[1207] 4-(3-Bromo-4-methoxy-phenyl)-2-(4-cyano-2-nitro-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester (Compound K4), which had been obtained from the above, was dissolved in THF (140 mL) and water (70 mL), added with $Na_2S_2O_4$ (26.13 g, 5.0 eq.) and stirred at 50°C overnight. The reaction solution was added to saturated brine and extracted with ethyl acetate. The organic layer was washed with 1 M aqueous solution of potassium carbonate and saturated brine in order, and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by crystallization in MeCN (80 ml) to obtain the title compound (yellow solid, 8.20 g, 62%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.15 (1 H, s), 8.07 (1 H, d, J = 8.4 Hz), 7.94 (1 H, s), 7.51 (1 H, dd, J = 8.5, 1.2 Hz), 7.33 (1 H, d, J = 2.1 Hz), 7.03 (1 H, dd, J = 8.7, 2.4 Hz), 6.96 (1 H, d, J = 8.4 Hz), 3.97 (2 H, q, J = 7.3 Hz), 3.78 (3 H, s), 1.80 (6 H, s), 1.09 (3 H, t, J = 7.2 Hz).

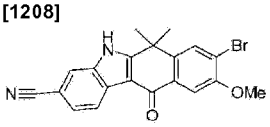
LCMS: m/z 441, 443 $[M+H]^+$
HPLC retention time: 2.85 min (analysis condition S)

[Example 472]

Compound K6

8-Bromo-9-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1208]



[1209] Phosphorus pentoxide-methanesulfonic acid (12 mL) was added with 2-[1-(3-bromo-4-methoxy-phenyl)-1-methyl-ethyl]-6-cyano-1H-indole-3-carboxylic acid ethyl ester (Compound K5, 1.0 g, 2.27 mmol), and the mixture was stirred at room temperature for 20 min. The reaction solution was diluted with MeCN (20 mL), poured into water (20 mL), and the precipitated solid was filtered to obtain the title compound (yellow solid, 763 mg, 85%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.84 (1 H, s), 8.32 (1 H, d, J = 8.1 Hz), 8.15 (1 H, s), 8.03 (1 H, s), 7.77 (1 H, s), 7.64 (1 H, dd, J = 8.2,1. 4 Hz), 3.97 (3 H, s), 1.75 (6 H, s).

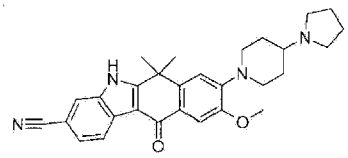
LCMS: m/z 395, 397 $[M+H]^+$
HPLC retention time: 2.58 min (analysis condition S)

[Example 473]

Compound K7-1

9-Methoxy-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1210]



[1211] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound K6 and 4-pyrrolidin-1-yl-piperidine.

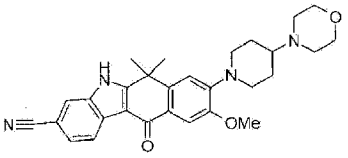
LCMS: m/z 469 $[M+H]^+$
HPLC retention time: 1.37 min (analysis condition S)

[Example 474]

Compound K7-2

9-Methoxy-6,6-dimethyl-8-(4-morpholin-1-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1212]



[1213] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound K6 and 4-piperidin-4-yl-morpholine.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.70 (1 H, s), 8.31 (1 H, d, J = 8.2 Hz), 7.99 (1 H, s), 7.63 (1 H, s), 7.60 (1 H, dd, J = 8.2, 1.2 Hz), 7.16 (1 H, s), 3.89 (3 H, s), 3.64 (2 H, brd), 2.72 (2 H, brd), 1.91 (2 H, brd), 1.73 (6 H, s), 1.57 (2 H, brd).

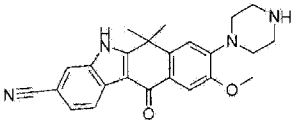
LCMS: m/z 485 $[M+H]^+$
HPLC retention time: 1.33 min (analysis condition S)

[Example 475]

Compound K7-3

9-Methoxy-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1214]



[1215] Under the same conditions as the method for synthesizing Compound B2-1, the target compound was prepared from Compound K6 and piperazine.

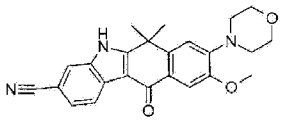
LCMS: m/z 401 $[M+H]^+$
HPLC retention time: 1.31 min (analysis condition S)

[Example 476]

Compound K7-4

9-Methoxy-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1216]



[1217] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound K6 and morpholine.

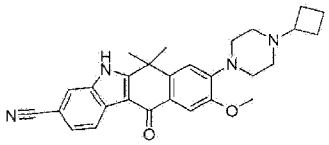
LCMS: m/z 402 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition S)

[Example 477]

Compound K8

8-(4-Cyclobutyl-piperazin-1-yl)-9-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1218]



[1219] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound K7-3 and cyclobutanone.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.70 (1 H, br. s), 8.31 (1 H, d, J = 8.2 Hz), 8.00 (1 H, s), 7.64 (1 H, s), 7.61 (1 H, dd, J = 8.1, 1.3 Hz), 7.16 (1 H, s), 3.88 (3 H, s), 3.60 (1 H, t, J = 6.2 Hz), 3.10-3.25 (4 H, m), 2.77 (1 H, t, J = 7.1 Hz), 2.35-2.51 (4 H, m), 1.74(6 H, s), 1.58-2.08(6 H, m).

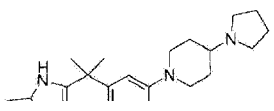
LCMS: m/z 455 $[M+H]^+$
HPLC retention time: 1.45 min (analysis condition S)

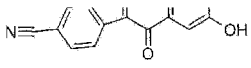
[Example 478]

Compound K9-1

9-Hydroxy-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1220]





[1221] The title compound was obtained as a by-product of the synthesis of Compound K7-1.

LCMS: m/z 455 $[M+H]^+$

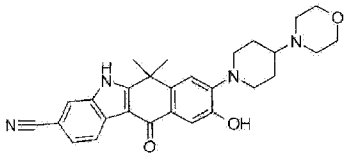
HPLC retention time: 1.22 min (analysis condition S)

[Example 479]

Compound K9-2

9-Hydroxy-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1222]



[1223] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound K7-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.65 (1 H, s), 9.61 (1 H, s), 8.30 (1 H, d, J = 8.2 Hz), 7.98 (1 H, s), 7.59-7.56 (2 H, m), 7.10 (1 H, s), 3.71 (2 H, brd, J = 11. 2 Hz), 3.60 (4 H, m), 2.66 (2 H, m), 1.88 (2 H, brd, J = 9.7 Hz), 1.71 (6 H, s), 1.57 (2 H, brd).

LCMS: m/z 471 $[M+H]^+$

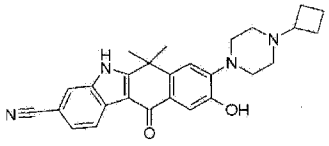
HPLC retention time: 1.20 min (analysis condition S)

[Example 480]

Compound K9-3

8-(4-Cyclobutyl-piperazin-1-yl)-9-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1224]



[1225] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound K8.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.66 (1 H, br. s), 9.67 (1 H, s), 8.31 (1 H, d, J = 8.2 Hz), 7.98 (1 H, s), 7.56-7. 60 (2 H, m), 7.09 (1 H, s), 3.10-3.24 (4 H, m), 2.77 (1 H, t, J = 7.5 Hz), 2.37-2.49 (4 H, m), 1.52-2.07 (6 H, m), 1.72 (6 H, s).

LCMS: m/z 441 $[M+H]^+$

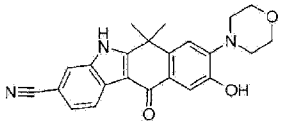
HPLC retention time: 1.31 min (analysis condition S)

[Example 481]

Compound K9-4

9-Hydroxy-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1226]



[1227] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound K7-4.

LCMS: m/z 388 $[M+H]^+$

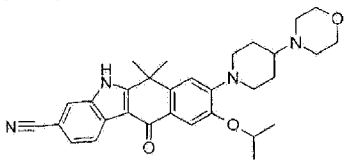
HPLC retention time: 1.67 min (analysis condition S)

[Example 482]

Compound K10-1

9-Isopropoxy-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1228]



[1229] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-2 and 2-bromopropane.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.68 (1 H, s), 8.30 (1 H, d, J = 8.1 Hz), 7.99 (1 H, s), 7.60 (2 H, m), 7.14 (1 H, s), 4.72-4.63 (2 H, m), 3.71 (2 H, brd, J = 10. 7 Hz), 3.59 (6 H, m), 2.68 (2 H, t, J = 12.9 Hz), 2.27 (2 H, brd), 1.90 (2 H, brd), 1.73 (6 H, s), 1.56 (2 H, br), 1.34 (6 H, d, J = 5.9 Hz).

LCMS: m/z 513 $[M+H]^+$

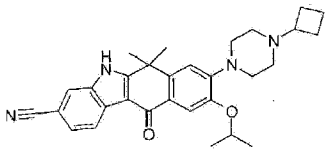
HPLC retention time: 1.48 min (analysis condition S)

[Example 483]

Compound K10-2

8-(4-Cyclobutyl-piperazin-1-yl)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1230]



[1231] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-3 and 2-iodopropane.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.29 (1 H, d, J = 8.1 Hz), 7.98 (1 H, s), 7.56-7.63 (2 H, m), 7.14 (1 H, s), 4.62-4.74 (1 H, m), 3.10-3.26 (4 H, m), 2.69-2. 85 (1 H, m), 2.35-2.48 (4 H, m), 1.57-2.08 (6 H, m), 1.73 (6 H, s), 1.32 (6 H, d, J = 6.1 Hz).

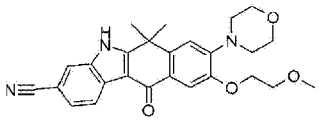
LCMS: m/z 483 $[M+H]^+$
HPLC retention time: 1.65 min (analysis condition S)

[Example 484]

Compound K10-3

9-(2-Methoxy-ethoxy)-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1232]



[1233] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-4 and 1-bromo-2-methoxyethane.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.67 (1 H, s), 8. 30 (1 H, d, 7.9 Hz), 7. 98 (1 H, s), 7.64 (1, s), 7.58 (1 H, d, 7.9 Hz), 7.16 (1 H, s), 4.18-4.22 (2 H, m), 3. 72-3.80 (6 H, m), 3.35 (3 H, s), 3.18-3.24 (4 H, s), 1.74 (1 H, s)

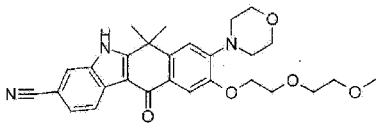
LCMS: m/z 446 $[M+H]^+$
HPLC retention time: 3.23 min (analysis condition W)

[Example 485]

Compound K10-4

9-[2-(2-Methoxy-ethoxy)-ethoxy]-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1234]



[1235] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-4 and 1-bromo-2-(2-methoxyethoxy)ethane.

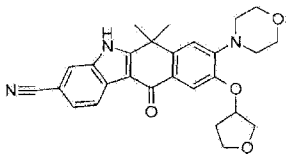
LCMS: m/z 490 $[M+H]^+$
HPLC retention time: 3.16 min (analysis condition W)

[Example 486]

Compound K10-5

6,6-Dimethyl-8-morpholin-1-yl-11-oxo-9-[(S)-(tetrahydro-furan-3-yl)oxy]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1236]



[1237] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-4 and 3-mesyloxytetrahydrofurane.

LCMS: m/z 458 $[M+H]^+$

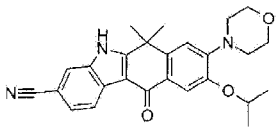
HPLC retention time: 3.20 min (analysis condition W)

[Example 487]

Compound K10-6

9-Isopropoxy-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1238]



[1239] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-4 and 2-bromopropane.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.70 (1 H, br. s), 8.32-8.29 (1 H, d, 8. 08 Hz), 8.00 (1 H, s), 7.63 (1 H, s), 7.62-7.59 (1 H, d, 8.08 Hz), 7.16 (1 H, s), 4.75-4.66 (1 H, m), 3.77 (4 H, m) 3.19 (4 H, m), 1.74 (6 H, s), 1.35 (3 H, s), 1.33 (3 H, s)

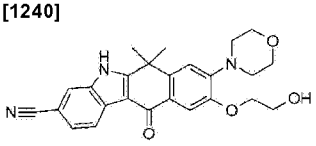
LCMS: m/z 430 $[M+H]^+$

[Example 488]

Compound K10-7

9-(2-Hydroxy-ethoxy)-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1240]



[1241] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-4 and 2-bromoethanol.

^{1}H-NMR(270 MHz, DMSO-d_6) δ : 12.71 (1 H, br. s), 8.33-8.30 (1 H, d, 8. 08 Hz), 8.00 (1 H, s), 7.63 (1 H, s), 7.62-7.59 (1 H, d, 8.08 Hz), 7.16 (1 H, s), 4.13-4.09 (2 H, t, 4.61 Hz), 3. 81-3.78 (2 H, t, 4.61 Hz), 3.78 (4 H, m) 3.23 (4 H, m), 1.75 (6 H, s)

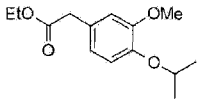
LCMS: m/z 432 $[M+H]^+$

[Example 489]

Compound L2-1

(4-Isopropoxy-3-methoxy-phenyl)-ethyl acetate ester

[1242]



[1243] (4-Hydroxy-3-methoxy-phenyl)-ethyl acetate ester (Compound L1-1, 3.0 g, 14.27 mmol) was dissolved in DMF (70 mL), added with 2-iodopropane (2.9 mL, 2.0 eq.) and potassium carbonate (3.94 g, 2.0 eq.), and stirred at 80°C overnight. The reaction solution was added to water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (yellow oily substance, 2.61 g, 73%).

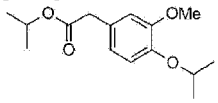
^{1}H-NMR (270 MHz, DMSO-d_6) δ : 6.88 (2 H, m), 6.74 (1 H, dd, J = 8.1, 2. 1 Hz), 4.52-4.43 (1 H, m), 4.07 (2 H, q, J = 7.1 Hz), 3.72 (3 H, s), 3.56 (2 H, s), 1.23 (6 H, d, J = 6.1 Hz), 1.18 (3 H, t, J = 7.1 Hz). LCMS: m/z 253 $[M+H]^+$
HPLC retention time: 2.18 min (analysis condition S)

[Example 490]

Compound L2-2

(4-Isopropoxy-3-methoxy-phenyl)-acetic acid isopropyl ester

[1244]



[1245] (4-Hydroxy-3-methoxy-phenyl)-acetic acid (Compound L1-2, 1.5 g, 8.23 mmol) was dissolved in DMF (30 mL), added with 2-iodopropane (3.3 mL, 4.0 eq.) and potassium carbonate (4.55 g, 4.0 eq.), and stirred at 80°C overnight. The reaction solution was added to water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (yellow oily substance, 1.21 g, 55%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 6.87 (2 H, s+d), 6.73 (1 H, dd, J = 8.1, 2. 1 Hz), 4.94-4. 84 (1 H, m), 4.52-4. 43 (1 H, m), 3.72 (3H, s), 3.52 (2 H, s), 1.23 (6 H, d, J = 6.1 Hz), 1.18 (6 H, d, J = 6.1 Hz).

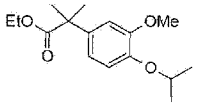
LCMS: m/z 267 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition S)

[Example 491]

Compound L3-1

2-(4-Isopropoxy-3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester

[1246]



[1247] Under the same conditions as the method for synthesizing Compound K2, the title compound was prepared from Compound L2-1.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 6. 90-6.76 (3 H, m), 4. 53-4.44 (1 H, m), 4.06 (2 H, q, J = 7.1 Hz), 3.73 (3 H, s), 1.47 (6 H, s), 1.23 (6 H, d, J = 6.1 Hz), 1.12 (3 H, t, J = 7.0 Hz).

LCMS: m/z 281 $[M+H]^+$

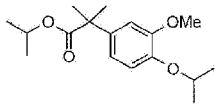
HPLC retention time: 2.57 min (analysis condition S)

[Example 492]

Compound L3-2

2-(4-Isopropoxy-3-methoxy-phenyl)-2-methyl-propionic acid isopropyl ester

[1248]



[1249] Under the same conditions as the method for synthesizing Compound K2, the title compound was prepared from Compound L2-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 6.88 (1 H, d, J = 8.2 Hz), 6.79 (2 H, m), 4.94-4.84 (1 H, m), 4.53-4. 44 (1 H, m), 3.72 (3 H, s), 1.45 (6 H, s), 1.23 (6 H, d, J = 6.1 Hz), 1.12 (6 H, d, J = 6.3 Hz).

LCMS: m/z 295 $[M+H]^+$

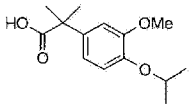
HPLC retention time: 2.75 min (analysis condition S)

[Example 493]

Compound L4

2-(4-Isopropoxy-3-methoxy-phenyl)-2-methyl-propionic acid

[1250]



[1251] 2-(4-Isopropoxy-3-methoxy-phenyl)-2-methyl-propionic acid ethyl ester (Compound L3-1, 1.45 g, 5.17 mmol) was dissolved in THF (13 mL) and EtOH (13 mL), added with 1 N aqueous solution of sodium hydroxide (10.3 mL, 2.0 eq.), and stirred at 80°C overnight. The reaction solution was added to water and extracted with ethyl acetate. The aqueous layer was acidified by using 1 N aqueous solution of hydrochloric acid, extracted with ethyl acetate, washed with saturated brine and dried over sodium sulfate. The

drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (white solid, 1.10 g, 84%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.26 (1 H, s), 6.90-6.80 (3 H, m), 4.49 (1 H, m), 3.73 (3 H, s), 1.45 (6 H, s), 1.23 (6 H, d, J = 6.1 Hz).

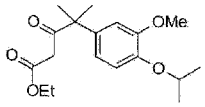
LCMS: m/z 253 $[M+H]^+$
HPLC retention time: 1.83 min (analysis condition S)

[Example 494]

Compound L5

4-(4-Isopropoxy-3-methoxy-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1252]



[1253] 2-(4-Isopropoxy-3-methoxy-phenyl)-2-methyl-propionic acid (Compound L4, 1.4 g, 5.55 mmol) was added with thionyl chloride (10 mL), and then stirred at room temperature for 5 hr. According to the concentration under reduced pressure, unreacted thionyl chloride was removed to obtain corresponding acid chloride.

[1254] To MeCN (40 mL), malonic acid monoethyl ester potassium salt (1.98 g, 2.1 eq.), triethylamine (2.47 mL, 3.2 eq.), and magnesium chloride (1.32 g, 2.5 eq.) were added and the mixture was stirred at room temperature for 2 hr. To the reaction solution, MeCN (15 mL) solution of the acid chloride prepared from the above was added dropwise. Upon the completion of the dropwise addition, the mixture was further stirred at room temperature for overnight. MeCN was removed by distillation and concentrated under reduced pressure, and the resulting residues were added with 1 N aqueous solution of hydrochloric acid, extracted with toluene, washed with saturated brine, and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (yellow oily substance, 1.45 g, 81%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 6.94 (1 H, d, J = 8.2 Hz), 6.76 (2 H, m), 4.56-4.47 (1 H, m), 4.00 (2 H, q, J = 7.1 Hz), 3.74 (3 H, s), 3.38 (2 H, s), 1.41 (6 H, s), 1.24 (6 H, d, J = 6.1 Hz), 1.12 (3 H, t, J = 7.3 Hz).

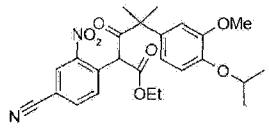
LCMS: m/z 323 $[M+H]^+$
HPLC retention time: 2.45, 3.03 min (analysis condition S)

[Example 495]

Compound L6

2-(4-Cyano-2-nitro-phenyl)-4-(4-isopropoxy-3-methoxy-phenyl)-4-methyl-3-oxo-pentanoic acid ethyl ester

[1255]



[1256] Under the same conditions as the method for synthesizing Compound K4, the title compound was prepared from Compound L5.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 8.35 (1 H, d, J = 1.8 Hz), 8.14 (1 H, dd, J = 8.2, 1.9 Hz), 7.67 (1 H, d, J = 8.2 Hz), 6.68 (1 H, d, J =

8.4 Hz), 6.59 (1 H, dd, J = 8.4, 2.0 Hz), 6.45 (1 H, d, J = 2.1 Hz), 5.44 (1 H, s), 4.43 (1 H, m), 4.09 (2 H, q, J = 7.1 Hz), 3.53 (3 H, s), 1.59 (3 H, s), 1.35 (3 H, s), 1.24 (6 H, dx2), 1.13 (3 H, t, J = 7.1 Hz).

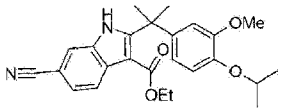
LCMS: m/z 469 $[M+H]^+$
HPLC retention time: 2.85, 3.10 min (analysis condition S)

[Example 496]

Compound L7

6-Cyano-2-[1-(4-isopropoxy-3-methoxy-phenyl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid ethyl ester

[1257]



[1258] Under the same conditions as the method for synthesizing Compound K5, the title compound was prepared from Compound L6.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.04 (1 H, s), 8.05 (1 H, d, J = 8.4 Hz), 7.93 (1 H, s), 7.49 (1 H, dd, J = 8.4, 1.5 Hz), 6.79 (2 H, m), 6.54 (1 H, dd, J = 8.3, 1. 9 Hz), 4.43 (1 H, t, J = 6.1 Hz), 3.94 (2 H, q, J = 7.0 Hz), 3.65 (3 H, s), 1.81 (6 H, s), 1.21 (6 H, d, J = 5.9 Hz), 1.05 (3 H, t, J = 7.1 Hz).

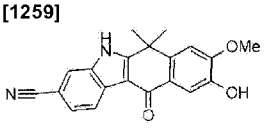
LCMS: m/z 421 $[M+H]^+$
HPLC retention time: 2.82 min (analysis condition S)

[Example 497]

Compound L8-1

9-Hydroxy-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1259]



[1260] 6-Cyano-2-[1-(4-isopropoxy-3-methoxy-phenyl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid ethyl ester (Compound L7, 1.25 g, 2.97 mmol) was dissolved in MeCN (18 mL), added with methanesulfonic acid (3.75 mL), and then stirred at 50°C for 8 hr. Hexane was added to the reaction solution, and the precipitated solid was filtered to obtain the title compound (yellow solid, 185 mg, 19%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.67 (1 H, s), 8.30 (1 H, d, J = 8.2 Hz), 7.99 (1 H, s), 7.59 (2 H, m), 7.28 (1 H, s), 3.93 (3 H, s), 1.75 (6 H, s).

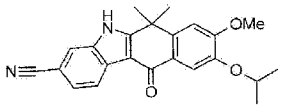
LCMS: m/z 333 $[M+H]^+$
HPLC retention time: 1.73 min (analysis condition S)

[Example 498]

Compound L8-2

9-Isopropoxy-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1261]



[1262] To the filtrate obtained from the synthesis of Compound L8-1, water was added and the extraction was carried out with ethyl acetate. The resultant was washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the concentration was performed under reduced pressure to obtain the target compound (red amorphous, 830 mg, 75%).

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.72 (1 H, s), 8.31 (1 H, d, J = 8.4 Hz), 8.01 (1 H, d, J = 0.7 Hz), 7.66 (1 H, s), 7.61 (1 H, dd, J = 8.2, 1.4 Hz), 7.33 (1 H, s), 4.65 (1 H, m), 3.93 (3 H, s), 1.77 (6 H, s), 1.32 (6 H, d, J = 6.1 Hz).

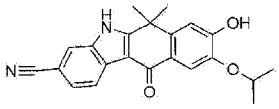
LCMS: m/z 375 $[M+H]^+$
HPLC retention time: 2.38 min (analysis condition S)

[Example 499]

Compound L9

8-Hydroxy-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1263]



[1264] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound L8-2.

^{1}H-NMR (270 MHz, DMSO-d_6) δ : 12.69 (1 H, s), 9.69 (1 H, s), 8.30 (1 H, d, J = 8.1 Hz), 7.99 (1 H, s), 7.65 (1 H, s), 7.60 (1 H, dd, J = 8.2, 1.2 Hz), 7.17 (1 H, s), 4.64 (1 H, m), 1.69 (6 H, s), 1.32 (6 H, d, J = 6.1 Hz).

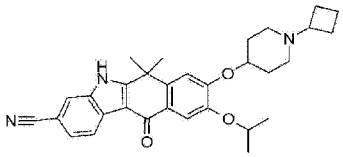
LCMS: m/z 361 $[M+H]^+$
HPLC retention time: 2.20 min (analysis condition S)

[Example 500]

Compound L10-1

8-(1-Cyclobutyl-piperidin-4-yloxy)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1265]



[1266] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound L9 and 1-cyclobutylpiperidin-4-ol.

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 9.31 (1 H, br. s), 8. 54-8.50 (1 H, d, 8.08 Hz), 7.90 (1 H, s), 7.77 (1 H, s), 7.59-7.55 (1 H, m), 7.09 (1 H, s), 4.70-4. 61 (1 H, m), 4.52-4.43 (1 H, m), 2.79-2.73 (1 H, m), 2.70-2.60 (2 H, m), 2.25-2.16 (2 H, m), 2.09-1.99 (4 H, m), 1.98-1.88 (4 H, m), 1.77 (6 H, s), 1.72-1.58 (2 H, m), 1.39 (3 H, s), 1.37 (3 H, s)

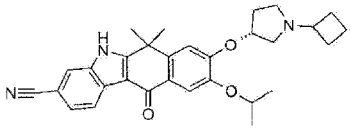
LCMS: m/z 498 $[M+H]^+$

[Example 501]

Compound L10-2

8-((R)-1-Cyclobutyl-pyrrolidin-3-yloxy)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1267]



[1268] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound L9 and (S)-1-cyclobutylpyrrolidin-3-ol.

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 10.63 (1 H, br. s), 8.51-8.48 (1 H, d, 8.08 Hz), 7.89 (1 H, s), 7.85 (1 H, s), 7.55-7.51 (1 H, m), 6.99 (1 H, s), 5.03-4.97 (1 H, m), 4.71-4.62 (1 H, m), 3.07-292 (2 H, m), 2.84-2.73 (2 H, m), 2.64-2.53 (1 H, m), 2.36-2.23 (2 H, m), 2.10-1.97 (2 H, m), 1.83-1.67 (2 H, m), 1.78 (6 H, s), 1.53-1. 46 (2 H, m), 1.39 (3 H, s), 1.37 (3 H, s)

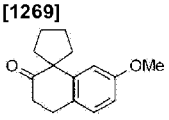
LCMS: m/z 484 $[M+H]^+$

[Example 502]

Compound M1

7-Methoxy-3,4-dihydro-2H-spiro[cyclopentane-1,1'-naphthalen]-2-one

[1269]



[1270] To the THF (300 ml) solution of 7-methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 0.5 g, 2.84 mmol), sodium hydride (36.4 mg, 2.2 eq.) was added at 0°C. After stirring for 20 min, 1,4-dibromobutane (0.74 ml, 1.2 eq.) was added dropwise thereto, and the mixture was stirred at 80°C for 4 hr. To the reaction solution, saturated aqueous solution of ammonium chloride was added followed by extraction with ethyl acetate. The organic layer was washed with saturated aqueous solution of ammonium chloride and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (yellow solid, 0.31 g, 47%).

^{1}H-NMR($CDCl_3$, 300 MHz) δ : 1.79-1.92(6 H, m), 2.42-2.27(m, 2 H), 3. 03(t, 2 H, J = 6.5 Hz), 3.81(t, 2 H, J = 6.5 Hz), 3.81(s, 3 H), 6.73(dd, 1 H, J = 2.7 Hz, 8.0 Hz), 6.83(d, 1 H, J = 2.7 Hz), 7.09(d, 1 H, J = 8.0 Hz)

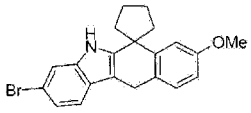
LCMS: m/z 231 $[M+H]^+$

[Example 503]

Compound M2

3-Bromo-8-methoxy-5,11-dihydrospiro[benzo[b]carbazole-6,1'-cyclopentane]

[1271]



[1272] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound M1 and (3-bromo-phenyl)-hydrazine.

LCMS: m/z 380, 382 $[M+H]^+$

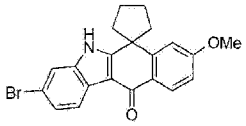
HPLC retention time: 2.90 min (analysis condition Y)

[Example 504]

Compound M3

3-Bromo-8-methoxyspiro[benzo[b]carbazole-6,1'-cyclopentan]-11(5H)-one

[1273]



[1274] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound M2.

^{1}H-NMR ($CDCl_3$, 300 MHz) δ : 2.11-2.51(8 H, m), 3.91(s, 3 H), 6.98(dd, 1 H, J = 2.3 Hz, 8.8 Hz), 7.01(d, 1H, J = 2.3 Hz), 7.41(dd, 1H, J = 1.5 Hz, 8.4 Hz), 7. 57(d, 1H, J = 1.5 Hz), 8.30(d, 1 H, J = 8.4 Hz), 8.35(d, 1H, J = 8.8 Hz), 8.69(s, 1 H)

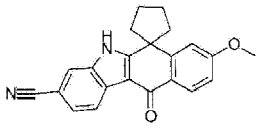
LCMS: m/z 396, 398 $[M+H]^+$

[Example 505]

Compound M4

8-Methoxy-11-oxo-5,11-dihydrospiro[benzo[b]carbazole-6,1'-cyclopentane]-3-carbonitrile

[1275]



[1276] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound M3.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ : 2.14-2.37(m, 8 H), 3.90(s, 3 H), 7.05-7. 10(m, 2 H), 7.60(dd, 1 H, J = 1.5 Hz, 8.4 Hz), 7.95(s, 1H), 8.13(d, 1H, J = 9.5 Hz), 8.30(d, 1H, J = 8.4 Hz), 12.24(s, 1H)

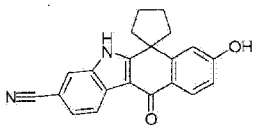
LCMS: m/z 343 $[M+H]^+$

[Example 506]

Compound M5

8-Hydroxy-11-oxo-5,11-dihydrospiro[benzo[b]carbazole-6,1'-cyclopentane]-3-carbonitrile

[1277]



[1278] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound M4.

^{1}H-NMR (DMSO-d_6, 300 MHz) δ : 2.06-2.39(m, 8 H), 6.87(dd, 1 H, J = 1.

9 Hz, 8.8 Hz), 6.90(d, 1 H, J = 1.9 Hz), 7.57(dd, 1 H, J = 1.1 Hz, 8.0 Hz), 7.95(s, 1 H), 8.02(d, 1 H, J = 8.8 Hz), 8.30(d, 1 H, J = 8.0 Hz), 10.29(s, 1H), 12.25(s, 1 H)

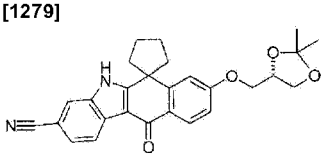
LCMS: m/z 329 $[M+H]^+$

[Example 507]

Compound M6-1

(S)-8-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-11-oxo-5,11-dihydrospiro[benzo[b]carbazole-6,1'-cyclopentane]-3-carbonitrile

[1279]



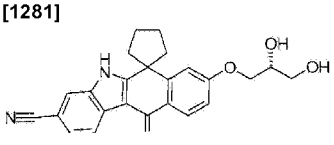
[1280] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared as a crude product from Compound M5 and toluene-4-sulfonic acid(R)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester.

[Example 508]

Compound M6-2

(R)-8-(2,3-Dihydroxypropoxy)-11-oxo-5,11-dihydrospiro[benzo[b]carbazole-6,1'-cyclopentane]-3-carbonitrile

[1281]



O

[1282] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound M6-1.

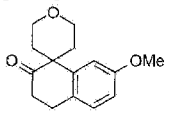
LCMS: m/z 403 $[M+H]^+$
HPLC retention time: 2.88 min (analysis condition U)

[Example 509]

Compound N1

7-Methoxy-2',3,3',4,5',6'-hexahydro-2H-spiro[naphthalene-1,4'-pyran]-2-one

[1283]



[1284] To the THF (300 ml) solution of 7-methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 20 g, 0.11 mol), sodium hydride (9.9 g, 3.7 eq.) was added at 0°C. After stirring for 10 min, 1-bromo-2-(2-bromo-ethoxy)-ethane (19 ml, 12 eq.) was added dropwise thereto, and the mixture was stirred at 80°C for 3 hr. To the reaction solution, saturated aqueous solution of ammonium chloride was added and the extraction was carried out twice with ethyl acetate. The organic layer was dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (white solid, 13 g, 51%).

^{1}H-NMR (300 MHz, $CDCl_3$) δ : 2.07(4 H, m), 2.70(t, 2 H, 6.8 Hz), 3.12(t, 2 H, 6.8 Hz), 3.81(s, 3 H), 3.89(m, 4 H), 6.75(dd, 1 H, 2.6 Hz, 8.3 Hz), 6.9(d, 1 H, 2. 6 Hz), 7.0(d, 1H, 8.3 Hz)

LCMS: m/z 247 $[M+H]^+$

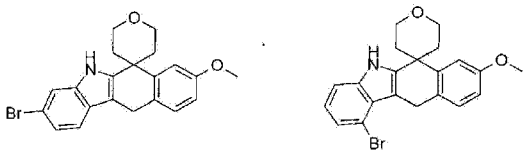
[Example 510]

Compound N2-1, Compound N2-2

3-Bromo-8-methoxy-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]

1-Bromo-8-methoxy-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]

[1285]



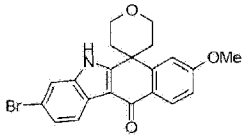
[1286] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared as a mixture from Compound N1.

[Example 511]

Compound N3

3-Bromo-8-methoxy-2',3',5',6'-tetrahydrospiro[benzo[b]carbazole-6,4'-pyran]-11(5H)-one

[1287]



[1288] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound N2-1.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.9(2 H, m), 2.4(m, 2 H), 3.9(s, 3 H), 4. 0(m, 2 H), 4.2(m, 2 H), 7.1(dd, 1 H, 2.2 Hz, 8.7 Hz), 7.3(m, 2 H), 7.8(d, 1 H, 2.2 Hz), 8.1(d, 2 H, 8.7 Hz), 11.8(s, 1H)

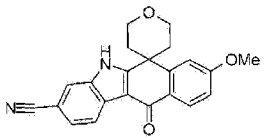
LCMS: m/z 413(M+1)$^+$

[Example 512]

Compound N4

8-Methoxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1289]



[1290] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound N3.

^{1}H-NMR(300 MHz, DMSO-d_6) δ : 1.9(m, 2 H), 2.4(m, 2 H), 3.9(s, 3 H), 4. 0(m, 2 H), 4.1(m, 2 H), 7.1(dd, 1 H, 2.2 Hz, 8.7 Hz), 7.4(d, 1H, 2.2 Hz), 7.6(dd, 1 H, 1.5 Hz, 8.3 Hz), 8.0(s, 1 H), 8.1(d, 1 H, 8.7 Hz), 8.3(d, 1H, 8.3 Hz), 12.2(s, 1H)

LCMS: m/z 359 [M+H]$^+$

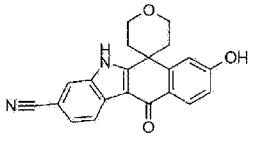
HPLC retention time: 2.80 min (analysis condition U)

[Example 513]

Compound N5

8-Hydroxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1291]



[1292] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound N4.

^{1}H-NMR(300 MHz, DMSO-d_6) d ppm 2.0(m, 2 H), 2.3(m,. 2 H), 4.0(m, 2 H), 4.1(m, 2 H), 6.9(dd, 1 H, 1.9 Hz, 8.3 Hz), 7.3(d, 1 H, 1.9 Hz), 7.6(dd, 1 H, 1.5 Hz, 8.3 Hz), 8.0(s, 1H), 8.1(d, 1 H, 8.3 Hz), 8. 3(d, 1 H, 8.3 Hz), 10.3(s, 1 H), 12.2(s, 1 H)

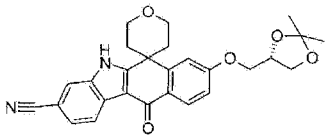
LCMS: m/z 345 $[M+H]^+$
HPLC retention time: 2.37 min (analysis condition U)

[Example 514]

Compound N6-1-1

(S)-8-((2,2-Dimethyl-1,3-dioxolan-4-yl) methoxy)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1293]



[1294] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound N6-2 and (S)-2,2-dimethyl-4-p-tolyloxymethyl-[1,3]dioxolane.

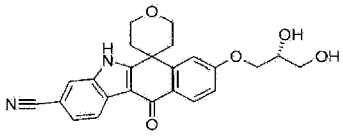
LCMS: m/z 459 $[M+H]^+$
HPLC retention time: 2.93 min (analysis condition Y)

[Example 515]

Compound N6-1-2

(R)-8-(2,3-Dihydroxypropoxy)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1295]



[1296] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound N6-1-1.

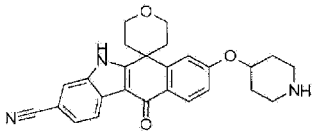
LCMS: m/z 419 $[M+H]^+$
HPLC retention time: 1.52 min (analysis condition S)

[Example 516]

Compound N6-2

11-Oxo-8-(piperidin-4-yloxy)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1297]



[1298] Under the same conditions as the method for synthesizing Compound A7-1 and Compound A8-1, the title compound was prepared from Compound N5.

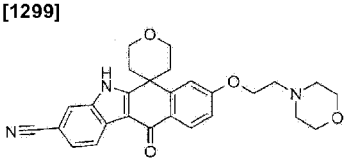
LCMS: m/z 428 $[M+H]^+$
HPLC retention time: 1.38 min (analysis condition S)

[Example 517]

Compound N6-3

8-(3-Morpholinoethoxy)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1299]



[1300] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound N5.

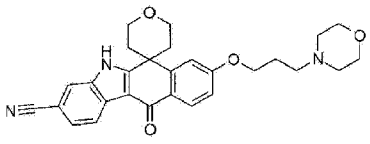
LCMS: m/z 458 $[M+H]^+$
HPLC retention time: 1.33 min (analysis condition S)

[Example 518]

Compound N6-4

8-(3-Morpholinopropoxy)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1301]



[1302] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound N5.

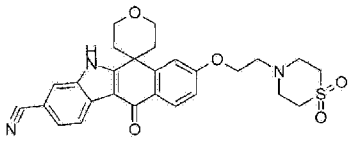
LCMS: m/z 472 $[M+H]^+$
HPLC retention time: 1.41 min (analysis condition S)

[Example 519]

Compound N6-5

3-Cyano-8-[2-(1,1-dioxo-thiomorpholin-4-yl)-ethoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-sulfonic acid dimethylamide

[1303]



[1304] Under the same conditions as the method for synthesizing Compound A8-17, the title compound was prepared from Compound N5.

LCMS: m/z 506 $[M+H]^+$

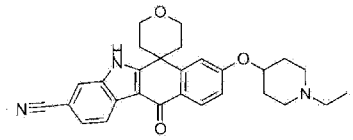
HPLC retention time: 1.53 min (analysis condition S)

[Example 520]

Compound N6-6

8-(1-Ethylpiperidin-4-yloxy)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1305]



[1306] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound N6-2. ^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.02 (3 H, t, 7.25 Hz), 1.18 (2 H, m), 1. 71 (2 H, m), 1.97 (4 H, m), 2.27 (2 H, m), 2.38 (3 H, m), 2.71 (2 H, m), 4.03 (2 H, m), 4.21 (2 H, m), 4.66 (1 H, s), 7.13 (1 H, dd, 8.77 Hz, 1.91 Hz), 7.39 (1 H, bs, 1.91 Hz), 7.60 (1 H, d, 8.40 Hz), 8.07 (1 H, s), 8.15 (1 H, d, 8.40 Hz), 8.37 (1 H, d, 8.01 Hz), 12.2 (1 H, s).

LCMS: m/z 456 $[M+H]^+$

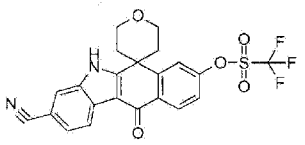
HPLC retention time: 1.48 min (analysis condition S)

[Example 521]

Compound N7

Trifluoromethanesulfonic acid 3-cyano-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl

[1307]



[1308] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound N5.

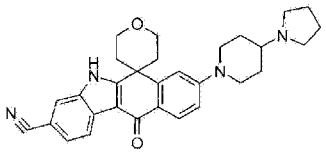
LCMS: m/z 477 $[M+H]^+$
HPLC retention time: 3.58 min (analysis condition Y)

[Example 522]

Compound N8-1

11-Oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1309]



[1310] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound N7 and 4-pyrrolidin-1-yl-piperidine.

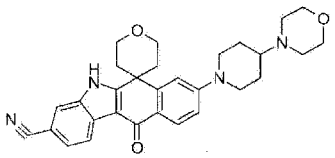
LCMS: m/z 481 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition U)

[Example 523]

Compound N8-2

8-(4-Morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1311]



[1312] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound N7 and 4-piperidin-4-yl-morpholine.

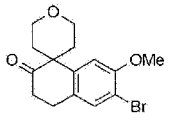
LCMS: m/z 497 $[M+H]^+$
HPLC retention time: 1.70 min (analysis condition U)

[Example 524]

Compound O1

6-Bromo-7-methoxy-2',3,3',4,5',6'-hexahydro-2H-spiro[naphthalene-1,4'-pyran]-2-one

[1313]



[1314] Under the same conditions as the method for synthesizing Compound E-1, the title compound was prepared from Compound N1.

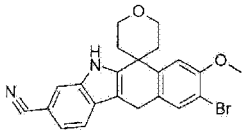
^{1}H-NMR (300 MHz, DMSO-d_6) δ : 2.01 (4 H, m), 2.66 (2 H, t, 6.87 Hz), 3. 08 (2 H, t, 6.87 Hz), 3.62 (2 H, m), 3.78 (2 H, m), 3.87 (3 H, s), 7.00 (1 H, s), 7.43 (1 H, s)

[Example 525]

Compound O2

9-Bromo-8-methoxy-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1315]



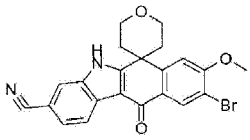
[1316] Under the same conditions as the method for synthesizing Compound E2-1, the title compound was prepared as a crude product from Compound O1.

[Example 526]

Compound O3

9-Bromo-8-methoxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran1-3-carbonitrile

[1317]



[1318] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound O2.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.95 (2 H, d, 14.87 Hz), 2.55 (2 H, m), 4.04 (2 H, m), 4.09 (3 H, s), 4.22 (2 H, m), 7.51 (1 H, s), 7.63 (1 H, dd, 8.01 Hz, 1. 53 Hz), 8.09 (1 H, s), 8.30 (1 H, s), 8.36 (1 H, d, 8.01 Hz), 12.3 (1 H, s).

LCMS: m/z 437, 439 $[M+H]^+$

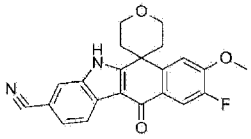
HPLC retention time: 2.65 min (analysis condition U)

[Example 527]

Compound O4

9-Fluoro-8-methoxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]1-3-carbonitrile

[1319]



[1320] Under the same conditions as the method for synthesizing Compound O5-3, the title compound was prepared from Compound O3.

LCMS: m/z 377 $[M+H]^+$

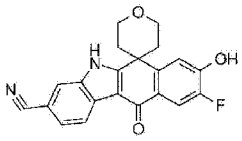
HPLC retention time: 2.29 min (analysis condition S)

[Example 528]

Compound O5-1

9-Fluoro-8-hydroxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1321]



[1322] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound O4.

LCMS: m/z 363 $[M+H]^+$

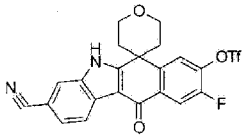
HPLC retention time: 1.88 min (analysis condition S)

[Example 529]

Compound O5-2

Trifluoromethanesulfonic acid 3-cyano-9-fluoro-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl

[1323]



[1324] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound O5-1.

LCMS: m/z 495 $[M+H]^+$

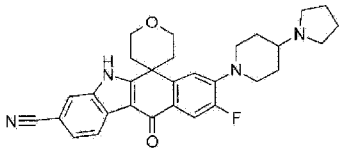
HPLC retention time: 3.47 min (analysis condition Y)

[Example 530]

Compound O5-3

9-Fluoro-11-oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1325]



[1326] To the THF (0.9 ml) solution of 9-bromo-6-tetrahydropyran-8-pyrrolidinopiperidin-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (Compound 08-1, 90 mg, 0.161 mmol), THF solution of n-butyl lithium (2 M solution, 0.241 ml, 3 eq.) was added at -78°C. After stirring for 30 min, THF (1 ml) solution of N-fluorobenzenesulfonimide (152 mg, 3 eq.) was added dropwise thereto. After rising to room temperature, the mixture was stirred for 18 hr. To the reaction solution, water was added and the extraction was carried out with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by high performance chromatography to obtain the target compound (white solid, 0.44 mg, 0.5%).

^{1}H-NMR($CDCl_3$+CD_3OD, 300 MHz) δ : 1.75-1.94(m, 11 H), 2.02-2.01(m, 2 H), 2.30-2.27(m, 1 H), 2.75-2.72(m, 2 H), 2.90-3. 00(m, 2 H), 3.61-3.47(m, 4 H), 4.01-3.90(m, 4 H), 7.08(dd, 1 H, J = 1, 2 Hz, 8.4 Hz), 7.29(dd, 1 H, J = 1, 5 Hz, 8.1 Hz), 7.68(d, 1 H, J = 12.9 Hz), 7.72(s, 1 H), 8.22(d, 1 H, J = 8.4 Hz)

LCMS: m/z 499 $[M+H]^+$

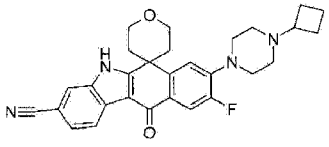
HPLC retention time: 1.95 min (analysis condition U)

[Example 531]

Compound O5-4

8-(4-Cyclobutyl-piperazin-1-yl)-9-fluoro-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1327]



[1328] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O5-2 and 1-cyclobutylpiperazine.

LCMS: m/z 485 $[M+H]^+$

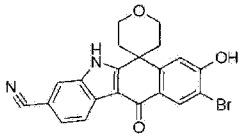
HPLC retention time: 1.97 min (analysis condition U)

[Example 532]

Compound O6-1

9-Bromo-8-hydroxy-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1329]



[1330] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound O3.

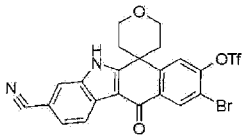
LCMS: m/z 423, 425 $[M+H]^+$
HPLC retention time: 2.30 min (analysis condition U)

[Example 533]

Compound O6-2

Trifluoromethanesulfonic acid 9-bromo-3-cyano-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl

[1331]



[1332] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound O6-1.

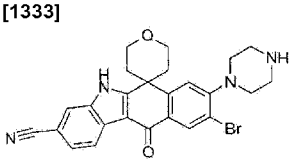
LCMS: m/z 555, 557 $[M+H]^+$
HPLC retention time: 3.13 min (analysis condition U)

[Example 534]

Compound O7-1

9-Bromo-11-oxo-8-(piperazin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1333]



[1334] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O6-2 and piperazine.

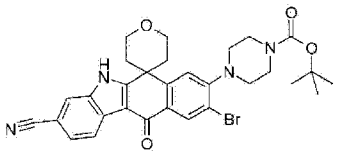
LCMS: m/z 491, 493 $[M+H]^+$
HPLC retention time: 1.88 min (analysis condition U)

[Example 535]

Compound O7-2

4-(9-Bromo-3-cyano-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl)piperazine-1-carboxylic acid tert-butyl

[1335]



[1336] To the dichloromethane (5 mL) solution of 9-bromo-11-oxo-8-(piperazin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile (Compound 07-1, 250 mg, 0.509 mmol) and mono-tert-butyl ester carbonic anhydride (122 mg, 0.560 mmol), triethylamine (0.21 mL, 1.53 mmol) was added at 0°C, and stirred at room temperature for 1 hr. The reaction mixture was concentrated under reduced pressure and the residues were purified by silica gel column chromatography (methanol/dichloromethane) to obtain the target compound as a white solid (212 mg, 70%).

^{1}H-NMR(300 MHz, DMSO-d_6) d ppm : 1. 44 (9 H, s), 1. 97 (2 H, m), 2. 44 (2 H, m), 1. 35 (4 H, m), 3. 54 (4 H, m), 4. 06 (2 H, m), 4. 18 (2 H, m), 7. 57 (1 H, s), 7. 63 (1 H, dd, 8. 01 Hz, 1. 52 Hz), 8. 08 (1 H, d, 1. 52 Hz), 8. 31 (1 H, s), 8. 36 (1 H, d, 8. 01 Hz), 12.3 (1 H,s)

LCMS: m/z 591, 593 $[M+H]^+$

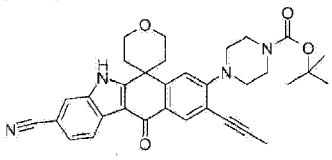
HPLC retention time: 3.23 min (analysis condition T)

[Example 536]

Compound O7-3

Tert-butyl 4-(3-cyano-11-oxo-9-(prop-1-ynyl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl)piperazine-1-carboxylic acid

[1337]



[1338] Under the same conditions as the method for synthesizing Compound O9-1, the title compound was prepared from Compound O7-2.

LCMS: m/z 551 $[M+H]^+$

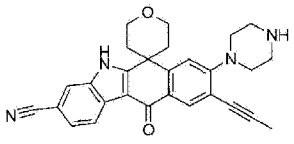
HPLC retention time: 3.92 min (analysis condition Y)

[Example 537]

Compound O7-4

11-Oxo-8-(piperazin-1-yl)-9-(prop-1-ynyl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1339]



[1340] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound O7-3.

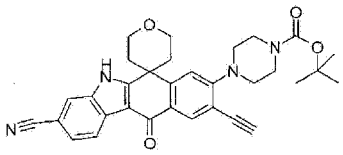
LCMS: 451 m/z $[M+H]^+$
HPLC retention time: 1.87 min (analysis condition U)

[Example 538]

Compound O7-5

4-(3-Cyano-9-ethynyl-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl)piperazine-1-carboxylic acid tert-butyl

[1341]



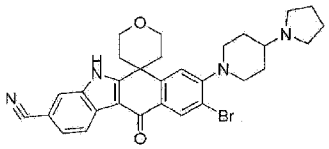
LCMS: m/z 537 $[M+H]^+$
HPLC retention time: 3.82 min (analysis condition Y)

[Example 539]

Compound O8-1

9-Bromo-11-oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1342]



[1343] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O6-2 and 4-pyrrolidin-1-yl-piperidine.

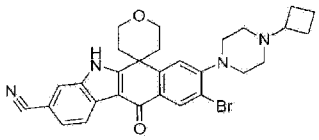
LCMS: m/z 559, 561 $[M+H]^+$
HPLC retention time: 2.05 min (analysis condition U)

[Example 540]

Compound O8-2

9-Bromo-8-(4-cyclobutylpiperazin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1344]



[1345] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O6-2 and 1-cyclobutylpiperazine.

LCMS: m/z 547 $[M+H]^+$

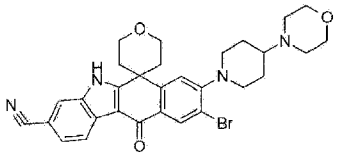
HPLC retention time: 1.61 min (analysis condition S)

[Example 541]

Compound O8-3

9-Bromo-8-(4-morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1346]



[1347] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O6-2 and 4-piperidin-4-yl-morpholine.

LCMS: m/z 575, 577 $[M+H]^+$

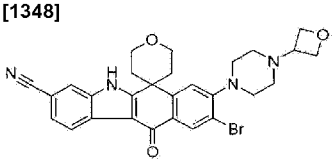
HPLC retention time: 1.95 min (analysis condition U)

[Example 542]

Compound O8-4

9-Bromo-8-(4-(oxetan-3-yl)piperazin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1348]



[1349] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound O7-1 and oxetan-3-one.

LCMS: m/z 547, 549 $[M+H]^+$

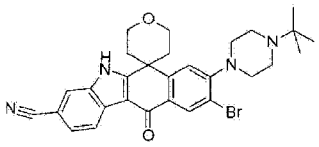
HPLC retention time: 1.43 min (analysis condition S)

[Example 543]

Compound O8-5

9-Bromo-8-(4-tert-butylpiperazin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1350]



[1351] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound O6-2 and 1-tert-butylpiperazine.

LCMS: 547, 549 m/z $[M+H]^+$

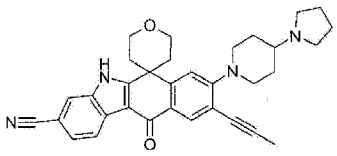
HPLC retention time: 2.07 min (analysis condition U)

[Example 544]

Compound O9-1

11-Oxo-9-(prop-1-ynyl)-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1352]



[1353] 9-Bromo-11-oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile (Compound O8-1, 100 mg, 0.170 mmol), tin tributyl(1-propynyl) (0.082 mL, 0.268 mmol), bis(acetonitrile) palladium dichloride (II) (2.64 mg, 0.00895 mmol), X-Phos (12.8 mg, 0.0269 mmol), and cesium carbonate (262.4 mg, 0.806 mmol) were suspended in acetonitrile (1 mL), and then stirred at 80°C for 2 hr. The reaction mixture was cooled to room temperature followed by addition of water and extracted with ethyl acetate. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane/methanol) to obtain the target compound (pale yellow solid, 3.8 mg, 4.1%).

^{1}H-NMR(300 MHz, DMSO) σppm 12. 20(bs, 1 H), 8. 35(d, 1 H, J = 8. 1 Hz), 8. 06(s, 1 H), 8. 06(d, 1 H, J = 10. 8 Hz), 7. 58(d, 1 H, J = 8. 4 Hz), 7. 29(s, 1 H), 4. 25-4. 23(m, 2 H), 4. 02-3. 98(m, 2 H), 3. 78(d, 2 H, J = 11.4 Hz), 2. 93(t, 2 H, J = 11. 1 Hz), 2. 55(s, 1 H), 2. 45-2. 28(m, 2 H), 2. 24-2. 05(m, 4 H), 2. 08-1. 81(m, 4 H), 1. 75-1. 50(m, 7 H)

LCMS: m/z 519 $[M+H]^+$

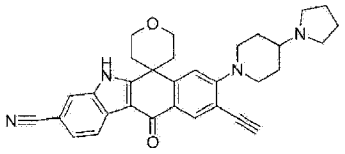
HPLC retention time: 1.98 min (analysis condition U)

[Example 545]

Compound O9-2

9-Ethynyl-11-oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1354]



[1355] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound O8-1.

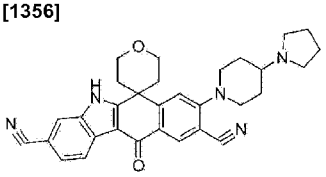
LCMS: m/z 505 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition U)

[Example 546]

Compound O9-3

11-Oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3,9-dicarbonitrile

[1356]



[1357] Under the same conditions as the method for synthesizing Compound A5-2, the title compound was prepared from Compound O8-1.

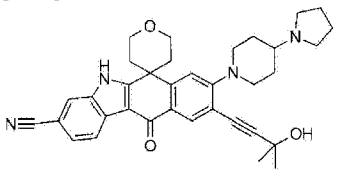
LCMS: 506 m/z $[M+H]^+$
HPLC retention time: 1.87 min (analysis condition U)

[Example 547]

Compound O9-4

9-(3-Hydroxy-3-methylbut-1-ynyl)-11-oxo-8-(4-(pyrrolidin-1-yl)piperidin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1358]



[1359] Under the same conditions as the method for synthesizing Compound E4-2-1, the title compound was prepared from Compound O8-1.

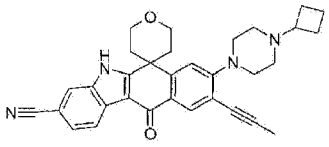
LCMS: m/z 563 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition U)

[Example 548]

Compound O9-5

8-(4-Cyclobutylpiperazin-1-yl)-11-oxo-9-(prop-1-ynyl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1360]



[1361] Under the same conditions as the method for synthesizing Compound O9-1, the title compound was prepared from Compound O8-2.

^{1}H-NMR(300 MHz, DMSO-d_6) δ : 1.6(m, 2 H), 1.8(m, 2 H), 1.9(m, 4 H), 2. 1(s, 3 H), 2.4(m, 6 H), 2.8(m, 1 H), 3.4(m, 4 H), 4.0(m, 2H), 4.1(m, 2 H), 7.3(s, 1 H), 7.6(d, 1 H, 8.0 Hz), 8.0(m, 2 H), 8.3(d, 1 H, 8.0 Hz), 12.2(s, 1 H)

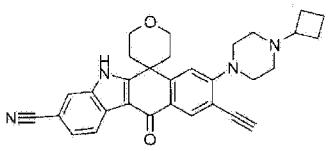
LCMS: m/z 505 $[M+H]^+$
HPLC retention time: 2.03 min (analysis condition U)

[Example 549]

Compound O9-6

8-(4-Cyclobutylpiperazin-1-yl)-9-ethynyl-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1362]



[1363] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from Compound O8-2.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.66 (2 H, m), 1.83 (2 H, t, 8.77 Hz), 1. 99 (4 H, m), 2.41 (6 H, m), 2.79 (1 H, t, 7.63 Hz), 3.35 (4 H, m), 4. 01 (2 H, m), 4.27 (2 H, m), 4.51 (1 H, s), 7.33 (1 H, s), 7.54 (1 H, m), 8.03 (1 H, s), 8.16 (1 H, s), 8.32 (1 H, d, 8.40 Hz), 12.3 (1 H, s).

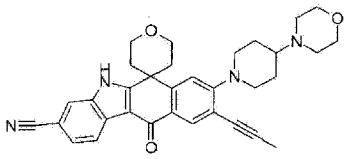
LCMS: m/z 491 $[M+H]^+$
HPLC retention time: 1.95 min (analysis condition U)

[Example 550]

Compound O9-7

8-(4-Morpholinopiperidin-1-yl)-11-oxo-9-(prop-1-ynyl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1364]



[1365] Under the same conditions as the method for synthesizing Compound O9-1, the title compound was prepared from Compound O8-3.

^{1}H-NMR (300 MHz, DMSO-d_6) δ : 1.57 (2 H, m), 1.95 (4 H, m), 2.14 (3 H, s), 2.37 (3 H, m), 3.35 (4 H, m), 2.83 (2 H, t, 12.6 Hz), 3.56 (4 H, s), 3.86 (2 H, d, 11. 8 Hz), 4.04 (2 H, m), 4.17 (2 H, m), 7.31 (1 H, s), 7.61 (1 H, d, 8.01 Hz), 8.06 (1 H, s), 8.07 (1 H, s), 8.36 (1 H, d, 8.01 Hz), 12.3 (1 H, s).

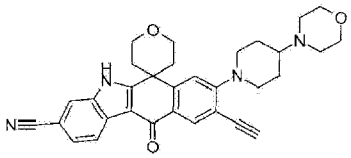
LCMS: m/z 535 $[M+H]^+$
HPLC retention time: 1.95 min (analysis condition U)

[Example 551]

Compound O9-8

9-Ethynyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1366]



[1367] Under the same conditions as the method for synthesizing Compound F5-43, the title compound was prepared from compound O8-3.

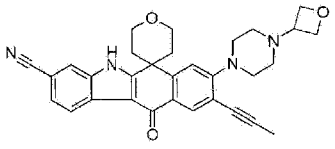
LCMS: m/z 521 $[M+H]^+$
HPLC retention time: 1.90 min (analysis condition U)

[Example 552]

Compound O9-9

8-(4-(Oxetan-3-yl)piperazin-1-yl)-11-oxo-9-(prop-1-ynyl)-2,3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1368]



[1369] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound O7-4 and oxetan-3-one.

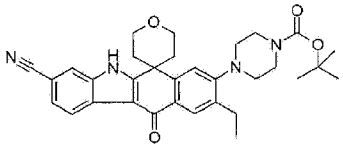
LCMS: m/z 507 $[M+H]^+$
HPLC retention time: 1.43 min (analysis condition S)

[Example 553]

Compound O10-1-1

Tert-butyl4-(3-cyano-9-ethyl-11-oxo-2',3',5,5a,5',6',11,11a-octahydrospiro[benzo[b]carbazole-6,4'-pyran]-8-yl)piperazine-1-carboxylic acid

[1370]



[1371] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound O7-5.

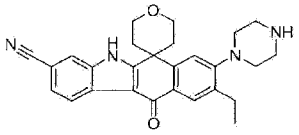
LCMS: m/z 541 $[M+H]^+$
HPLC retention time: 3.08 min (analysis condition S)

[Example 554]

Compound O10-1-2

9-Ethyl-11-oxo-8-(piperazin-1-yl)-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1372]



[1373] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound O10-1-1.

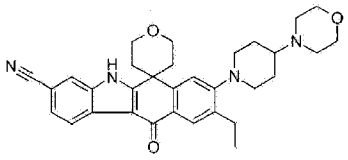
LCMS: m/z 441 $[M+H]^+$
HPLC retention time: 1.42 min (analysis condition S)

[Example 555]

Compound O10-2

9-Ethyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1374]



[1375] According to the same method as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound O9-8.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.23-8. 21 (1H, m), 8.02-8.00 (1 H, m), 7.88-7.86 (1 H, m), 7.39-7.36 (2 H, m), 4.63-4.59 (2 H, m), 3.89-3.85 (2 H, m), 3. 60-3.56 (6 H, m), 3.22-3.19 (4 H, m), 2.76-2.68 (4 H, m), 2.37-2.32 (3 H, m), 1.92-1.88 (2 H, m), 1.75-1.72 (2 H, m), 1.61-1.57 (2 H, m), 1.27-1.25 (3 H, m)

LCMS: m/z 525 $[M+H]^+$

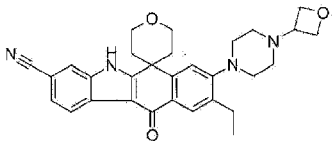
HPLC retention time: 1.48 min (analysis condition S)

[Example 556]

Compound 010-3

9-Ethyl-8-(4-(oxetan-3-yl)piperazin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1376]



[1377] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound O10-1-2 and oxetan-3-one.

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.26 (1 H, s), 8.39 (1 H, d, 7.9 Hz), 8. 09-8.07 (2 H, m), 7.63 (1 H, d, 8.5 Hz), 7.51 (1 H, s), 4.60-4.50 (4 H, m), 4.20-4.09 (4 H, m), 3.56-3.51 (1 H, m), 3.07-3.05 (4 H, m), 2.76-2.70 (2 H, m), 2.44-2.40 (2 H, m), 2.02-1.98 (2 H, m), 1.29-1.26 (4 H, m)

LCMS: m/z 497 $[M+H]^+$

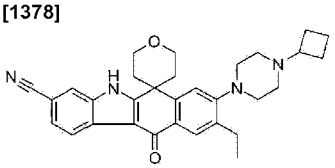
HPLC retention time: 1.42 min (analysis condition S)

[Example 557]

Compound O10-4

8-(4-Cyclobutylpiperazin-1-yl)-9-ethyl-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazole-6,4'-pyran]-3-carbonitrile

[1378]



[1379] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound O10-1-2 and cyclobutanone.

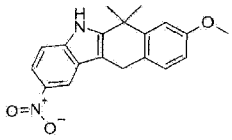
LCMS: m/z 495 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition S)

[Example 558]

Compound P1 (intermediate)

8-Methoxy-6,6-dimethyl-2-nitro-6,11-dihydro-5H-benzo[b]carbazole

[1380]



[1381] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound A2 and 4-nitrophenylhydrazine.

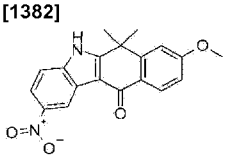
LCMS: m/z 323 $[M+H]^+$
HPLC retention time: 4.08 min (analysis condition W)

[Example 559]

Compound P2 (intermediate)

8-Methoxy-6,6-dimethyl-2-nitro-5,6-dihydro-benzo[b]carbazol-11-one

[1382]



[1383] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound P1.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.85 (1 H, s), 9.03 (1 H, d, J = 1.9 Hz), 8.17-8.20 (2 H, m), 7.71(1 H, d, J = 9.1 Hz), 7.38 (1 H, d, J = 2.4 Hz), 7.12 (1 H, dd, J = 8.5, 2.4 Hz), 3.93 (3 H, s), 1.79 (6 H, s)

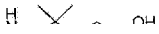
LCMS: m/z 337 $[M+H]^+$
HPLC retention time: 3.55 min (analysis condition W)

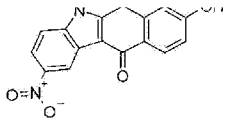
[Example 560]

Compound P3 (intermediate)

8-Hydroxy-6,6-dimethyl-2-nitro-5,6-dihydro-benzo[b]carbazol-11-one

[1384]





[1385] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound P2.

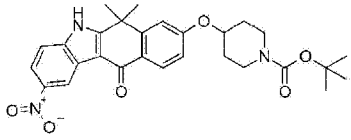
LCMS: m/z 323 $[M+H]^+$
HPLC retention time: 3.11 min (analysis condition W)

[Example 561]

Compound P4 (intermediate)

4-(6,6-Dimethyl-2-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1386]



[1387] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound P3.

^{1}H-NMR (400 MHz, $CDCl_3$) δ : 9.40 (1 H, s), 9.37 (1 H, s), 8.41 (1 H, d, J = 8.5 Hz), 8.24 (1 H, d, J = 11.0 Hz), 7.51 (1 H, d, J = 8.5 Hz), 7.13 (1 H, s), 7.03 (1 H, d, J = 9.1 Hz), 4.61-4.71 (1 H, m), 3.69-3.84 (2 H, m), 3.35-3. 49 (2 H, m), 1.94-2.10 (2 H, m), 1.75-1.93 (8 H, m), 1.50 (9 H, s)

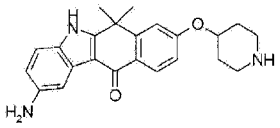
LCMS: m/z 506 $[M+H]^+$
HPLC retention time: 4.17 min (analysis condition W)

[Example 562]

Compound P5

2-Amino-6,6-dimethyl-8-(piperidin-4-yloxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1388]



[1389] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound P6.

^{1}H-NMR (400 MHz, CD_3OD) δ : 8.23 (1 H, d, J = 8.5 Hz), 7.68 (1 H, d, J = 2.4 Hz), 7.26 (1 H, d, J = 8.5 Hz), 7.24 (1 H, d, J = 2.4 Hz), 7.06 (1 H, dd, J = 8.5, 2. 4 Hz), 6.80 (1 H, dd, J = 8.5, 2.4 Hz), 4.64-4.71 (1 H, m), 3.06-3.15 (2 H, m), 2.73-2.83 (2 H, m), 2.02-2.13 (2 H, m), 1.67-1.82 (8 H, m)

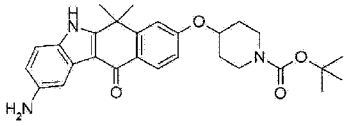
LCMS: m/z 506 $[M+H]^+$
HPLC retention time: 4.17 min (analysis condition W)

[Example 563]

Compound P6 (intermediate)

4-(2-Amino-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1390]



[1391] To the ethanol (8 ml) suspension of 4-(6,6-dimethyl-2-nitro-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester (Compound P4, 103 mg, 0.204 mmol), iron powder (228 mg, 20 eq.), ammonium chloride (109 mg, 10 eq.), and distilled water (4 ml) were added and the mixture was stirred at 90°C for 30 min. Upon the completion of the reaction, insoluble matters were filtered off, and the filtrate was extracted with ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (115 mg, 57%).

LCMS: m/z 476 $[M+H]^+$

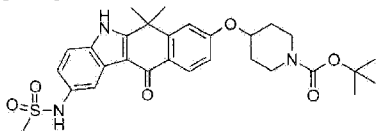
HPLC retention time: 2.82 min (analysis condition W)

[Example 564]

Compound P7 (intermediate)

4-(2-Methanesulfonylamino-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1392]



[1393] To the pyridine (2 ml) solution of 4-(2-amino-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester (Compound P6, 50 mg, 0.105 mmol), mesyl chloride (9 µl, 1.2 eq.) was added and stirred at room temperature for 30 min. Upon the completion of the reaction, the reaction solution was concentrated under reduced pressure to obtain the title compound as an unpurified product.

LCMS: m/z 554 $[M+H]^+$

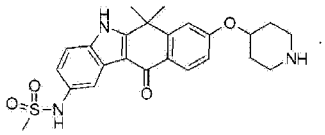
HPLC retention time: 3.60 min (analysis condition W)

[Example 565]

Compound P8

N-[6,6-Dimethyl-11-oxo-8-(piperidin-4-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-2-yl]-methanesulfonamide

[1394]



[1395] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound P7.

^{1}H-NMR (400 MHz, CD_3OD) δ : 8.25 (1 H, d, J = 8.5 Hz), 8.16 (1 H, d, J = 1.8 Hz), 7.46 (1 H, d, J = 9.1 Hz), 7.27-7.29 (2 H, m), 7.09 (1 H, dd, J = 9.1, 1.8 Hz), 4.67-4.75 (1 H, m), 3.09-3.18 (2 H, m), 2.95 (3H, s), 2.77-2.87 (2 H, m), 1.70-1.84 (8 H, m)

LCMS: m/z 454 $[M+H]^+$

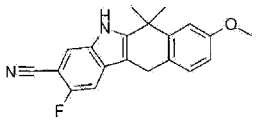
HPLC retention time: 2.22 min (analysis condition W)

[Example 566]

Compound Q3 (intermediate)

2-Fluoro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1396]



[1397] Under the same conditions as the method for synthesizing Compound A3-1, the title compound was prepared from Compound A2 and 3-cyano-4-fluorophenylhydrazine.

LCMS: m/z 321 $[M+H]^+$

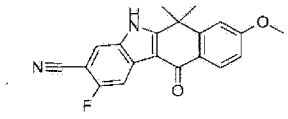
HPLC retention time: 4.13 min (analysis condition W)

[Example 567]

Compound Q4 (intermediate)

2-Fluoro-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1398]



[1399] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound Q3.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.89 (1 H, s), 8.16 (1 H, d, J = 8.5 Hz), 8.07 (1 H, d, J = 4.9 Hz), 8.04 (1 H, d, J = 9.8 Hz), 7.36 (1 H, d, J = 2.4 Hz), 7.10 (1 H, dd, J = 8.5, 2.4 Hz), 3.91 (3 H, s), 1.78 (3H, s)

LCMS: m/z 335 $[M+H]^+$

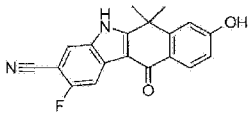
HPLC retention time: 3.61 min (analysis condition W)

[Example 568]

Compound Q5 (intermediate)

2-Fluoro-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1400]



[1401] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound Q4.

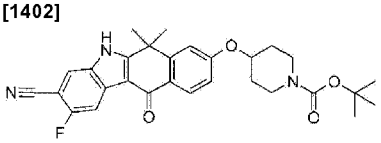
LCMS: m/z 321 $[M+H]^+$
HPLC retention time: 3.16 min (analysis condition W)

[Example 569]

Compound Q6 (intermediate)

4-(3-Cyano-2-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1402]



[1403] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound Q5.

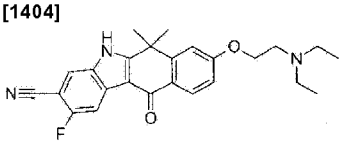
LCMS: m/z 504 $[M+H]^+$
HPLC retention time: 4.25 min (analysis condition W)

[Example 570]

Compound Q7

8-(2-Diethylamino-ethoxy)-2-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1404]



[1405] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound Q5.

^{1}H-NMR (400 MHz, CD_3OD) δ : 8.25 (1 H, d, J = 8.5 Hz), 8.09 (1 H, d, J = 9.8 Hz), 7.83 (1 H, d, J = 5.5 Hz), 7.30 (1 H, d, J = 2.4 Hz), 7.09 (1 H, dd, J = 8.5, 2. 4 Hz), 4.26 (2 H, t, J = 5.7 Hz), 2.98 (2 H, t, J = 5.7 Hz), 2.72 (4 H, q, J = 7.2 Hz), 1. 81 (6 H, s), 1.13 (6 H, t, J = 7.2 Hz)

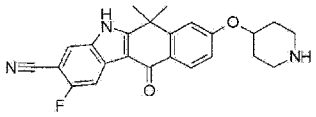
LCMS: m/z 420 $[M+H]^+$
HPLC retention time: 2.65 min (analysis condition W)

[Example 571]

Compound Q8

2-Fluoro-6,6-dimethyl-11-oxo-8-(piperidin-4-yloxy)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1406]



[1407] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from Compound Q6.

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 8.11 (1 H, d, J = 8.5 Hz), 7.98 (1 H, d, J = 5.5 Hz), 7.96 (1 H, d, J = 9.8 Hz), 7.29 (1 H, s), 7.08 (1 H, d, J = 8.5 Hz), 4.58-4. 69 (1 H, m), 2.93-3. 05 (2 H, m), 2.60-2.69 (2 H, m), 1.94-2.03 (2 H, m), 1.74 (6 H, s), 1.45-1.57 (2 H, m)

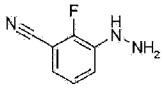
LCMS: m/z 404 $[M+H]^+$
HPLC retention time: 2.67 min (analysis condition W)

[Example 572]

Compound R2

2-Fluoro-3-hydrazinylbenzonitrile

[1408]



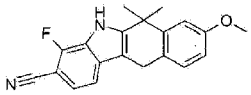
[1409] 3-Amino-2-fluoro-benzonitrile (100 mg, 0.735 mmol) was dissolved in water (0.94 mL), added with conc. hydrochloric acid (0.74 mL) at 0°C, and then further added with an aqueous solution (0.294 mL) of sodium nitrite (61 mg, 0.882 mmol). The resulting mixture was stirred at 0°C for 1 hr. To the reaction mixture, conc. hydrochloric acid solution (0.94 mL) of tin chloride (321 mg, 1.69 mmol) was added and stirred at room temperature for 1 hr. Thereafter, the reaction solution was neutralized with aqueous solution of sodium hydroxide, and extracted with dichloromethane. The organic layer was washed with saturated brine and dried over anhydrous magnesium sulfate. The drying agent was removed by filtration and the residues were obtained after concentration under reduced pressure to give the target compound as a crude product.

[Example 573]

Compound R3

4-Fluoro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1410]



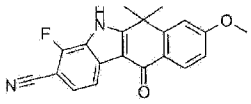
[1411] Under the same conditions as the method for synthesizing Compound E2-1, the title compound was prepared as a crude product from Compound A2 and Compound R2.

[Example 574]

Compound R4

4-Fluoro-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1412]



[1413] Under the same conditions as the method for synthesizing Compound A4, the title compound was prepared from Compound R3.

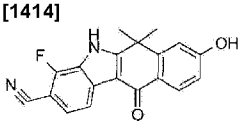
LCMS: m/z 335 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition U)

[Example 575]

Compound R5

4-Fluoro-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1414]



[1415] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound R4.

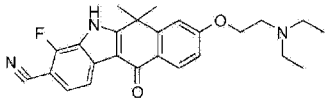
LCMS: m/z 321 $[M+H]^+$
HPLC retention time: 2.32 min (analysis condition U)

[Example 576]

Compound R6

8-(2-Diethylamino-ethoxy)-4-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1416]



[1417] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound R5.

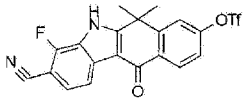
LCMS: m/z 420 $[M+H]^+$
HPLC retention time: 1.51 min (analysis condition S)

[Example 577]

Compound R7

Trifluoromethanesulfonic acid 3-cyano-4-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl

[1418]



[1419] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound R5.

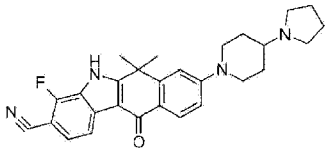
LCMS: m/z 453 $[M+H]^+$
HPLC retention time: 3.82 min (analysis condition Y)

[Example 578]

Compound R8-1

4-Fluoro-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1420]



[1421] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound R7 and 4-pyrrolidin-1-yl-piperidine.

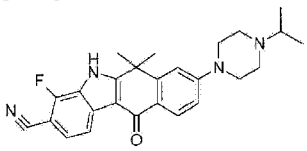
LCMS: m/z 457 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition U)

[Example 579]

Compound R8-2

4-Fluoro-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1422]



[1423] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound R7.

LCMS: m/z 431 $[M+H]^+$

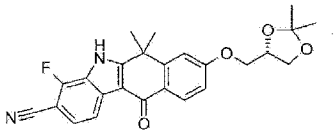
HPLC retention time: 2.07 min (analysis condition U)

[Example 580]

Compound R9-1

8-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-4-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1424]



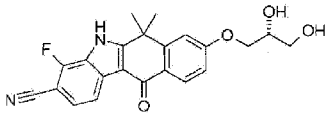
[1425] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared as a crude product from Compound R5 and (R)-(-)-2,2-dimethyl-1,3-dioxolan-4-methanol.

[Example 581]

Compound R9-2

8-((R)-2,3-Dihydroxy-propoxy)-4-fluoro-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1426]



[1427] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound R9-1 (9.9 mg, 80%).

LCMS: m/z 395 $[M+H]^+$

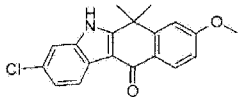
HPLC retention time: 2.38 min (analysis condition C)

[Example 582]

Compound S1-1

3-Chloro-8-methoxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one

[1428]



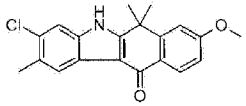
[1429] Under the same conditions as the method for synthesizing Compound A3-1 and Compound A4, the title compound was prepared as a crude product from Compound A2 and (3-chlorophenyl)-hydrazine hydrochloric acid salt.

[Example 583]

Compound S1-2

3-Chloro-8-methoxy-2,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1430]



[1431] 7-Methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 99.1 mg, 0.485 mmol) and (3-chloro-4-methyl-phenyl)hydrazine hydrochloric acid salt (100.4 mg, 1.1 eq.) were dissolved in TFA (1 mL) and the mixture was irradiated with microwave at 80°C for 10 min under nitrogen atmosphere. After cooling, the reaction solution was added with ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate and saturated brine and dried over magnesium sulfate. After filtration and concentration under reduced pressure, the residues obtained therefrom were dissolved in THF (2 mL) and water (0.2 mL), added with DDQ (125.7 mg, 1.1 eq.), and stirred at room temperature overnight. The reaction solution was added with the mixture solvent of hexane and ethyl acetate, and the starting-point components were removed by dry type silica gel column. The eluent was concentrated under reduced pressure, and the resulting residues were purified by preparative TLC (methanol/dichloromethane) to obtain the title compound (19.4 mg, 12%). ^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.2 (1 H, s), 8.15 (1 H, d, J = 8.8 Hz), 8. 12 (1 H, s), 7.52 (1 H, s), 7.32 (1 H, s), 7.07 (1 H, dd, J = 2.4, 8.8 Hz), 3.90 (3 H, s), 2.45 (3 H, s), 1.73 (6 H, s),

LCMS: m/z 340 $[M+H]^+$

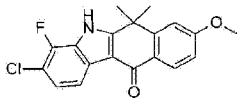
HPLC retention time: 2.80 min (analysis condition F)

[Example 584]

Compound S1-3

3-Chloro-4-fluoro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1432]



[1433] According to the same method as the method for synthesizing Compound A3-1, the title compound was prepared from Compound A2 and (3-chloro-2-fluoro-phenyl)-hydrazine.

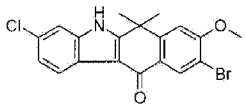
LCMS: m/z 344, 346 $[M+H]^+$
HPLC retention time: 2.68 min (analysis condition S)

[Example 585]

Compound S1-4

9-Bromo-3-chloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1434]



[1435] 6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1 H-naphthalen-2-one (Compound E1, 0.2 g, 0.71 mmol) and 3-chlorophenylhydrazine hydrochloric acid salt (0.17 g, 1.3 eq.) were dissolved in acetic acid (0.5 mL). Under nitrogen atmosphere, the reaction solution was stirred at 90°C for 8 hr. After cooling to room temperature, the reaction solution was added with ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate and saturated brine and dried over magnesium sulfate. After filtration and concentration under reduced pressure, the residues obtained therefrom were dissolved in THF (3 mL) comprising 10% water, added with DDQ (227 mg, 3 eq.) at room temperature, and the mixture was stirred at room temperature for 2 hr. The reaction solution was added with the mixture liquid of THF/diethyl ether (1 : 1) and washed with 0.5 N aqueous solution of sodium hydroxide and saturated brine. After drying with sodium sulfate, the mixture was filtered and the resulting residues obtained after concentration under reduced pressure were washed with the mixture liquid of hexane/diethyl ether (1 : 1) to obtain the title compound (brown powder, 86 mg).

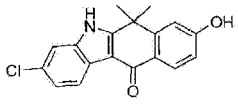
LCMS: m/z 404, 406, 408 $[M+H]^+$
HPLC retention time: 3.02 min (analysis condition C)

[Example 586]

Compound S2-1

3-Chloro-8-hydroxy-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one

[1436]



[1437] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound S1-1.

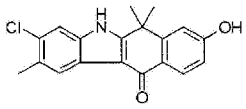
LCMS: m/z 312 $[M+H]^+$
HPLC retention time: 4.18 min (analysis condition H)

[Example 587]

Compound S2-2

3-Chloro-8-hydroxy-2,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1438]



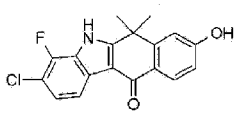
[1439] 3-Chloro-8-methoxy-2,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S1-2, 18.9 mg, 0.0556 mmol) and pyridinium chloride (220 mg, 34 eq.) were stirred at 185°C for 2.5 hr. After cooling, the reaction solution was added with water and ethyl acetate, and the organic layer was washed with water and saturated brine, dried over magnesium sulfate, filtered and concentrated under reduced pressure to obtain the title compound as a crude product.

[Example 588]

Compound S2-3

3-Chloro-4-fluoro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1440]



[1441] 3-Chloro-4-fluoro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S1-3, 220.0 mg, 0.640 mmol) and pyridinium chloride (800 mg, 6.922 mmol) were mixed with each other, heated to 160°C, and then stirred for 20 hr. The reaction solution was added with water. As a result, black solid was obtained as a precipitate, which was then filtered and subjected to purification by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (139.4 mg, 66%).

LCMS: m/z 330 $[M+H]^+$

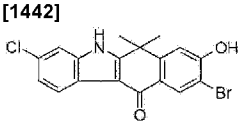
HPLC retention time: 2.60 min (analysis condition F)

[Example 589]

Compound S2-4

9-Bromo-3-chloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1442]



[1443] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound S1-4.

LCMS: m/z 390, 392, 394 $[M+H]^+$

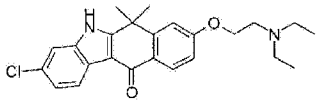
HPLC retention time: 2.75 min (analysis condition C)

[Example 590]

Compound S3

3-Chloro-8-(2-diethylaminoethoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (CH5263231-000)

[1444]



[1445] 3-Chloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S2-1, 10 mg, 0.03207 mmol) was dissolved in DMF (0.1 mL), added with (2-chloroethyl)diethylamine (5.5 mg, 0.03207 mmol) and cesium carbonate (20.9 mg, 0.06414 mmol), and stirred at 80°C for 2 hr. The reaction solution was added to water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by NH silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (11.6 mg, 76%).

LCMS: m/z 411 $[M+H]^+$

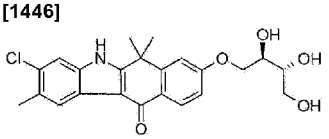
HPLC retention time: 4.49 min (analysis condition H)

[Example 591]

Compound S4

3-Chloro-2,6,6-trimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1446]



[1447] Crude product of Compound S2-2 was dissolved in THF (0.4 mL) under nitrogen atmosphere, together with THF (0.2 mL) solution of triphenylphosphine (18.9 mg, 1.3 eq.) and [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (17 mg, 1.2 eq.). DEAD (40% toluene solution, 0.0031 mL, 1.2 eq.) was added to the solution, which was then stirred at room temperature for 40 min and at 40°C for 4 hr. The reaction solution was added with triphenylphosphine (18.9 mg, 1.3 eq.) and DEAD (40% toluene solution, 0.002 mL, 0.8 eq.) and stirred at 40°C overnight. The reaction solution was added with ethyl acetate, washed with water and saturated brine, dried over magnesium sulfate, and filtered. The residues obtained after concentration under reduced pressure were purified by praparative TLC (ethyl acetate/hexane) to obtain the crude product of 8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-3-chloro-2,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one (12.6 mg).

[1448] The resultant was dissolved in THF (0.15 mL) and methanol (0.03 mL) under nitrogen atmosphere, added with 0.5 M sulfuric acid (0.05 mL) and stirred at 60°C for 3 hr. After cooling, diethyl ether was added and sodium hydrogen carbonate (8.4 mg) and water were further added thereto. The organic layer was washed with saturated brine. The aqueous layer was extracted with ethyl acetate, and the combined organic layer was dried over magnesium sulfate, and filtered. The solid obtained from the concentration under reduced pressure was washed with dichloromethane to obtain the target compound (white solid, 5.3 mg, 22%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 12.18(1 H, s), 8.14 (1 H, d, J = 8.8 Hz), 8.12 (1 H, s), 7.52 (1 H, s), 7.31 (1 H, d, J = 2.4 Hz), 7.06(1 H, dd, J = 2.4, 8.8 Hz), 4.78(1 H, d, J = 5.9 Hz), 4.60 (1 H, d, J = 5.9 Hz), 4.52 (1 H, t, J = 5.4 Hz), 4.18-4. 22(1 H, m), 4.02-4.06 (1 H, m), 3.85-3. 95 (1 H, m), 3.50-3.60(2 H, m), 3.40-3.46 (1 H, m), 2.45 (3 H, s), 1.73 (3 H, s),

LCMS: m/z 430 $[M+H]^+$

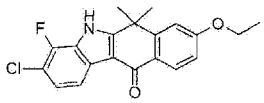
HPLC retention time: 2.27 min (analysis condition F)

[Example 592]

Compound S5

3-Chloro-8-ethoxy-4-fluoro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1449]



[1450] The title compound was obtained as a by-product of the synthesis of Compound S6.

LCMS: m/z 358 $[M+H]^+$

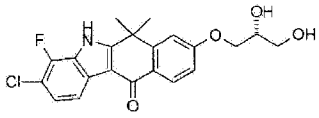
HPLC retention time: 3.16 min (analysis condition F)

[Example 593]

Compound S6

3-Chloro-8-((R)-2,3-dihydroxy-propoxy)-4-fluoro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1451]



[1452] 3-Chloro-4-fluoro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S2-3, 20.0 mg, 0.061 mmol) was dissolved in THF (0.25 mL), added with ((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (9.8 μL, 0.079 mmol), triphenylphosphine (20.7 mg, 0.079 mmol) and diethyl azodicarboxylic acid (35.9 μl, 0.079 mmol), and then stirred at 40°C for 5 hr. The reaction solution was concentrated under reduced pressure, and the resulting residues were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the intermediate, 3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-4-fluoro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one. This compound was dissolved in THF (0.10 mL) and MeOH (0.08 ml), added with sulfuric acid (0.5 M, 0.045 ml), and then stirred at 60°C for 1 hr. The reaction solution was added with saturated aqueous solution of sodium hydrogen carbonate, extracted with ethyl acetate and dried over anhydrous magnesium sulfate. The yellow solid obtained after concentration under reduced pressure was washed with methylene chloride/hexane solvent and filtered to obtain the title compound (4.3 mg, 18%).

LCMS: m/z 404 $[M+H]^+$

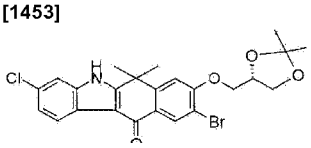
HPLC retention time: 2.34 min (analysis condition F)

[Example 594]

Compound S7-1

3-Chloro-9-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1453]



[1454] Under nitrogen atmosphere, 9-bromo-3-chloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S2-4, 76 mg, 0.2 mmol) and triphenylphosphine (69 mg, 1.3 eq.) were added with THF (2 ml), and ((S)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (35 mg, 1.3 eq.) and 2.19 N toluene solution (118 µL, 1.3 eq.) of diethyl azodicarboxylic acid were added dropwise thereto, followed by stirring at 50°C for 2 hr. After cooling, the reaction solution was added with ethyl acetate, washed with brine, dried over sodium sulfate and filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/dichloromethane) to give a solid, which was then washed with dichloromethane to obtain the title compound (brown powder, 53 mg).

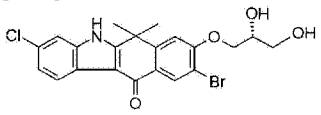
LCMS: m/z 504, 506, 508 $[M+H]^+$
HPLC retention time: 3.17 min (analysis condition C)

[Example 595]

Compound S7-2

9-Bromo-3-chloro-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1455]



[1456] 3-Chloro-9-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S7-1, 56 mg, 0.11 mmol) was dissolved in methanol (5 mL), added with 1 N hydrochloric acid (0.2 ml), and stirred at 50°C for 2 hr. After cooling, the reaction solution was concentrated under reduced pressure and the resulting residues were added with methanol to obtain a precipitated solid, which was then filtered to obtain the title compound (white powder, 26 mg).

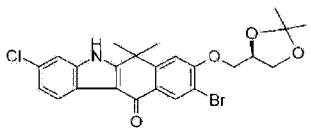
LCMS: m/z 464, 466, 468 $[M+H]^+$
HPLC retention time: 2.77 min (analysis condition C)

[Example 596]

Compound S7-3

3-Chloro-9-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1457]



[1458] Under nitrogen atmosphere, 9-bromo-3-chloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S2-4, 112 mg, 0.29 mmol) and triphenylphosphine (227 mg, 3 eq.) were added with THF (2 ml), and ((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (114 mg, 3 eq.) and 2.19 N toluene solution (0.4 mL, 3 eq.) of diethyl azodicarboxylic acid were added dropwise thereto, followed by stirring at 40°C for 12 hr under nitrogen atmosphere. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/dichloromethane) to obtain the title compound (white powder, 100 mg).

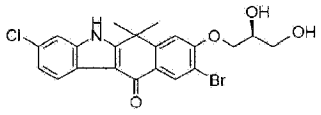
LCMS: m/z 504, 506, 508 $[M+H]^+$
HPLC retention time: 3.15 min (analysis condition C)

[Example 597]

Compound S7-4

9-Bromo-3-chloro-8-((S)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1459]



[1460] Under the same conditions as the method for synthesizing Compound S7-2, the title compound was prepared from Compound S7-3.

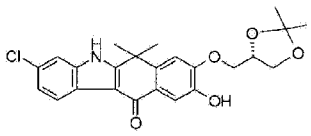
LCMS: m/z 464, 466, 468 $[M+H]^+$
HPLC retention time: 2.77 min (analysis condition C)

[Example 598]

Compound S8-1

9-Hydroxy-3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1461]



[1462] 9-Bromo-3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S7-1, 30 mg, 0.06 mmol) was dissolved in the mixture solvent of water · dioxane (1 : 1) (0.5 mL), added with tris(benzylidenacetone dipalladium)chloroform complex (3.1 mg, 0.05 eq.), 2-di-tert-butylphosphino-2',4',6'-triisopropylbiphenyl (2.5 mg, 0.1 eq.) and KOH (0.5 N aqueous solution 180 µL, 1.5 eq.), and stirred at 60°C for 12 hr. After cooling, the reaction solution was concentrated under reduced pressure, and the resulting residues were purified by HPLC to obtain the title compound (white solid, 4.6 mg).

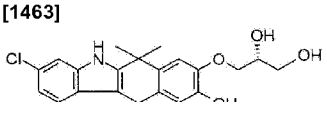
LCMS: m/z 442, 444 $[M+H]^+$
HPLC retention time: 2.78 min (analysis condition C)

[Example 599]

Compound S8-2

3-Chloro-8-((R)-2,3-dihydroxy-propoxy)-9-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1463]



[1464] Under the same conditions as the method for synthesizing Compound S7-2, the title compound was prepared from Compound S8-1.

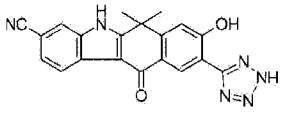
LCMS: m/z 402, 404 $[M+H]^+$
HPLC retention time: 0.90 min (analysis condition I)

[Example 600]

Compound S9-1

8-Hydroxy-6,6-dimethyl-11-oxo-9-(1H-tetrazol-5-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1465]



[1466] 9-Bromo-3-chloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S1-4, 150 mg, 0.37 mMol) was dissolved in NMP, added with CuCN (100 mg, 3 eq.), and stirred at 210°C for 1.5 hr under irradiation with microwave. After cooling, the reaction solution was added with water and ethyl acetate, and the precipitated solid was filtered to remove the solvent. The obtained residues were dissolved in DMF (1 ml), added with sodium azide (100 mg, 8 eq.) and ammonium chloride (5 mg), and then stirred at 120°C for 24 hr in a sealed tube. After adding water, the insoluble matters were filtered and purified by HPLC to obtain the title compound (6.5 mg).

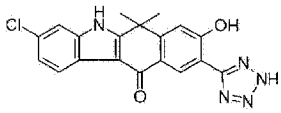
LCMS: m/z 371 $[M+H]^+$
HPLC retention time: 2.22 min (analysis condition C)

[Example 601]

Compound S9-2

3-Chloro-8-hydroxy-6,6-dimethyl-9-(1H-tetrazol-5-yl)-5,6-dihydro-benzo[b]carbazol-11-one

[1467]



[1468] The title compound was obtained as an intermediate for the synthesis of Compound S9-1.

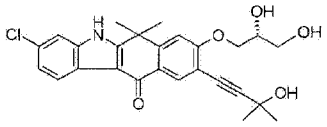
LCMS: m/z 380, 382 $[M+H]^+$
HPLC retention time: 2.38 min (analysis condition C)

[Example 602]

Compound S10

3-Chloro-8-((R)-2,3-dihydroxy-propoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1469]



[1470] To the mixture of 9-bromo-3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S7-1, 50 mg, 0.1 mmol), bis(acetonitrile) palladium (II) dichloride (2.6 mg, 0.01 eq.), cesium carbonate (195 mg, 6 eq.) and 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (14.3 mg, 0.03 eq.), acetonitrile (2 mL) was added and stirred at 80°C for 12 hr. Tar-like residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (brown powder, 105 mg).

[1471] The resulting 3-chloro-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-9-(3-hydroxy-3-methyl-but-1-ynyl)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (20 mg, 0.04 mmol) was dissolved in methanol (3 mL), added with 1 N hydrochloric acid (1 ml), and stirred at room temperature for 12 hr. After cooling, the reaction solution was concentrated under reduced pressure, and the resulting residues were washed with methylene chloride to obtain the title compound (pale yellow powder, 5.2 mg).

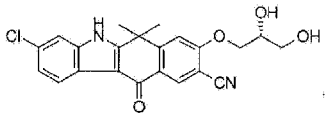
LCMS: m/z 468, 470 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition C)

[Example 603]

Compound S11-1

3-Chloro-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-carbonitrile

[1472]



[1473] 3-Chloro-9-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound S7-2, 17 mg, 37 µmol) was dissolved in DMA, added with CuCN (17 mg, 5 eq.), and stirred at 220°C for 2 hr under irradiation with microwave. After cooling, the reaction solution was added with ethyl acetate, and the precipitated solid was filtered to remove the solvent. The resulting residues were purified by HPLC to obtain the title compound (4 mg).

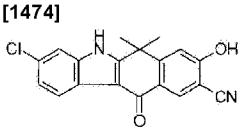
LCMS: m/z 409, 411 $[M+H]^+$
HPLC retention time: 2.65 min (analysis condition C)

[Example 604]

Compound S11-2

3-Chloro-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-9-carbonitrile

[1474]



[1475] The title compound was obtained as a by-product of the synthesis of Compound S11-1.

LCMS: m/z 337, 339 $[M+H]^+$

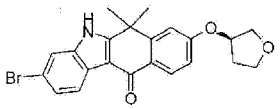
HPLC retention time: 2.35 min (analysis condition C)

[Example 605]

Compound T1-1

3-Bromo-6,6-dimethyl-8-[(R)-(tetrahydro-furan-3-yl)oxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1476]



[1477] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and (S)-tetrahydro-furan-3-ol.

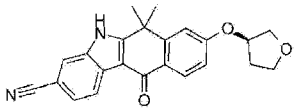
LCMS: m/z 426 $[M+H]^+$
HPLC retention time: 2.08 min (analysis condition D)

[Example 606]

Compound T1-2

6,6-Dimethyl-11-oxo-8-[(R)-(tetrahydro-furan-3-yl)oxy]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1478]



[1479] According to the same method as the method for synthesizing Compound A5-2, the title compound was prepared from Compound T1-1.

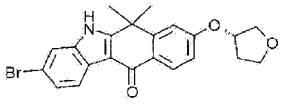
LCMS: m/z 373 $[M+H]^+$
HPLC retention time: 1.98 min (analysis condition A)

[Example 607]

Compound T2-1

3-Bromo-6,6-dimethyl-8-[(S)-(tetrahydro-furan-3-yl)oxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1480]



[1481] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and (R)-tetrahydro-furan-3-ol.

LCMS: m/z 426 $[M+H]^+$

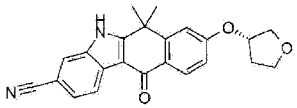
HPLC retention time: 6.12 min (analysis condition H)

[Example 608]

Compound T2-2

6,6-Dimethyl-11-oxo-8-[(S)-(tetrahydro-furan-3-yl)oxy]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1482]



[1483] According to the same method as the method for synthesizing Compound A5-2, the title compound was prepared from Compound T2-1.

LCMS: m/z 373 $[M+H]^+$

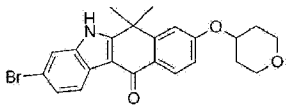
HPLC retention time: 2.00 min (analysis condition D)

[Example 609]

Compound T3-1

3-Bromo-6,6-dimethyl-8-(tetrahydro-pyran-4-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1484]



[1485] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and tetrahydro-pyran-4-ol.

LCMS: m/z 440 $[M+H]^+$

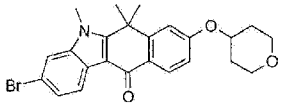
HPLC retention time: 8.07 min (analysis condition H)

[Example 610]

Compound T3-2

3-Bromo-5,6,6-trimethyl-8-(tetrahydro-pyran-4-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1486]



[1487] According to the same method as the method for synthesizing Compound A10-2, the title compound was prepared from Compound T3-1.

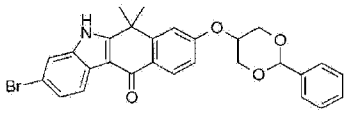
LCMS: m/z 454 $[M+H]^+$
HPLC retention time: 6.88 min (analysis condition H)

[Example 611]

Compound T4-1

3-Bromo-6,6-dimethyl-8-(2-phenyl-[1,3]dioxan-5-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1488]



[1489] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and 5-phenyl-[1,3]dioxan-2-ol.

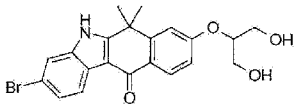
LCMS: m/z 518 $[M+H]^+$
HPLC retention time: 2.68 min (analysis condition D)

[Example 612]

Compound T4-2

3-Bromo-8-(2-hydroxy-1-hydroxymethyl-ethoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1490]



[1491] According to the same method as the method for synthesizing Compound A7-13-2, the title compound was prepared from Compound T4-1.

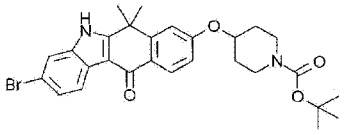
LCMS: m/z 430 $[M+H]^+$
HPLC retention time: 4.64 min (analysis condition H)

[Example 613]

Compound T5-1

4-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1492]



[1493] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and 4-hydroxy-piperidine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 539 $[M+H]^+$

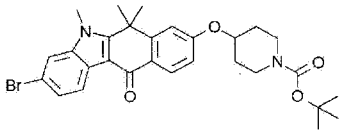
HPLC retention time: 2.72 min (analysis condition D)

[Example 614]

Compound T5-2

4-(3-Bromo-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-piperidine-1-carboxylic acid tert-butyl ester

[1494]



[1495] According to the same method as the method for synthesizing Compound A10-1, the title compound was prepared from Compound T5-1.

LCMS: m/z 553 $[M+H]^+$

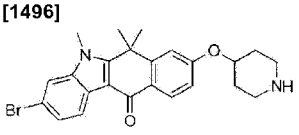
HPLC retention time: 2.93 min (analysis condition D)

[Example 615]

Compound T5-3

3-Bromo-5,6,6-trimethyl-8-(piperidin-4-yloxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1496]



[1497] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T5-2.

LCMS: m/z 453 $[M+H]^+$

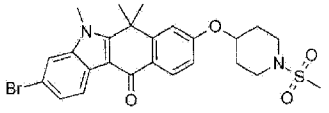
HPLC retention time: 1.98 min (analysis condition D)

[Example 616]

Compound T5-4

3-Bromo-8-(1-methanesulfonyl-piperidin-4-yloxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1498]



[1499] According to the same method as the method for synthesizing Compound A9-7, the title compound was prepared from Compound T5-3 and methanesulfonyl chloride.

LCMS: m/z 531 $[M+H]^+$

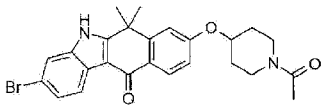
HPLC retention time: 2.38 min (analysis condition D)

[Example 617]

Compound T5-5

8-(1-Acetyl-piperidin-4-yloxy)-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1500]



[1501] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T5-3 and acetic anhydride.

LCMS: m/z 482 $[M+H]^+$

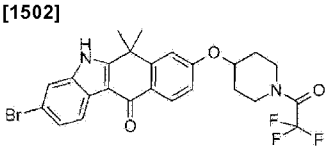
HPLC retention time: 2.10 min (analysis condition D)

[Example 618]

Compound T6-1

3-Bromo-6,6-dimethyl-8-[1-(2,2,2-trifluoro-acetyl)-piperidin-4-yloxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1502]



[1503] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T6-2 and trifluoroacetic anhydride.

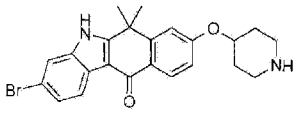
LCMS: m/z 535 $[M+H]^+$
HPLC retention time: 2.53 min (analysis condition D)

[Example 619]

Compound T6-2

3-Bromo-6,6-dimethyl-8-(piperidin-4-yloxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1504]



[1505] 3-Bromo-6,6-dimethyl-8-[1-(2,2,2-trifluoro-acetyl)-piperidin-4-yloxy]-5,6-dihydro-benzo[b]carbazol-11-one (Compound T6-1, 28.0 mg, 52.3 μmol) was dissolved in THF (1.00 mL) and methanol (0.50 mL), added with aqueous solution of potassium hydroxide (1.00 mL, 20 wt%), and stirred at room temperature for 1 hr. The reaction solution was added to water, and extracted with mixture solution of chloroform and methanol, and dried over sodium sulfate. Then, after filtering and concentration under reduced pressure, 3-bromo-6,6-dimethyl-8-(piperidin-4-yloxy)-5,6-dihydro-benzo[b]carbazol-11-one was obtained as a crude product.

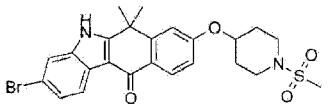
LCMS: m/z 439 $[M+H]^+$
HPLC retention time: 1.83 min (analysis condition D)

[Example 620]

Compound T6-3

3-Bromo-8-(1-methanesulfonyl-piperidin-4-yloxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1506]



[1507] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T6-2 and mesyl chloride.

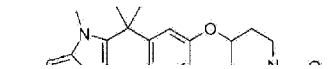
LCMS: m/z 517 $[M+H]^+$
HPLC retention time: 2.23 min (analysis condition D)

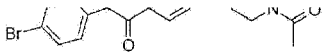
[Example 621]

Compound T6-4

8-(1-Acetyl-piperidin-4-yloxy)-3-bromo-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1508]





[1509] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T6-2 and acetic anhydride.

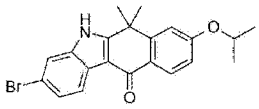
LCMS: m/z 496 $[M+H]^+$
HPLC retention time: 2.27 min (analysis condition D)

[Example 622]

Compound T7-1

3-Bromo-8-isopropoxy-6,6-dimethyl-5,6-dihydro-benzo[b]-carbazol-11-one

[1510]



[1511] The title compound was obtained as a by-product of the synthesis of Compound T4-1.

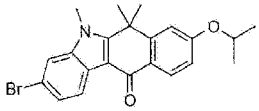
LCMS: m/z 398 $[M+H]^+$
HPLC retention time: 3.18 min (analysis condition F)

[Example 623]

Compound T7-2

3-Bromo-8-isopropoxy-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1512]



[1513] According to the same method as the method for synthesizing Compound A10-2, the title compound was prepared from Compound T7-1.

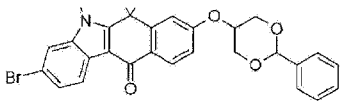
LCMS: m/z 413 $[M+H]^+$
HPLC retention time: 2.70 min (analysis condition D)

[Example 624]

Compound T8-1

3-Bromo-5,6,6-trimethyl-8-(2-phenyl-[1,3]dioxan-5-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1514]



[1515] According to the same method as the method for synthesizing Compound A10-2, the title compound was prepared from Compound T4-1.

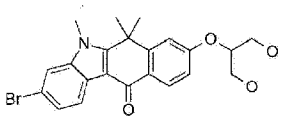
LCMS: m/z 532 $[M+H]^+$
HPLC retention time: 2.90 min (analysis condition D)

[Example 625]

Compound T8-2

3-Bromo-8-(2-hydroxy-1-hydroxymethyl-ethoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1516]



[1517] According to the same method as the method for synthesizing Compound A7-13-2, the title compound was prepared from Compound T4-1.

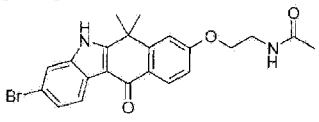
LCMS: m/z 444 $[M+H]^+$
HPLC retention time: 1.90 min (analysis condition D)

[Example 626]

Compound T9

N-[2-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-ethyl]-acetamide

[1518]



[1519] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A5-1 and (N-(2-chloro-ethyl)-acetamide.

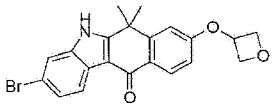
LCMS: m/z 441 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition D)

[Example 627]

Compound T10

3-Bromo-6,6-dimethyl-8-(oxetan-3-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1520]



[1521] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A5-1 and toluene-4-sulfonic acid oxetan-3-yl ester.

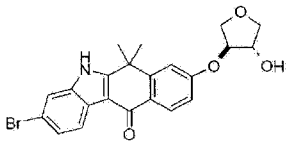
LCMS: m/z 412 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition D)

[Example 628]

Compound T11

3-Bromo-8-(4-hydroxy-tetrahydro-furan-3-yl oxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1522]



[1523] Under nitrogen atmosphere, tetrahydro-furo[3,4-d][1,3,2]dioxathiol 2,2-dioxide (71.5 mg, 0.420 mmol) was dissolved in DMF (1.40 mL), added with 3-bromo-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound A5-1, 50.0 mg, 0.140 mmol) and cesium carbonate (228 mg, 0.700 mmol), and stirred at 80°C for 15 hr. Subsequently, sulfuric acid (0.10 mL, 18 M), THF (3.00 mL) and water (0.50 mL) were added to the mixture, which was then stirred at room temperature for 24 hr and further at 60°C for 24 hr. The reaction solution was added to water, extracted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate, and saturated brine, and dried over sodium sulfate. After filtering and concentration under reduced pressure, the resulting residues were washed with dichloromethane and purified by NH silica gel column chromatography (ethyl acetate/THF) to obtain the target compound (44.7 mg, 72%).

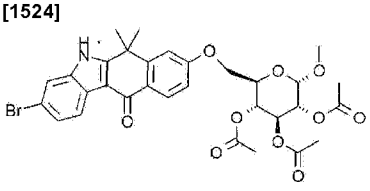
LCMS: m/z 442 $[M+H]^+$
HPLC retention time: 1.98 min (analysis condition D)

[Example 629]

Compound T12-1

Acetic acid (2S,3R,4S,SR,6R)-4,5-diacetoxy-6-(3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxymethyl)-2-methoxy-tetrahydro-pyran-3-yl ester

[1524]



[1525] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from

Compound A5-1 and methyl 2,3,4-tri-O-acetyl-α-D-glucopyranoside.

LCMS: m/z 658 $[M+H]^+$

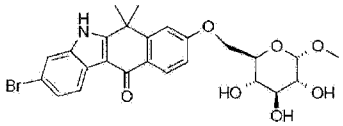
HPLC retention time: 2.38 min (analysis condition D)

[Example 630]

Compound T12-2

3-Bromo-6,6-dimethyl-8-((2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-methoxy-tetrahydro-pyran-2-yl methoxy)-5,6-dihydro-benzo[b] carbazol-11-one

[1526]



[1527] Under nitrogen atmosphere, to acetic acid (2S,3R,4S,5R,6R)-4,5-diacetoxy-6-(3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxymethyl)-2-methoxy-tetrahydro-pyran-3-yl ester (Compound T12-1, 34.0 mg, 51.63 μmol), methanol solution (2.50 mL, 2 M) of ammonia was added, and the mixture was stirred at room temperature for 21 hr. The reaction solution was concentrated under reduced pressure, and the resulting resides were washed with diethyl ether to obtain the target compound (25.7 mg, 94%).

LCMS: m/z 532 $[M+H]^+$

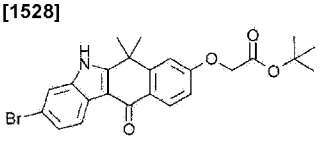
HPLC retention time: 2.42 min (analysis condition D)

[Example 631]

Compound T13-1

(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-acetic acid tert-butyl ester

[1528]



[1529] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A5-1 and bromo-acetic acid tert-butyl ester.

LCMS: m/z 470 $[M+H]^+$

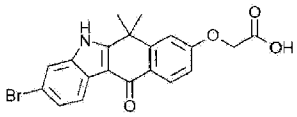
HPLC retention time: 2.53 min (analysis condition D)

[Example 632]

Compound T13-2

(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-acetic acid

[1530]



[1531] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T13-1.

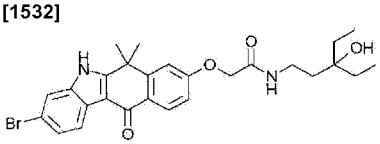
LCMS: m/z 414 $[M+H]^+$
HPLC retention time: 1.50 min (analysis condition D)

[Example 633]

Compound T13-3

2-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-N-(3-ethyl-3-hydroxy-pentyl)-acetamide

[1532]



[1533] Under nitrogen atmosphere, (3-azide-1,1-diethyl-propoxy)-trimethyl-silane (16.6 mg, 72.42 μmol) was dissolved in toluene (0.48 mL), added with 3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-acetic acid (20.0 mg, 48.28 μmol) and Molecular Sieves 4 angstrom, and the mixture was stirred at room temperature for 5 min. Thereafter, the mixture was added with trimethylphosphine (10.2 μL, 96.56 μmol) and stirred at 80°C for 22 hr. The reaction solution was added to hydrochloric acid (1 M), extracted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate, saturated brine and dried over sodium sulfate. After filtering and concentration under reduced pressure, the resulting residues were purified by silica gel column chromatography (methanol/dichloromethane) to obtain the target compound (0.7 mg, 3%).

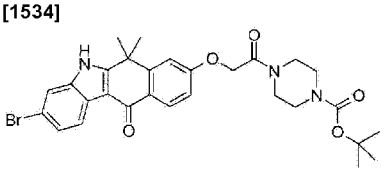
LCMS: m/z 527 $[M+H]^+$
HPLC retention time: 2.93 min (analysis condition D)

[Example 634]

Compound T13-4

4-[2-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-acetyl]-piperazine-1-carboxylic acid tert-butyl ester

[1534]



[1535] According to the same method as the method for synthesizing Compound A9-10, the title compound was prepared from Compound T13-2 and 1-(tert-butoxycarbonyl)piperazine.

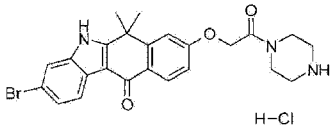
LCMS: m/z 582 $[M+H]^+$
HPLC retention time: 2.32 min (analysis condition D)

[Example 635]

Compound T13-5

3-Bromo-6,6-dimethyl-8-(2-oxo-2-piperazin-1-yl-ethoxy)-5,6-dihydro-benzo[b]carbazol-11-one hydrochloric acid salt

[1536]



[1537] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T13-4.

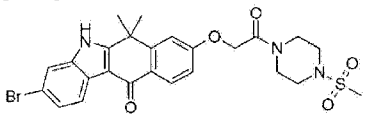
LCMS: m/z 482 $[M+H]^+$
HPLC retention time: 1.75 min (analysis condition D)

[Example 636]

Compound T13-6

3-Bromo-8-[2-(4-methanesulfonyl-piperazin-1-yl)-2-oxo-ethoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1538]



[1539] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T13-5 and methanesulfonyl chloride.

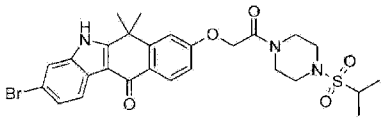
LCMS: m/z 560 $[M+H]^+$
HPLC retention time: 2.00 min (analysis condition D)

[Example 637]

Compound T13-7

3-Bromo-6,6-dimethyl-8-{2-oxo-2-[4-(propane-2-sulfonyl)-piperazin-1-yl]-ethoxy}-5,6-dihydro-benzo[b]carbazol-11-one

[1540]



[1541] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from

Compound T13-5 and isopropylsulfonyl chloride.

LCMS: m/z 588 $[M+H]^+$

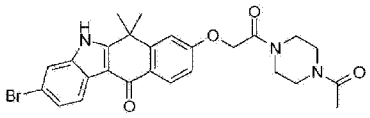
HPLC retention time: 2.47 min (analysis condition D)

[Example 638]

Compound T13-8

8-[2-(4-Acetyl-piperazin-1-yl)-2-oxo-ethoxy]-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1542]



[1543] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T13-5 and acetic anhydride.

LCMS: m/z 524 $[M+H]^+$

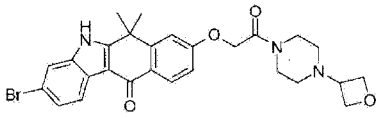
HPLC retention time: 1.85 min (analysis condition D)

[Example 639]

Compound T13-9

3-Bromo-6,6-dimethyl-8-[2-(4-oxetan-3-yl-piperazin-1-yl)-2-oxo-ethoxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1544]



[1545] According to the same method as the method for synthesizing Compound B3-32, the title compound was prepared from Compound T13-5 and 3-oxetanone.

LCMS: m/z 538 $[M+H]^+$

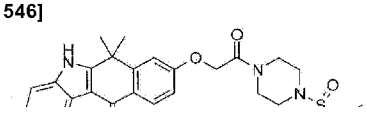
HPLC retention time: 1.88 min (analysis condition D)

[Example 640]

Compound T13-10

4-[2-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl-oxy)-acetyl]-piperazine-1-sulfonic acid methylamide

[1546]



[1547] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T13-5 and 2-oxo-oxazolidine-3-sulfonic acid methylamide.

LCMS: m/z 575 $[M+H]^+$

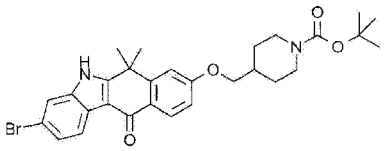
HPLC retention time: 2.29 min (analysis condition A)

[Example 641]

Compound T14-1

4-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxymethyl)-piperidine-1-carboxylic acid tert-butyl ester

[1548]



[1549] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and 1-(tert-butoxycarbonyl)-4-(hydroxymethyl)piperidine.

LCMS: m/z 553 $[M+H]^+$

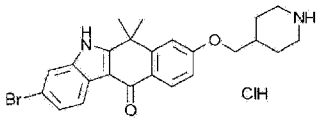
HPLC retention time: 2.80 min (analysis condition D)

[Example 642]

Compound T14-2

3-Bromo-6,6-dimethyl-8-(piperidin-4-ylmethoxy)-5,6-dihydro-benzo[b]carbazol-11-one hydrochloric acid salt

[1550]



[1551] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T14-1.

LCMS: m/z 454 $[M+H]^+$

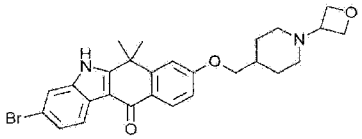
HPLC retention time: 1.90 min (analysis condition D)

[Example 643]

Compound T14-3

3-Bromo-6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-ylmethoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1552]



[1553] According to the same method as the method for synthesizing Compound B3-32, the title compound was prepared from Compound T14-2 and 3-oxetanone.

^{1}H-NMR(400 MHz, $CDCl_3$) δ : 9.24 (1 H, s), 8.37 (1 H, d, 8.8 Hz), 8.30 (1 H, d, 8.3 Hz), 7.57 (1 H, d, 1.5 Hz), 7.41 (1 H, dd, 8.3, 1.5 Hz), 7.08 (1 H, d, 2.4 Hz), 6.98 (1 H, dd, 8.8, 2.4 Hz) 4.60-4.95 (7 H, m), 3.93 (2 H, d, 5.9 Hz), 3.50 (1 H, m), 2.83 (2 H, d, 11.2 Hz), 1.89 (4 H, m), 1.78 (6 H, s),

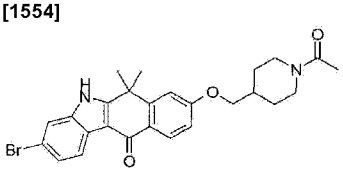
LCMS: m/z 509 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition A)

[Example 644]

Compound T14-4

8-(1-Acetyl-piperidin-4-ylmethoxy)-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1554]



[1555] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T14-2 and acetic anhydride.

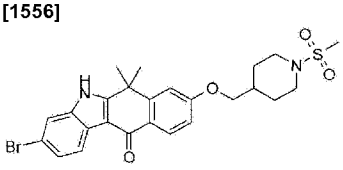
LCMS: m/z 495 $[M+H]^+$
HPLC retention time: 2.53 min (analysis condition A)

[Example 645]

Compound T14-5

3-Bromo-8-(1-methanesulfonyl-piperidin-4-ylmethoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1556]



[1557] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T14-2 and methanesulfonyl chloride.

LCMS: m/z 531 $[M+H]^+$

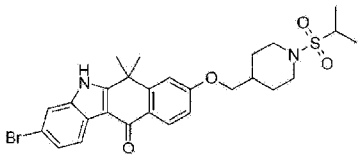
HPLC retention time: 2.30 min (analysis condition D)

[Example 646]

Compound T14-6

3-Bromo-6,6-dimethyl-8-[1-(propane-2-sulfonyl)-pipendin-4-ylmethoxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1558]



[1559] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T14-2 and isopropylsulfonyl chloride.

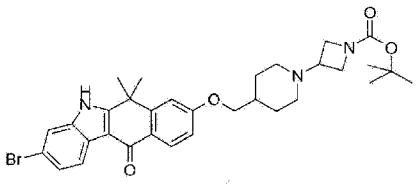
LCMS: m/z 559 $[M+H]^+$
HPLC retention time: 2.58 min (analysis condition D)

[Example 647]

Compound T14-7

3-[4-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxymethyl)-piperidin-1-yl]-azetidine-1-carboxylic acid tert-butyl ester

[1560]



[1561] According to the same method as the method for synthesizing Compound B3-32, the title compound was prepared from Compound T14-2 and 3-oxo-azetidine-1-carboxylic acid tert-butyl ester.

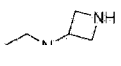
LCMS: m/z 608 $[M+H]^+$
HPLC retention time: 2.29 min (analysis condition A)

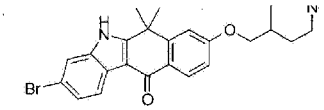
[Example 648]

Compound T14-8

8-(1-Azetidin-3-yl-piperidin-4-ylmethoxy)-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1562]





[1563] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T14-7.

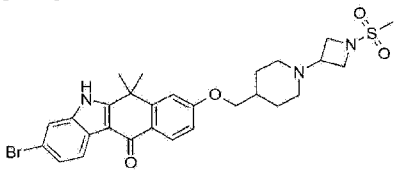
LCMS: m/z 508 $[M+H]^+$
HPLC retention time: 1.90 min (analysis condition A)

[Example 649]

Compound T14-9

3-Bromo-8-[1-(1-methanesulfonyl-azetidin-3-yl)-piperidin-4-ylmethoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1564]



[1565] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T14-8 and mesyl chloride.

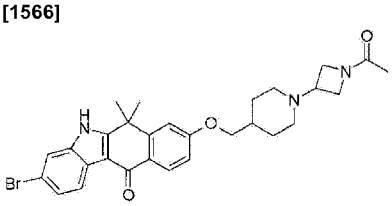
LCMS: m/z 586 $[M+H]^+$
HPLC retention time: 2.06 min (analysis condition A)

[Example 650]

Compound T14-10

8-[1-(1-Acetyl-azetidin-3-yl)-piperidin-4-ylmethoxy]-3-bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1566]



[1567] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T14-8 and acetic anhydride.

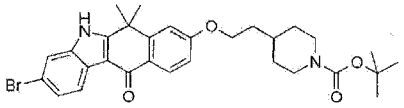
LCMS: m/z 550 $[M+H]^+$
HPLC retention time: 2.53 min (analysis condition A)

[Example 651]

Compound T15-1

4-[2-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester

[1568]



[1569] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and N-(tert-butoxycarbonyl)-4-piperidine ethanol.

LCMS: m/z 567 $[M+H]^+$

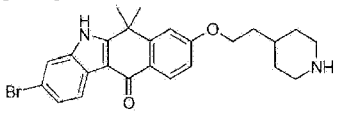
HPLC retention time: 2.29 min (analysis condition D)

[Example 652]

Compound T15-2

3-Bromo-6,6-dimethyl-8-(2-piperidin-4-yl-ethoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1570]



[1571] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T15-1.

LCMS: m/z 467 $[M+H]^+$

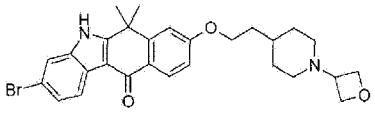
HPLC retention time: 1.95 min (analysis condition D)

[Example 653]

Compound T15-3

3-Bromo-6,6-dimethyl-8-[2-(1-oxetan-3-yl-piperidin-4-yl)-ethoxy]-5,6-dihydro-benzo[b]carbazol-11-one

[1572]



[1573] According to the same method as the method for synthesizing Compound B3-32, the title compound was prepared from Compound T15-2 and 3-oxetanone.

LCMS: m/z 523 $[M+H]^+$

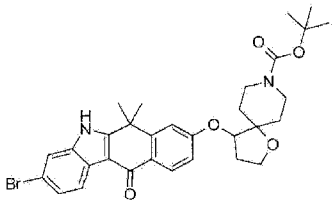
HPLC retention time: 2.28 min (analysis condition D)

[Example 654]

Compound T16-1

4-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-8-yl oxy)-1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester

[1574]



[1575] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and 3-hydroxy-1-oxa-8-aza-spiro[4.5]decane-8-carboxylic acid tert-butyl ester.

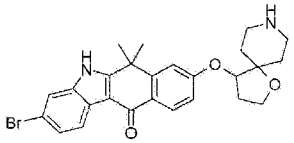
LCMS: m/z 595 $[M+H]^+$
HPLC retention time: 3.08 min (analysis condition A)

[Example 655]

Compound T16-2

3-Bromo-6,6-dimethyl-8-(1-oxa-8-aza-spiro[4.5]decan-4-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1576]



[1577] According to the same method as the method for synthesizing Compound A8-1, the title compound was prepared from Compound T16-1.

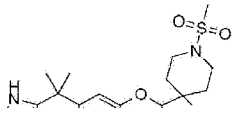
LCMS: m/z 496 $[M+H]^+$
HPLC retention time: 1.99 min (analysis condition A)

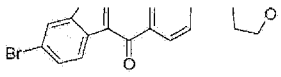
[Example 656]

Compound T16-3

3-Bromo-8-(8-methanesulfonyl-1-oxa-8-aza-spiro[4.5]decan-4-yl oxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1578]





[1579] According to the same method as the method for synthesizing Compound A9-1, the title compound was prepared from Compound T16-2 and mesyl chloride.

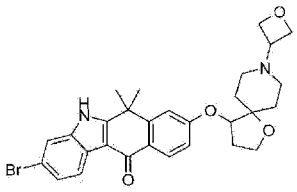
LCMS: m/z 573 $[M+H]^+$
HPLC retention time: 2.56 min (analysis condition A)

[Example 657]

Compound T16-4

3-Bromo-6,6-dimethyl-8-(8-oxetan-3-yl-1-oxa-8-aza-spiro[4.5]decan-4-yl oxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1580]



[1581] According to the same method as the method for synthesizing Compound B3-32, the title compound was prepared from Compound T16-2 and 3-oxetanone.

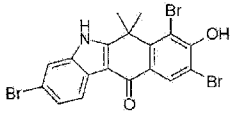
LCMS: m/z 551 $[M+H]^+$
HPLC retention time: 2.01 min (analysis condition A)

[Example 658]

Compound T17-1

3,7,9-Tribromo-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1582]



[1583] Under nitrogen atmosphere, 4-[1,3]dithian-2-ylidene-piperidine-1-carboxylic acid tert-butyl ester (100 g, 0.332 mmol) was dissolved in dichloromethane (2.50 mL), added with trifluoromethanesulfonic acid (30.8 μL, 0.348 mmol) at -20°C, and stirred at room temperature for 30 min. The reaction solution was cooled to -70°C, and then added dropwise with the dichloromethane (2.50 mL) solution of 3-bromo-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound A5-1, 177 mg, 0.498 mmol) and triethylamine (78.6 μL, 0.564 mmol). Thereafter, triethylamine hydrotrifluoric acid salt (262 μL, 1.610 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (460 mg, 1.610 mmol) were added thereto and stirred at -70°C for 1 hr. The reaction solution was added to aqueous solution of sodium hydroxide (1 M), extracted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate, saturated brine and dried over sodium sulfate. After filtering and concentration under reduced pressure, the resulting residues were purified by silica gel column chromatography (ethyl acetate/hexane) and aminosilica gel column chromatography (ethyl acetate/hexane) to obtain the target compound (42.0 mg, 25%).

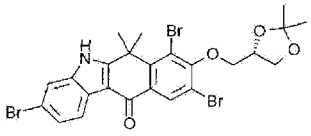
LCMS: m/z 511 $[M+H]^+$
HPLC retention time: 6.34 min (analysis condition B)

[Example 659]

Compound T17-2

3,7,9-Tribromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1584]



[1585] According to the same method as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A17-1 and (S)-(+)-2,2-dimethyl-1,3-dioxolan-4-methanol.

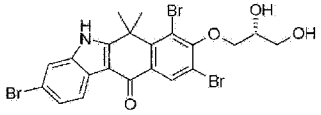
LCMS: m/z 625 $[M+H]^+$
HPLC retention time: 3.41 min (analysis condition A)

[Example 660]

Compound T17-3

3,7,9-Tribromo-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1586]



[1587] According to the same method as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T17-2.

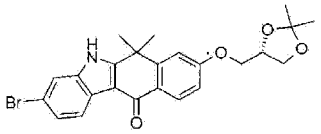
LCMS: m/z 585 $[M+H]^+$
HPLC retention time: 2.44 min (analysis condition A)

[Example 661]

Compound T18-1

3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1588]



[1589] 3-Bromo-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound A5-1, 18.0 mg, 50.5 µmol) was dissolved in DMF (0.18 mL), added with toluene-4-sulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester (14.5 mg, 0.0505 mmol) and potassium carbonate (10.0 mg, 0.07575 mmol), and the mixture was stirred at 70°C for 3 days. The reaction solution was added to water, extracted with ethyl acetate, and the organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by preparative TLC (methylene chloride/methanol) to obtain the title compound (16.6 mg, 70%).

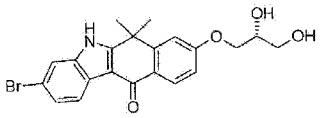
LCMS: m/z 470 $[M+H]^+$
HPLC retention time: 3.01 min (analysis condition F)

[Example 662]

Compound T18-2

3-Bromo-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1590]



[1591] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T18-1.

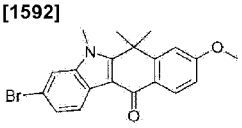
LCMS: m/z 430 $[M+H]^+$
HPLC retention time: 4.72 min (analysis condition H)

[Example 663]

Compound T19-1-1

3-Bromo-8-methoxy-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1592]



[1593] Under the same conditions as the method for synthesizing Compound A10-1, the title compound was prepared from Compound A4.

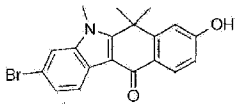
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 2.84 min (analysis condition D)

[Example 664]

Compound T19-1

3-Bromo-8-hydroxy-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1594]



[1595] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound T19-1-1.

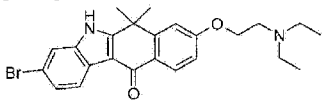
LCMS: m/z 370 $[M+H]^+$
HPLC retention time: 2.40 min (analysis condition D)

[Example 665]

Compound T19-2

3-Bromo-8-(2-diethylaminoethoxy)-6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1596]



[1597] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound A5-1 (9.8 mg, 36%).

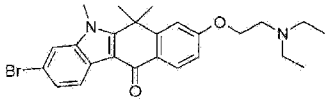
LCMS: m/z 455 $[M+H]^+$
HPLC retention time: 1.96 min (analysis condition D)

[Example 666]

Compound T19-3

3-Bromo-8-(2-diethylaminoethoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1598]



[1599] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound T19-1.

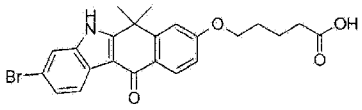
LCMS: m/z 469 $[M+H]^+$
HPLC retention time: 2.09 min (analysis condition D)

[Example 667]

Compound T20

5-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl oxy)-pentanoic acid

[1600]



[1601] Under the same conditions as the method for synthesizing Compound A7-17, Compound A5-1 and methyl 5-bromovalerate were reacted, added with 1 N NaOH (140 μL), and then stirred at room temperature for 2 hr. The reaction mixture was added with 2 N HCl (70 μL), and concentrated under reduced pressure. The resulting residues were purified by preparative TLC (methylene chloride : methanol = 15 : 1) to obtain 7 mg (55%).

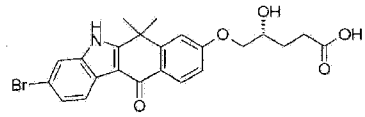
LCMS: m/z 456 $[M+H]^+$
HPLC retention time: 5.88 min (analysis condition H)

[Example 668]

Compound T21

(R)-5-(3-Bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl oxy)-4-hydroxy-pentanoic acid

[1602]



[1603] Under the same conditions as the method for synthesizing Compound T20, the title compound was prepared from the reaction between Compound A5-1 and toluene-4-sulfonic acid (R)-5-oxo-tetrahydrofuran-2-yl methyl ester.

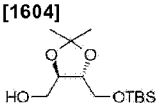
LCMS: m/z 471 $[M+H]^+$
HPLC retention time: 4.57 min (analysis condition H)

[Example 669]

Compound T22-0

[5-(Tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol

[1604]



[1605] To THF (50 mL), NaH (1.41 g, 0.032 mmol) was added at room temperature, followed by addition of ((4R,5R)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (5.0 g, 0.031 mmol) at room temperature. The mixture was stirred at room temperature for 1 hr. After that, TBSCl (5.11 g, 0.034 mmol) was added at room temperature and stirred at room temperature overnight. The reaction solution was added with saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (8.21 g, 96%).

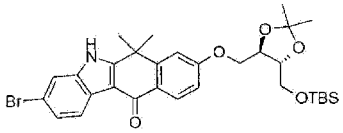
^{1}H-NMR(270 MHz, DMSO-d_6) δ : 3.64-4.98(6 H, m), 2.37 (1 H, m), 1. 41 (3 H, s), 1.40 (3 H, s), 0.90 (9 H, s), 0.08 (6 H, s)

[Example 670]

Compound T22-1

3-Bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxmethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1606]



[1607] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound A5-1 and [5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl] -methanol (Compound T22-0) (704 mg, 80%).

LCMS: m/z 614 $[M+H]^+$

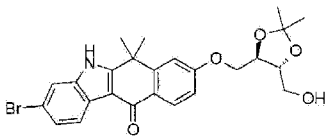
HPLC retention time: 4.00 min (analysis condition F)

[Example 671]

Compound T22-1-1

3-Bromo-8-((1R,5R)-5-hydroxymethyl-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1608]



[1609] Under nitrogen atmosphere, to the DMF (0.4 mL) suspension of 3-bromo-8-[(1R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound T22-1, 50.3 mg, 0.0818 mmol) and copper (I) iodide (34 mg), sodium methoxide (1 M methanol solution, 0.82 mL, 0.818 mmol) was added and the mixture was stirred for 6 hr and 45 min at ambient temperature of 90°C. After cooling to room temperature, the reaction mixture was added with diethyl ether and ethyl acetate, and the insoluble matters were removed by Celite filtration. The concentrated residues were added with diethyl ether, hexane, ethyl acetate and water, and then the mixture was extracted twice with diethyl ether. The organic layer was washed with water and subsequently with brine, dried over sodium sulfate and concentrated under reduced pressure. The resulting crude product was purified by preparative TLC (Merck60 F_{254}, 0.5 mm) {solution for elution: hexane/ethyl acetate (1 : 2)} to obtain the title compound (colorless oily substance, 22.6 mg, 55%).

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.44-8.38 (1 H, b), 8.39 (1 H, d, 8.6 Hz), 8. 31 (1 H, d, 8.2 Hz), 7.60 (1 H, d, 1.3 Hz), 7. 44 (1 H, dd, 8.2 Hz, 1.3 Hz), 7.12 (1 H, d, 2.3 Hz), 7.02 (1 H, dd, 8.6 Hz, 2.3 Hz), 4.41-4.10 (4 H, m), 4.00-3.88 (1 H, m), 3.86-3.76 (1 H, m), 1.78 (6 H, s), 1.50 (3 H, s), 1.49 (3 H, s)

LCMS: m/z 500 $[M+H]^+$

HPLC retention time: 2.85 min (analysis condition C)

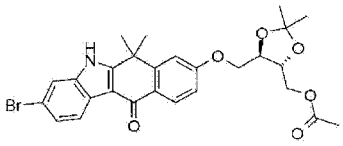
[Example 672]

Compound T22-1-2

Acetic acid (3R,4R)-5-(3-bromo-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl oxymethyl)-2,2-

dimethyl[1,3]dioxolan-4-yl methyl ester

[1610]



[1611] The title compound was obtained as a by-product of the synthesis of T22-1-1 (white solid, 17.8 mg, 40%).

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.92-8.80 (1 H, b), 8.40 (1 H, d, 8.9 Hz), 8. 31 (1 H, d, 8.6 Hz), 7.58 (1 H, d, 1.7 Hz), 7. 43 (1 H, dd, 8.6 Hz, 1.7 Hz), 7.14 (1 H, d, 2.3 Hz), 7.02 (1 H, dd, 8.9 Hz, 2.3 Hz), 4.51-4.38 (1 H, m), 4.34-4.16 (4 H, m), 2.13 (3 H, s), 1.78 (6 H, s), 1.50 (6 H, s)

LCMS: m/z 542 $[M+H]^+$

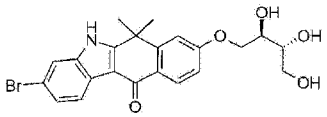
HPLC retention time: 3.00 min (analysis condition C)

[Example 673]

Compound T22-2

3-Bromo-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1612]



[1613] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T22-1 (2.83 g, 95%).

LCMS: m/z 460 $[M+H]^+$

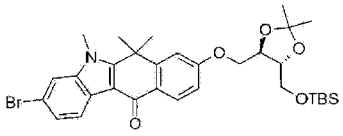
HPLC retention time: 4.50 min (analysis condition H)

[Example 674]

Compound T22-3

3-Bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxmethyl)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1614]



[1615] Under the same conditions as the method for synthesizing Compound B3-4, the title compound was prepared from Compound T22-1.

LCMS: m/z 628 $[M+H]^+$

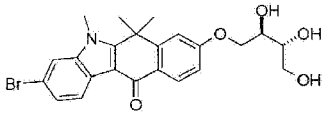
HPLC retention time: 4.74 min (analysis condition F)

[Example 675]

Compound T22-4

3-Bromo-8-((2R,3R)-2,3-dihydroxy-pentyloxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1616]



[1617] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T22-3.

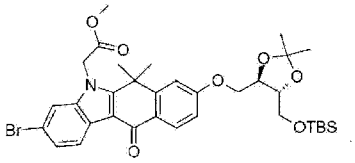
LCMS: m/z 475 $[M+H]^+$
HPLC retention time: 4.86 min (analysis condition H)

[Example 676]

Compound T22-5

{3-Bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6 6-dimethyl-11-oxo-6,11-dihydro-benzo[b]carbazol-5-yl}-acetic acid methyl ester

[1618]



[1619] Under nitrogen atmosphere, 3-bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound T22-1, 40.0 mg, 65.2 μmol) was dissolved in DMF (0.20 mL), added at 0°C with methyl bromoacetate (30.5 μL, 134.5 μmol) and sodium hydride (4.5 mg, 132 μmol), and then stirred at room temperature for 2 hr. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (44.5 mg, 85%).

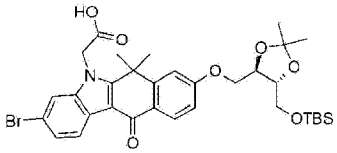
LCMS: m/z 686 $[M+H]^+$
HPLC retention time: 3.35 min (analysis condition D)

[Example 677]

Compound T22-6

{3-Bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]carbazol-5-yl}-acetic acid

[1620]



[1621] {3-Bromo-8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]carbazol-5-yl}-acetic acid methyl ester (Compound T22-5, 40 mg, 60.0 µmol) was dissolved in the mixture solvent of methanol (120 µl) and water (30 µl), added with lithium hydroxide monohydrate (10 mg, 240 µmol), and then stirred 40°C for 15 min. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (methylene chloride/methanol) to obtain the target compound (35.2 mg, 96%).

LCMS: m/z 672 $[M+H]^+$

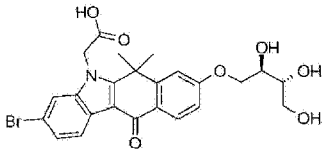
HPLC retention time: 3.41 min (analysis condition D)

[Example 678]

Compound T22-7

[3-Bromo-6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[b]carbazol-5-yl]-acetic acid

[1622]



[1623] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T22-6 (6.2 mg, 31%).

LCMS: m/z 518 $[M+H]^+$

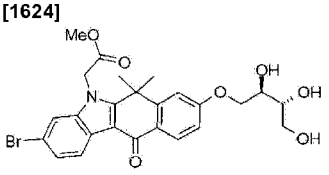
HPLC retention time: 1.30 min (analysis condition D)

[Example 679]

Compound T22-8

[3-Bromo-6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[b]carbazol-5-yl]-acetic acid methyl ester

[1624]



[1625] [3-Bromo-6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[b]carbazol-5-yl]-acetic acid (Compound T22-6, 15.0 mg, 29.0 µmol) was dissolved in methanol (0.30 mL), added with trimethylsilyldiazomethane (0.10 mL), and then stirred at room temperature for 1 hr. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (methylene chloride/methanol) to obtain the target compound (15.2 mg, 96%).

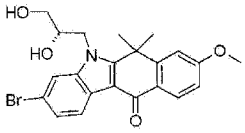
LCMS: m/z 532 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition D)

[Example 680]

Compound T23-1

3-Bromo-5-((R)-1,2-dihydroxyethyl)-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1626]



[1627] Under the same conditions as the method for synthesizing Compound T18-1 and Compound T18-2, the title compound was prepared from Compound A5-1 and toluene-4-sulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester.

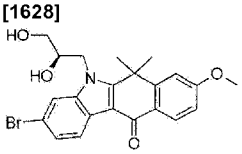
LCMS: m/z 366 $[M+H]^+$
HPLC retention time: 4.50 min (analysis condition H)

[Example 681]

Compound T23-2

3-Bromo-5-((S)-1,2-dihydroxyethyl)-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1628]



[1629] Under the same conditions as the method for synthesizing Compound T18-1 and Compound T18-2, the title compound was prepared from Compound A4 and toluene-4-sulfonic acid (S)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester.

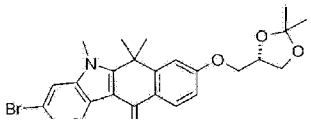
LCMS: m/z 366 $[M+H]^+$
HPLC retention time: 4.50 min (analysis condition H)

[Example 682]

Compound T24-1

3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1630]



[1631] Under nitrogen atmosphere, to the DMF (1 mL) suspension of 3-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound T18-1, 112.2 mg, 0.239 mmol) and sodium hydride (60%) (19 mg, 0.477 mmol), cooled in an ice bath, methyl iodide (37 mL, 0.596 mmol) was added. The reaction mixture was stirred at room temperature for 45 min, and then added with saturated aqueous solution of ammonium chloride and saturated aqueous solution of sodium thiosulfate under ice cooling. The mixture was extracted twice with ethyl acetate/diethyl ether/hexane. The organic layer was washed with water and subsequently with aqueous solution of ammonium chloride, dried over sodium sulfate, and then concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography {Merck Kieselgel60, solution for elution: hexane/ethyl acetate (1 : 1)} to obtain the title compound (white solid, 107.3 mg, 93%).

^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.41 (1 H, d, 8.6 Hz), 8.35 (1 H, d, 8.9 Hz), 7.56 (1 H, d, 1.7 Hz), 7.46 (1 H, dd, 8.6 Hz, 1.7 Hz), 7.14 (1 H, d, 2.3 Hz), 7.00 (1 H, dd, 8.9 Hz, 2.3 Hz), 4.60-4.49 (1 H, m), 4.20-3.90 (4 H, m), 4.03 (3 H, s), 1.88 (6 H, s), 1.50 (3 H, s), 1.43 (3 H, s)

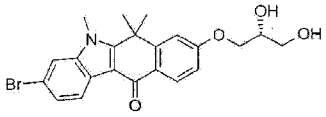
LCMS: m/z 484 $[M+H]^+$
HPLC retention time: 6.59 min (analysis condition B)

[Example 683]

Compound T24-2

3-Bromo-8-((R)-2,3-dihydroxy-propoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1632]



[1633] Under nitrogen atmosphere, to the THF (0.15 mL) - MeOH (0.1 mL) solution of 3-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound T24-1, 15.5 mg, 0.0320 mmol), 0.5 M aqueous solution of sulfuric acid (128 µL, 0.0640 mmol) was added at room temperature. The reaction mixture was stirred at ambient temperature of 55°C for 2 hr, cooled to room temperature, and then added with diethyl ether and subsequently with sodium hydrogen carbonate (11 mg). The mixture was extracted twice with diethyl ether/ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate and concentrated under reduced pressure to obtain the title compound (white solid, 11.9 mg, 84%).

^{1}H-NMR(270 MHz, CD_3OD) δ : 8.26 (1 H, d, 8.6 Hz), 8.20 (1 H, d, 8.9 Hz), 7.77 (1 H, d, 1.7 Hz), 7.42 (1 H, dd, 8.6 Hz, 1.7 Hz), 7.33 (1 H, d, 2.3 Hz), 7. 09 (1 H, dd, 8.9 Hz, 2.3 Hz), 4.26-3.96 (3 H, m), 4.10 (3 H, s), 3.74-3.66 (1 H, m), 1.92 (6 H, s)

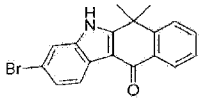
LCMS: m/z 444 $[M+H]^+$
HPLC retention time: 4.65 min (analysis condition B)

[Example 684]

Compound T25

3-Bromo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1634]



[1635] Under the same conditions as the method for synthesizing Compound A3-1 and Compound A4, the title compound was

prepared from 3,4-dihydro-1H-naphthalen-2-one (560 mg).

LCMS: m/z 340 $[M+H]^+$

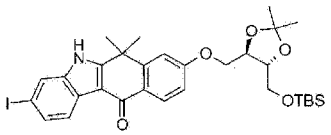
HPLC retention time: 4.57 min (analysis condition H)

[Example 685]

Compound T26-1

8-[(4R,5R)-5-(Tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-3-iodo-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1636]



[1637] Under nitrogen atmosphere, 3-bromo-8-[(4R,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound T22-1, 300 mg, 0.47 mmol), sodium iodide (147 mg, 0.94 mmol) and copper iodide (9.40 mg, 0.047 mmol) were dissolved in dioxane (1.00 ml), added with (1R,2R)-N,N,N',N'-tetramethyl-cyclohexane-1,2-diamine (15.4 µl, 0.094 mmol), and then stirred at 110°C for 16 hr. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (methylene chloride/methanol) to obtain the title compound (220 mg, 70%).

LCMS: m/z 662 $[M+H]^+$

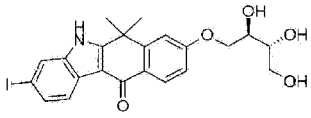
HPLC retention time: 3.40 min (analysis condition D)

[Example 686]

Compound T26-2

3-Iodo-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1638]



[1639] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound T26-1 (17.0 mg, 90%).

LCMS: m/z 508 $[M+H]^+$

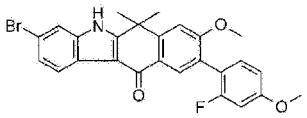
HPLC retention time: 1.77 min (analysis condition D)

[Example 687]

Compound T27-1

3-Bromo-9-(2-fluoro-4-methoxy-phenyl)-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1640]



[1641] To the mixture of 6-bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound E1, 410 mg, 1.44 mmol), tetrakistriphenylphosphine palladium (80 mg, 0.05 eq.) and sodium carbonate (614 mg, 4 eq.), toluene (3 mL) and water (1 ml) were added and then stirred at room temperature and at 90°C for 3 hr. The mixture was extracted by adding water and diethyl ether, and the organic layer was washed with brine, and dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 6-(2-fluoro-4-methoxy-phenyl)-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (white solid, 320 mg).

[1642] Thus-obtained 6-(2-fluoro-4-methoxy-phenyl)-7-methoxy-1,1 -dimethyl-3,4-dihydro-1H-naphthalen-2-one (320 mg, 0.1 mmol) and 3-bromophenylhydrazine (0.29 g, 1.3 eq.) were dissolved in acetic acid (1 mL), and stirred under nitrogen atmosphere at 90°C for 8 hr. After cooling, the reaction solution was added with ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate, and saturated brine, dried over magnesium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were dissolved in THF (3 mL) comprising 10% water, added with DDQ (227 mg, 3 eq.) at room temperature, and stirred at room temperature for 2 hr. To the reaction solution, the mixture solution of THF/diethyl ether (1 : 1) was added, and the reaction solution was washed with 0.5 N aqueous solution of sodium hydroxide and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (red solid, 75 mg).

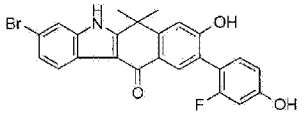
LCMS: m/z 494, 496 $[M+H]^+$
HPLC retention time: 3.10 min (analysis condition C)

[Example 688]

Compound T27-2

3-Bromo-9-(2-fluoro-4-hydroxy-phenyl)-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1643]



[1644] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound T27-1.

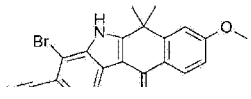
LCMS: m/z 464, 466 $[M+H]^+$
HPLC retention time: 2.68 min (analysis condition C)

[Example 689]

Compound U5

4-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1645]



[1646] 2-Bromo-3-nitro-benzonitrile (Compound U1, 678 mg, 2.987 mmol) was dissolved in ethanol (20.9 mL) and water (8.96 mL), added with acetic acid (2.39 mL, 41.81 mmol) and iron (1.17 g, 20.91 mmol), and stirred at 60°C for 18 hr. The reaction solution was poured into aqueous solution of sodium hydroxide (1 M), extracted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and then filtered. After concentration under reduced pressure, 3-amino-2-bromo-benzonitrile (Compound U2) was obtained as a crude product.

[1647] The crude product obtained from the above was dissolved in 12 M aqueous solution of hydrochloric acid (4.00 mL), added slowly at 0°C with aqueous solution in which sodium nitrite (247 mg, 3.584 mmol) is dissolved in water (3.58 mL), and then the mixture was stirred at 0°C for 30 min. Under light-shielding conditions, aqueous solution in which tin chloride dihydrate (2.02 g, 8.961 mmol) is dissolved in 12 M aqueous solution of hydrochloric acid (4.00 mL) was slowly added to the reaction solution at 0°C, and then the mixture was stirred at 0°C for 1 hr. The reaction solution was poured into 5 M aqueous solution of sodium hydroxide, extracted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, and filtered. After concentration under reduced pressure, 2-bromo-3-hydrazino-benzonitrile (Compound U3) was obtained as a crude product. Under nitrogen atmosphere, the above crude product and 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 462 mg, 2.260 mmol) were added with TFA (6.78 mL) and stirred at 100°C for 2 hr. After cooling, the reaction solution was poured into saturated aqueous solution of sodium bicarbonate, extracted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and filtered. After concentration under reduced pressure, 4-bromo-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U4) was obtained as a crude product. The above crude product was dissolved in THF (10.0 mL) and water (1.00 mL), added with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (1.54 g, 6.780 mmol), and stirred at room temperature for 20 hr. The reaction solution was poured into 1 M aqueous solution of sodium hydroxide, extracted with cyclopentylmethyl ether, washed with 1 M aqueous solution of sodium hydroxide, water and saturated brine, dried over sodium sulfate, and filtered. The residues obtained after concentration under reduced pressure were washed with cyclopentylmethyl ether to obtain the title compound (460 mg, 52%).

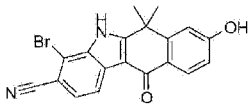
LCMS: m/z 395 $[M+H]^+$
HPLC retention time: 2.25 min (analysis condition D)

[Example 690]

Compound U6

8-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1648]



[1649] 4-Bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U5, 325 mg, 0.822 mmol) was added with pyridine hydrochloride salt (3.80 g, 32.89 mmol) and stirred at 160°C for 28 hr. The reaction solution was poured into water, extracted with ethyl acetate, washed with water, dried over sodium sulfate, and filtered. After concentration under reduced pressure, the title compound was obtained as a crude product.

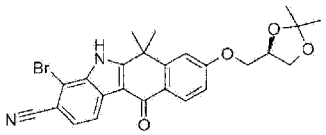
LCMS: m/z 381 $[M+H]^+$
HPLC retention time: 1.92 min (analysis condition D)

[Example 691]

Compound U7-1

4-Bromo-8-((R)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1650]



[1651] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from the reaction between Compound U6 and (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-methanol (354 mg, 87%).

LCMS: m/z 495 $[M+H]^+$

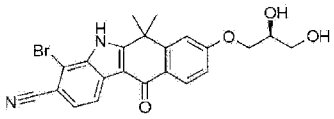
HPLC retention time: 2.35 min (analysis condition D)

[Example 692]

Compound U7-2

4-Bromo-8-((S)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1652]



[1653] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U7-1.

LCMS: m/z 455 $[M+H]^+$

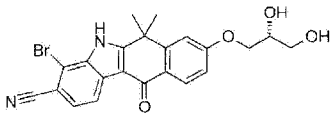
HPLC retention time: 2.40 min (analysis condition C)

[Example 693]

Compound U8-2

8-((R)-2,3-Dihydroxy-propoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1654]



[1655] Under the same conditions as the method for synthesizing Compound U7-1 and Compound U7-2, the title compound was prepared from the reaction between Compound U6 and (S)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol (4.5 mg, 29%).

LCMS: m/z 455 $[M+H]^+$

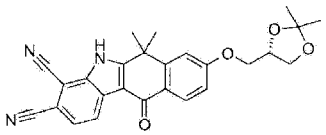
HPLC retention time: 2.37 min (analysis condition C)

[Example 694]

Compound U8-3-1

8-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3,4-dicarbonitrile

[1656]



[1657] Under nitrogen atmosphere, 4-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U6, 20.0 mg, 40.37 µmol) was dissolved in DMA (0.35 mL), added with copper (I) cyanide (18.1 mg, 201.9 µmol), and stirred at 200°C for 1 hr under irradiation with microwave. The reaction solution was poured into water, extracted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound as a crude product.

LCMS: m/z 442 $[M+H]^+$

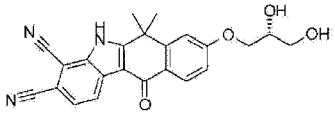
HPLC retention time: 2.30 min (analysis condition D)

[Example 695]

Compound U8-3-2

8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3,4-dicarbonitrile

[1658]



[1659] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-3-1 (9.5 mg, 59%).

LCMS: m/z 402 $[M+H]^+$

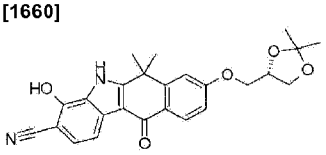
HPLC retention time: 2.40 min (analysis condition D)

[Example 696]

Compound U8-4-1

8-((R)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-4-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1660]



[1661] Under the same conditions as the method for synthesizing Compound U9, the title compound was prepared as a crude product from Compound U8-1 (9.5 mg, 59%).

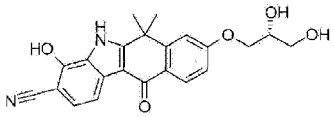
LCMS: m/z 433 $[M+H]^+$
HPLC retention time: 2.34 min (analysis condition A)

[Example 697]

Compound U8-4-2

8-((R)-2,3-Dihydroxy propoxy)-4-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1662]



[1663] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-4-1 (crude product) (9.7 mg, 52%).

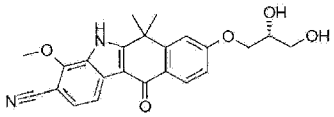
LCMS: m/z 393 $[M+H]^+$
HPLC retention time: 1.69 min (analysis condition A)

[Example 698]

Compound U8-4-3

8-((R)-2,3-Dihydroxy-propoxy)-4-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1664]



[1665] Under nitrogen atmosphere, 8-((R)-2,3-dihydroxy-propoxy)-4-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U8-4-2, 8.0 mg, 20.39 μmol) was dissolved in methanol (2.0 mL) and chloroform (2.00 mL), added with trimethylsilyldiazomethane (diethyl ether solution, 2 M, 15.3 μL, 30.58 μmol) and diisopropylethylamine (0.05 mL), and then stirred at room temperature for 31 hr. The residues obtained from the reaction solution after concentration under reduced pressure were purified by silica gel column chromatography (methanol/dichloromethane) to obtain the title compound (5.1 mg, 62%).

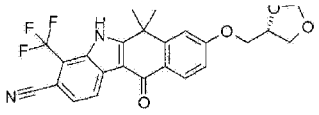
LCMS: m/z 407 $[M+H]^+$
HPLC retention time: 3.74 min (analysis condition A)

[Example 699]

Compound U8-5-1

8-((R)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-4-trifluoromethyl-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1666]



[1667] Under nitrogen atmosphere, 4-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U8-1, 25.0 mg, 50.47 µmol) was dissolved in DMF (0.75 mL), added with copper iodide (I) (48.0 mg, 252.3 µmol) and difluoro-fluorosulfonyl-acetic acid methyl ester (31.9 µL, 252.3 µmol), and then stirred at 100°C for 2 days. The reaction solution was poured into hydrochloric acid (1 M), extracted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound as a crude product.

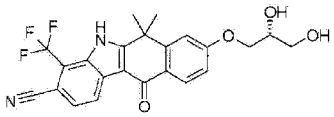
LCMS: m/z 485 $[M+H]^+$
HPLC retention time: 2.88 min (analysis condition A)

[Example 700]

Compound U8-5-2

8-((R)-2,3 -Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-4-trifluoromethyl-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1668]



[1669] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-5-1 (4.0 mg, 30%).

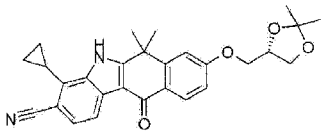
LCMS: m/z 445 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition A)

[Example 701]

Compound U8-6-1

4-Cyclopropyl-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1670]



[1671] Under nitrogen atmosphere, 2-cyclopropyl-4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (13.2 mg, 78.73 µmol) and potassium phosphate (212.27 mg, 212.0 µmol) were dissolved in water (0.20 mL), and the mixture was stirred at room temperature for 15 min. To the reaction solution, 4-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U8-1, 30.0 mg, 60.56 µmol), palladium acetate (1.36 mg, 6.056 µmol), and tricyclohexylphosphine (toluene solution, 20 wt%, 17.0 mg, 12.11 µmol) were added and the mixture was stirred at 80°C for 24 hr. The reaction solution was poured into hydrochloric acid (1 M), extracted with ethyl acetate, washed with saturated aqueous solution of

sodium bicarbonate and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (13.6 mg, 49%).

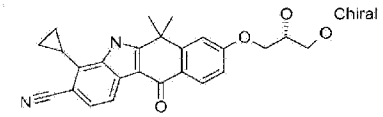
LCMS: m/z 457 $[M+H]^+$
HPLC retention time: 2.38 min (analysis condition D)

[Example 702]

Compound U8-6-2

4-Cyclopropyl-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1672]



[1673] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-6-1.

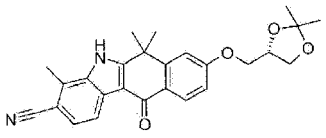
LCMS: m/z 417 $[M+H]^+$
HPLC retention time: 2.42 min (analysis condition A)

[Example 703]

Compound U8-7-1

(S)-8-((2,2-Dimethyl-1,3-dioxolan-4-yl)methoxy)-4,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1674]



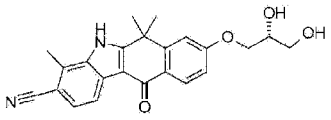
[1675] Under nitrogen atmosphere, 4-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U8-1, 30.0 mg, 60.56 µmol) and lithium chloride (7.70 mg, 181.7 µmol) were dissolved in DMF (1.00 mL), added with tetramethyl tin (12.5 µL, 90.84 µmol), tetrakistriphenylphosphine palladium (3.50 mg, 6.056 µmol) and tricyclohexylphosphine (toluene solution, 20 wt%, 17.0 mg, 3.028 µmol), and the mixture was stirred at 100°C for 24 hr. The reaction solution was poured into hydrochloric acid (1 M), extracted with ethyl acetate, washed with water, saturated aqueous solution of sodium bicarbonate and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-4,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile as a crude product (20.9 mg, 80%).

[Example 704]

Compound U8-7-2

8-((R)-2,3-Dihydroxy-propoxy)-4,6,6-trimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1676]



[1677] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-7-1.

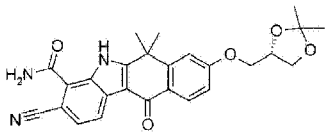
LCMS: m/z 391 $[M+H]^+$
HPLC retention time: 1.82 min (analysis condition A)

[Example 705]

Compound U8-8-1

3-Cyano-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-4-carboxylic acid amide

[1678]



[1679] Under nitrogen atmosphere, 4-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U8-1, 30.0 mg, 60.56 μmol), palladium acetate (1.36 mg, 6.056 μmol), 1,1'-bis(diphenylphosphino)ferrocene (3.36 mg, 6.056 μmol), imidazole (4.12 mg, 60.56 μmol) and tert-potassium butoxy (10.2 mg, 90.84 μmol) were dissolved in formamide (3.00 mL) and the mixture was stirred at 180°C for 5 min under irradiation with microwave. The reaction solution was poured into water, extracted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (methanol/dichloromethane) to obtain the target compound (7.6 mg, 27%).

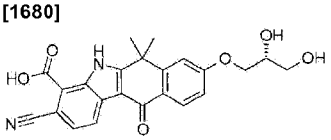
LCMS: m/z 460 $[M+H]^+$
HPLC retention time: 1.82 min (analysis condition A)

[Example 706]

Compound U8-8-2

3-Cyano-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-4-carboxylic acid

[1680]



[1681] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound U8-8-1.

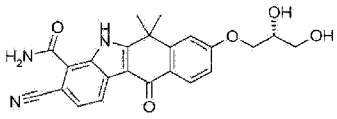
LCMS: m/z 421 $[M+H]^+$
HPLC retention time: 1.57 min (analysis condition A)

[Example 707]

Compound U8-8-3

3-Cyano-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-4-carboxylic acid amide

[1682]



[1683] The title compound was obtained as a by-product of the synthesis of Compound U8-8-2.

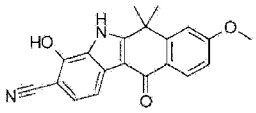
LCMS: m/z 420 $[M+H]^+$
HPLC retention time: 1.27 min (analysis condition A)

[Example 708]

Compound U9

4-Hydroxy-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1684]



[1685] Under nitrogen atmosphere, 4-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U5, 10.0 mg, 25.30 µmol), X-phos (1.07 mg, 2.530 µmol), sodium hydroxide (4.36 mg, 75.90 µmol) and $Pd_2dba_3 \cdot CHCl_3$ (1.31 mg, 1.265 µmol) were dissolved in dioxane (0.50 mL) and water (0.50 mL) and the mixture was stirred at 100°C for 1 hr. The reaction solution was poured into hydrochloric acid (1 M), extracted with ethyl acetate, washed with saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) and washed with dichloromethane to obtain the title compound (5.4 mg, 64%).

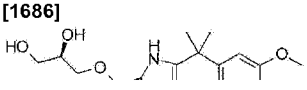
LCMS: m/z 333 $[M+H]^+$
HPLC retention time: 1.62 min (analysis condition D)

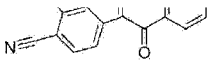
[Example 709]

Compound U10-1

4-((R)-2,3-Dihydroxy-propoxy)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1686]





[1687] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from the reaction between Compound U9 and (S)-(+)-2,2-dimethyl-1,3-dioxolane-4-methanol.

LCMS: m/z 407 $[M+H]^+$

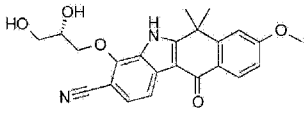
HPLC retention time: 2.06 min (analysis condition A)

[Example 710]

Compound U10-2

4-((S)-2,3-Dihydroxy-propoxy)-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1688]



[1689] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from the reaction between Compound U9 and (R)-(-)-2,2-dimethyl-1,3-dioxolane-4-methanol.

LCMS: m/z 407 $[M+H]^+$

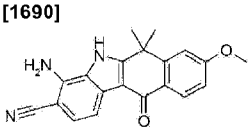
HPLC retention time: 2.06 min (analysis condition A)

[Example 711]

Compound U11

4-Amino-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1690]



[1691] Under nitrogen atmosphere, 4-bromo-8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound U5, 25.0 mg, 63.25 μmol), copper iodide (2.41 mg, 12.65 μmol), sodium azide (20.6 mg, 316.3 μmol), (1S,2S)-N,N'-dimethyl-cyclohexane-1,2-diamine (2.70 mg, 18.98 μmol), and sodium ascorbate (1.25 mg, 6.325 μmol) were dissolved in ethanol (0.70 mL) and water (0.30 mL) and the mixture was stirred at 100°C for 2 hr. The reaction solution was poured into aqueous solution of sodium hydroxide (1 M), extracted with ethyl acetate, washed with water and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (methanol/dichloromethane) to obtain the title compound (5.6 mg, 27%).

LCMS: m/z 332 $[M+H]^+$

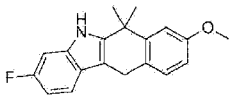
HPLC retention time: 2.16 min (analysis condition A)

[Example 712]

Compound V2

3-Fluoro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole

[1692]



[1693] Under nitrogen atmosphere, the acetic acid (1 mL) suspension of 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 101.0 mg, 0.495 mmol) and (3-fluoro-phenyl)-hydrazine hydrochloric acid salt (Compound V1, 96.5 mg, 0.593 mmol) was stirred at ambient temperature of 95°C for 3.75 hr. After cooling to room temperature, the reaction mixture was added with water (1 mL) and hexane/ethyl acetate (15 : 1) (0.5 mL), and stirred at room temperature for 15 min. The solid was filtered, washed with hexane/ethyl acetate (15 : 1), and then dried under reduced pressure to obtain the title compound (beige powder, 72.7 mg, 50%).

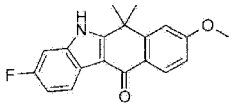
^{1}H-NMR(270 MHz, $CDCl_3$) δ : 7.92-7.82 (1 H, b), 7.47 (1 H, dd, 8.9 Hz, 5. 6 Hz), 7.10-7.03 (2 H, m), 6.95-6.81 (2 H, m), 4.05 (2 H, s), 3.86 (3 H, s), 1.67 (6 H, s)

[Example 713]

Compound V3

3-Fluoro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1694]



[1695] Under nitrogen atmosphere, to the THF (1.8 mL)-water (0.18 mL) solution of 3-fluoro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole (Compound V2, 72.4 mg, 0.245 mmol), DDQ (122.4 mg, 0.539 mmol) was added and the mixture was stirred at room temperature for 5 hr. The reaction mixture was added with diethyl ether and 0.5 N aqueous solution of sodium hydroxide (2 mL), and the resulting mixture was extracted twice with diethyl ether. The organic layer was washed twice with 0.5 N aqueous solution of sodium hydroxide (2 mL) and subsequently twice with brine (2 mL), and dried over sodium sulfate. After concentration under reduced pressure, hexane/ethyl acetate (5 : 1) and diethyl ether were added to the obtained crude product, and the solid was triturated. After removing the supernatant and drying under reduced pressure, the title compound was obtained (yellow solid, 57.0 mg, 75%).

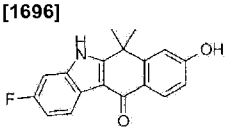
^{1}H-NMR(270 MHz, $CDCl_3$) δ: 8.54-8.44 (1 H, b), 8.43-8.33 (2 H, m), 7.16-6.98 (4 H, m), 3.93 (3 H, s), 1.77 (6 H, s)

[Example 714]

Compound V4

3-Fluoro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1696]



[1697] Mixture of 3-fluoro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol- 11-one (Compound V3, 56.6 mg, 0.183 mmol) and

pyridinium chloride (0.65 g) was stirred at ambient temperature of 160°C for 12 hr. The reaction mixture was cooled to room temperature, added with ethyl acetate and water, and the resulting mixture was extracted four times with ethyl acetate. The organic layer was washed with water three times, dried over sodium sulfate, and concentrated under reduced pressure. The obtained crude product was used for the next step without further purification (brown solid, 61.6 mg, 100%).

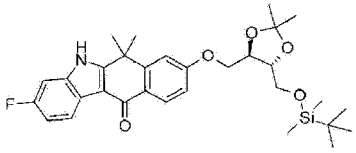
^{1}H-NMR(270 MHz, CD_3OD) δ : 8.20 (1 H, dd, 8.9 Hz, 5.3 Hz), 8.15 (1 H, d, 9.6 Hz), 7.17 (1 H, dd, 9.6 Hz, 2.3 Hz), 7.12 (1 H, d, 2.3 Hz), 7.05-6.95 (1 H, m), 6.88 (1 H, dd, 8.9 Hz, 2.3 Hz), 1.74 (6 H, s) [0911]

[Example 715]

Compound V5-1

8-[(1R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-3-fluoro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1698]



[1699] Under nitrogen atmosphere, to the THF (1.5 mL) solution of 3-fluoro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound V4, 0.183 mmol), (4S,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl[1,3]dioxolan-4-ol (75.9 mg, 0.275 mmol) and triphenylphosphine (72 mg, 0.275 mmol), toluene solution (125 µL, 0.275 mmol) of DEAD was added dropwise at room temperature. The reaction mixture was stirred at ambient temperature of 40°C for 7 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by preparative TLC (Merck 60 F_{254}, 0.5 mm) {solution for elution: hexane/ethyl acetate (3 : 1)} to obtain the title compound (pale orange amorphous, 54.1 mg, 53.4%).

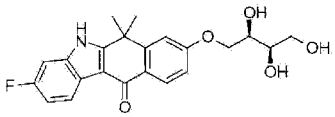
^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.54-8.45 (1 H, b), 8.42-8.33 (2 H, m), 7. 17-6.99 (4 H, m), 4.41-4.27 (2 H, m), 4.25-4.15 (1 H, m), 4.06-3.96 (1 H, m), 3.96-3.88 (1 H, m), 3.83-3.74 (1 H, m), 1.76 (3 H, s), 1.75 (3 H, s), 1.48 (3 H, s), 1.47 (3 H, s), 0.87 (9 H, s), 0.092 (6 H, s)

[Example 716]

Compound V5-2

3-Fluoro-6,6-dimethyl-8-((3R,4R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1700]



[1701] Under nitrogen atmosphere, to the THF (0.3 mL)-MeOH (0.1 mL) solution of 8-[(1R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-3-fluoro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound V5-1, 52.8 mg, 0.0954 mmol), 0.5 M aqueous solution of sulfuric acid (0.19 mL, 0.0954 mmol) was added at room temperature. The reaction mixture was stirred at ambient temperature of 55°C for 4 hr, cooled to room temperature, and then added with diethyl ether, sodium hydrogen carbonate (20 mg) and water in order. The mixture was extracted twice with diethyl ether and subsequently twice with ethyl acetate, and the organic layer was washed with brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting crude product was washed with dichloromethane, and dried under reduced pressure to obtain the title compound (white powder, 29.9 mg, 78%).

^{1}H-NMR(270 MHz, CD_3OD) δ : 8.24 (1 H, d, 8.9 Hz), 8.19 (1 H, dd, 8.6 Hz, 5.3 Hz), 7.30 (1 H, d, 2.3 Hz), 7.18 (1 H, dd, 9.2 Hz, 2.3

Hz), 7.09 (1 H, dd, 8. 9 Hz, 2.3 Hz), 7.06-6.96 (1 H, m), 4.32-4.22 (1 H, m), 4.21-4.12 (1 H, m), 4.11-4. 02 (1 H, m), 3.84-3.75 (1 H, m), 3.74-3.61 (2 H, m), 1.77 (6 H, s)

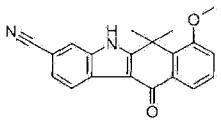
LCMS: m/z 400 $[M+H]^+$
HPLC retention time: 4.02 min (analysis condition H)

[Example 717]

Compound W2

7-((S)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1702]



[1703] To the toluene suspension of sodium t-butoxide (700 mg, 2.5 eq.), 8-methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound W1, 500 mg, 2.9 mmol) was added dropwise at 0°C. After 15 minutes, the solution turned into blackish green color. The mixture solution was added dropwise with methyl iodide (1.03 g, 2.5 eq.) and stirred at 15°C overnight. Brown solid precipitated. The reaction solution was added to saturated aqueous solution of ammonium chloride/diethyl ether under stirring and cooling. After that, the solution was extracted with diethyl ether, and dried over sodium sulfate. After removing the solvent under reduced pressure, the resulting residues were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 8-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (350 mg).

[1704] Thus-obtained 8-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (250 mg, 1.23 mmol) and 3-cyanophenylhydrazine (0.2 g, 1.2 eq.) were dissolved in trifluoroacetic acid (1 mL), and stirred at 120°C for 1 hr under irradiation with microwave. After cooling, the reaction solution was added with ethyl acetate, washed with water, saturated aqueous solution of sodium hydrogen carbonate, and saturated brine, dried over magnesium sulfate, and filtered. The residues obtained after concentration under reduced pressure were dissolved in THF (3 mL) comprising 10% water and added at room temperature with DDQ (227 mg, 3 eq.). The mixture was then stirred at room temperature for 2 hr. The reaction solution was added with mixture solution of THF/diethyl ether (1 : 1), washed with 0.5 N aqueous solution of sodium hydroxide and saturated brine, dried over sodium sulfate, and then filtered. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain 7-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (brown solid, 54 mg).

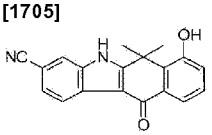
LCMS: m/z 317 $[M+H]^+$
HPLC retention time: 1.00 min (analysis condition I)

[Example 718]

Compound W3

7-Hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1705]



[1706] Under the same conditions as Compound A6, the title compound was prepared from Compound W2.

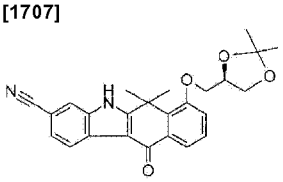
LCMS: m/z 316 $[M+H]^+$
HPLC retention time: 0.93 min (analysis condition I)

[Example 719]

Compound W4-1

7-((R)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1707]



[1708] Under nitrogen atmosphere, 7-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile (Compound W3, 15 mg, 0.05 mmol) and triphenylphosphine (40 mg, 3 eq.) were added with THF (1 ml), further added dropwise with ((R)-2,2-dimethyl-[1,3]dioxolan-4-yl)-methanol (20 mg, 3 eq.) and 2.19 N toluene solution of diethyl azodicarboxylate (68 µL, 3 eq.), and the mixture was stirred at 50°C for 2 hr. After cooling, the reaction solution was added with ethyl acetate, washed with brine, dried over sodium sulfate, and filtered. The residues obtained after concentration under reduced pressure were purified by preparative TLC (ethyl acetate/dichloromethane), and the resulting solid was washed with dichloromethane to obtain the target compound (brown powder, 5 mg).

LCMS: m/z 417 $[M+H]^+$

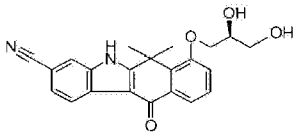
HPLC retention time: 1.04 min (analysis condition I)

[Example 720]

Compound W4-2

7-((S)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbzaole-3-carbonitrile

[1709]



[1710] Under the same conditions as Compound S7-2, the title compound was prepared from Compound W4-1.

LCMS: m/z 377 $[M+H]^+$

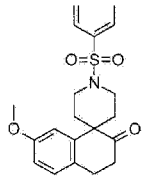
HPLC retention time: 0.88 min (analysis condition I)

[Example 721]

Compound X1

1,1-Spiro-4-piperidine-N-paratoluenesulfonyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one

[1711]



[1712] 7-Methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound A1, 100 mg, 0.568 mmol) was dissolved in toluene (4 mL), added with NaH (60% in oil, 68 mg, 3 eq.), and stirred at room temperature for 10 min. The mixture solution was added with bis-(2-iodo-ethyl)-p-toluenesulfonamide (172 mg, 0.568 mmol), and stirred at 70°C for 2 hr under nitrogen stream. After cooling, the reaction solution was added to saturated aqueous solution of ammonium chloride, extracted with ethyl acetate, washed with saturated brine, and then dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane : ethyl acetate / 3 : 1) to obtain the title compound (colorless oily substance, 62 mg, 33%).

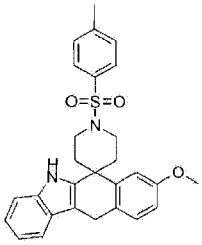
LCMS: m/z 400 $[M+H]^+$
HPLC retention time: 2.02 min (analysis condition B)

[Example 722]

Compound X2

1,1-Spiro-4-piperidine-N-paratoluenesulfonyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one

[1713]



[1714] 1,1-Spiro-4-piperidine-N-paratoluenesulfonyl-7-methoxy-3,4-dihydro-1H-naphthalen-2-one (Compound X1, 400 mg, 1.0 mmol) and phenylhydrazine (217 mg, 1.5 eq.) were dissolved in acetic acid (6 mL), and the mixture was stirred at 120°C for 4 hr under nitrogen atmosphere. After cooling, the reaction solution was added to water, extracted with ethyl acetate, washed with saturated brine, and then dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane : ethyl acetate / 4 : 1) to obtain the title compound (brown solid, 185 mg, 43%).

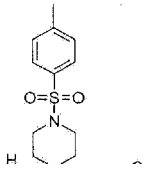
LCMS: m/z 473 $[M+H]^+$
HPLC retention time: 7.23 min (analysis condition B)

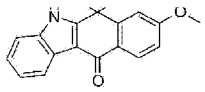
[Example 723]

Compound X3

6,6-Spiro-4-piperidine-N-paratoluenesulfonyl-8-methoxy-5,6-dihydro-benzo[b]carbazol-11-one

[1715]





[1716] 6,6-Spiro-4-piperidine-N-paratoluenesulfonyl-8-methoxy-5,6-dihydro-5H-benzo[b]carbazole (Compound X2, 400 mg, 0.848 mmol) and DDQ (770 mg, 4 eq.) were dissolved in THF (10 mL) and water (2 mL), and then the mixture was stirred at 50°C for 5 hr. After cooling, the reaction solution was added to saturated aqueous solution of sodium hydrogen carbonate, extracted with ethyl acetate, washed with saturated brine, and then dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (hexane : ethyl acetate / 3 : 1) to give a solid, which was then washed with ethyl ether to obtain the title compound (yellow solid, 86 mg, 21%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 11.9 (1 H, s), 8.22 (2 H, m), 7.75 (2 H, d), 7.60(4 H, m) 7.30(2 H, m), 7.11(1 H, d), 3.81(2 H, m), 3.68(3 H, s), 3.62(2 H, m), 2.49(3 H, s), 2.21(2H, m), 2.10(2 H, m),

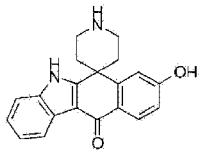
LCMS: m/z 487 $[M+H]^+$
HPLC retention time: 6.05 min (analysis condition B)

[Example 724]

Compound X4

6,6-Spiro-4-piperidine-8-hydroxy-5,6-dihydro-benzo[b]carbazol-11-one

[1717]



[1718] Mixture of 6,6-spiro-4-piperidine-N-paratoluenesulfonyl-8-methoxy-5,6-dihydro-benzo[b]carbazol-11-one (Compound X3, 35 mg, 0.072 mmol) and pyridine hydrochloride salt (800 mg) was stirred in a sealing tube at 160°C for 10 hr. After cooling, the reaction solution was added to water, extracted with ethyl acetate, washed with saturated brine, and then dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane : methanol / 4 : 1) to obtain the title compound (yellow solid, 30 mg, 98%).

^{1}H-NMR(400 MHz, DMSO-d_6) δ : 8.20 (1 H, m), 8.10(1 H, m), 7.53(1 H, m), 7.25(3 H, m), 6.80(1 H, m), 3.60(2 H, m), 3. 45(2 H, m), 2.52(2 H, m), 2.05(2 H, m).

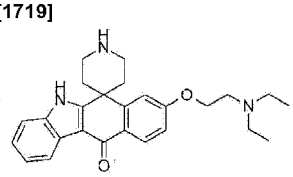
LCMS: m/z 319 $[M+H]^+$
HPLC retention time: 2.86 min (analysis condition B)

[Example 725]

Compound X5

8-(2-Diethylaminoethoxy)-6,6-spiro-4-piperidine-8-hydroxy-5,6-dihydro-benzo[b]carbazol-11-one

[1719]



[1720] 6,6-Spiro-4-piperidine-8-hydroxy-5,6-dihydro-benzo[b]carbazol-11-one (Compound X4, 30 mg, 0.094 mmol), diethylaminoethanol (22 mg, 2 eq.), triphenylphosphine (50 mg, 2 eq.) and DIAD (39 mg, 2 eq.) were dissolved in THF (4 mL) and the mixture was stirred at room temperature for 4 hr. The reaction solution was added to water, extracted with ethyl acetate, washed with saturated brine, and then dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (dichloromethane : methanol / 4 : 1) to obtain the title compound (yellow oily substance, 6.8 mg, 17%).

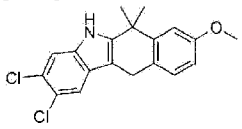
LCMS: m/z 418 $[M+H]^+$
HPLC retention time: 2.75 min (analysis condition B)

[Example 726]

Compound Y2

2,3-Dichloro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole

[1721]



[1722] Under nitrogen atmosphere, the acetic acid (1 mL) suspension of 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 92.3 mg, 0.452 mmol) and (3,4-dichlorophenyl)hydrazine hydrochloric acid salt (Compound Y1, 96.5 mg, 0.452 mmol) was stirred at ambient temperature of 90°C for 3.5 hr. After cooling to room temperature, the reaction mixture was added with diethyl ether and water, and the resulting mixture was extracted twice with diethyl ether. The organic layer was washed three times with water, dried over sodium sulfate, and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography {Merck Kieselgel60, solution for elution: hexane/ethyl acetate (4 : 1)} to obtain the title compound (pale yellow solid, 62.1 mg, 40%).

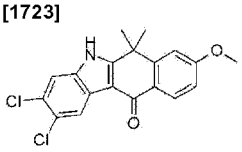
^{1}H-NMR(270 MHz, $CDCl_3$) δ : 7.92-7.84 (1 H, b), 7.62 (1 H, s), 7.46 (1 H, s), 7.05 (1 H, d, 2.6), 6.84 (1 H, dd, 8.6 Hz, 2.6 Hz), 4.01 (2 H, s), 3.86 (3 H, s), 1. 67 (6 H, s)

[Example 727]

Compound Y3

2,3-Dichloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1723]



[1724] Under nitrogen atmosphere, to the 1,4-dioxane (1.7 mL)-water (0.1 mL) solution of 2,3-dichloro-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazole (Compound Y2, 61.0 mg, 0.176 mmol), DDQ (120 mg,0.529 mmol) was added and the mixture was stirred at room temperature for 16 hr and 15 min. The reaction mixture was purified by flash column chromatography {Merck Kieselgel60, solution for elution: hexane/ethyl acetate (2 : 1)} to obtain the title compound (pale orange solid, 16.7 mg, 26%).

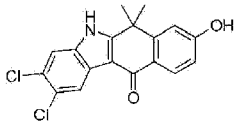
^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.55 (1 H, s), 8.42-8.36 (1 H, b), 8.39 (1 H, d, 8.6 Hz), 7.54 (1 H, s), 7.08 (1 H, d, 2.3 Hz), 7.03 (1 H, dd, 8.6 Hz, 2.3 Hz), 3.93 (3 H, s), 1.76 (6 H, s)

[Example 728]

Compound Y4

2,3-Dichloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1725]



[1726] Mixture of 2,3-dichloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound Y3, 16.5 mg, 0.0457 mmol) and pyridinium chloride (0.2 g) was stirred at ambient temperature of 160°C for 7 hr. The reaction mixture was cooled to room temperature and added with ethyl acetate and water. The mixture was extracted three times with ethyl acetate. The organic layer was washed twice with water, dried over sodium sulfate, and concentrated under reduced pressure. The resulting crude product was used for the next step without further purification (brown solid, 14.8 mg, 94%).

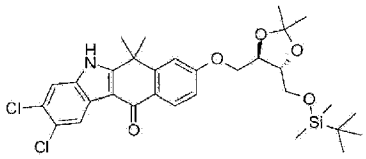
^{1}H-NMR(270 MHz, CD_3OD) δ : 8.34 (1 H, s), 8.14 (1 H, d, 8.6 Hz), 7. 61 (1 H, s), 7.10 (1 H, d, 2.3 Hz), 6.89 (1 H, dd, 8.6 Hz, 2.3 Hz), 1.75 (1 H, s)

[Example 729]

Compound Y5-1

8-[(1R,5R)-5-(Tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-2,3-dichloro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[1727]



[1728] Under nitrogen atmosphere, to the THF (0.3 mL) solution of 2,3-dichloro-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound Y4, 12.9 mg, 0.0373 mmol), (4S,5R)-5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-ol (15.5 mg, 0.0559 mmol) and triphenylphosphine (14.7 mg, 0.0559 mmol), toluene solution (25.4 µL, 0.0559 mmol) of DEAD was added dropwise at room temperature. The reaction mixture was stirred at ambient temperature of 40°C for 4 hr. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, and the resulting crude product was purified by preparative TLC (Merck 60 F_{254}, 0.5 mm) {solution for elution: hexane/ethyl acetate (3 : 1)} to obtain the title compound (white solid, 15.1 mg, 67%).

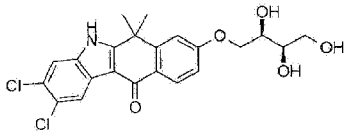
^{1}H-NMR(270 MHz, $CDCl_3$) δ : 8.55 (1 H, s), 8.44-8.37 (1 H, b), 8.37 (1 H, d, 8.6 Hz), 7.54 (1 H, s), 7.15 (1 H, d, 2.6 Hz), 7.03 (1 H, dd, 8.6 Hz, 2.6 Hz), 4.41-4.26 (2 H, m), 4.25-4.15 (1 H, m), 4.06-3.86 (2 H, m), 3.83-3.73 (1 H, m), 1.76 (3 H, s), 1.75 (3 H, s), 1.48 (3 H, s), 1.47 (3 H, s), 0.90 (9 H, s), 0.092 (6 H, s)

[Example 730]

Compound Y5-2

2,3-Dichloro-6,6-dimethyl-8-((3R,4R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[1729]



[1730] Under nitrogen atmosphere, to the THF (0.2 mL)-MeOH (0.1 mL) solution of 8-[(1R,5R)-5-(tert-butyldimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-2,3-dichloro-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (Compound Y5-1, 14.6 mg, 0.0242 mmol), 0.5 M aqueous solution of sulfuric acid (96.6 (μL, 0.0483 mmol) was added at room temperature. The reaction mixture was stirred at ambient temperature of 55°C for 3 hr, cooled to room temperature, and then added with diethyl ether and sodium hydrogen carbonate (10 mg) in order. The mixture was extracted twice with diethyl ether, and the organic layer was washed with water and brine, dried over sodium sulfate, and concentrated under reduced pressure. The resulting crude product was washed with dichloromethane, and dried under reduced pressure to obtain the title compound (white solid, 8.3 mg, 76%).

^{1}H-NMR(270 MHz, CD_3OD) δ : 8.35 (1 H, s), 8.24 (1 H, d, 8.9 Hz), 7.62 (1 H, s), 7.31 (1 H, d, 2.3 Hz), 7.10 (1 H, dd, 8.9 Hz, 2.3 Hz), 4.31-4.23 (1 H, m), 4. 12-4.12 (1 H, m), 4.11-4.02 (1 H, m), 3.84-3.74 (1 H, m), 3.73-3.61 (1 H, m), 1.78 (6 H, s)

LCMS: m/z 450 $[M+H]^+$

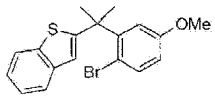
HPLC retention time: 4.92 min (analysis condition H)

[Example 731]

Compound Z3

2-[1-(2-Bromo-5-methoxy-phenyl)-1-methylethyl]-benzo[b]thiophene

[1731]



[1732] 2-(2-Bromo-5-methoxyphenyl)-2-methyl-propinoic acid (1.5 g, 5.5 mmol) was dissolved in methylene chloride (15 mL), added with oxalyl chloride (1.5 mL) and dimethylformamide (2 micro liter) at room temperature, and the mixture was stirred at room temperature for 30 min. After removing the solvent, the residues were dissolved in toluene, added at room temperature with 2-[(triphenyl-5-phosphanyl)-methyl]-benzenethiol hydrobromide (2.56 g, 5.5 mmol) and triethylamine (2.27 mL), and then the mixture was refluxed under heating for 30 min. Thereafter, the mixture was cooled to 0°C, added with lithium hexamethyldisilazide (1 M tetrahydrofuran solution, 5.5 mL), and refluxed under heating for 24 hr. The reaction mixture was extracted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (0.55 g, 28%).

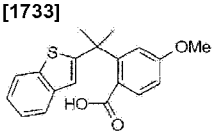
^{1}H-NMR (270 MHz, $CDCl_3$) δ : 6.61 (1 H, s), 3.37 (3 H, s), 1.83 (6 H, s)

[Example 732]

Compound Z4

2-(1-Benzo[b]thiophen-2-yl-1-methyl-ethyl)-4-methoxy-benzoic acid

[1733]



[1734] 2-[1-(2-Bromo-5-methoxy-phenyl)-1-methylethyl]-benzo[b]thiophene (Compound Z3, 40 mg, 0.11 mmol) was dissolved in tetrahydrofuran (0.5 mL), cooled to -78°C, added with n-butyl lithium (1.57 M, hexane solution, 0.07 mL), and the mixture was stirred for 10 min. The reaction mixture was added with dry ice and then maintained for 1 hr. After that, the mixture was added with 0.5 N hydrochloric acid, extracted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (22 mg, 55%).

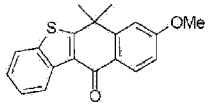
^{1}H-NMR (270 MHz, $CDCl_3$) δ : 7.46 (1 H, d), 7.44 (1 H, d), 6.92 (s, 1 H), 6. 70 (d, 1 H), 3.84 (s, 3 H), 1.89 (6 H, s)

[Example 733]

Compound Z5

8-Methoxy-6,6-dimethyl-6H-benzo[b]naphth[2,3-d]thiophen-11-one

[1735]



[1736] To 2-(1-benzo[b]thiophen-2-yl-1-methylethyl)-4-methoxy-benzoic acid (Compound Z4, 68 mg, 0.22 mmol), polyphosphoric acid (3.5 g) was added, and the mixture was stirred for 1 hr at 100°C under heating. The mixture was added with water, extracted with ethyl acetate and washed with water. The organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (41 mg, 63%).

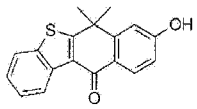
LCMS: m/z 309 $[M+H]^+$
HPLC retention time: 2.89 min (analysis condition C)

[Example 734]

Compound Z6

8-Hydroxy-6,6-dimethyl-6H-benzo[b]naphth[2,3-d]thiophen-11-one

[1737]



[1738] Under the same conditions as Compound A6, the title compound was prepared from Compound Z5.

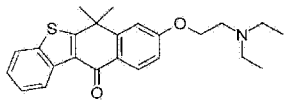
LCMS: m/z 295 $[M+H]^+$
HPLC retention time: 2.91 min (analysis condition F)

[Example 735]

Compound Z7

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-6H-benzo[b]nahth[2,3-d]thiophen-11-one

[1739]



[1740] According to the same method as the method for synthesizing Compound A7-17, the title compound was prepared from Compound Z6.

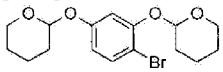
LCMS: m/z 394 $[M+H]^+$
HPLC retention time: 5.06 min (analysis condition F)

[Example 736]

Compound Z9

2-Bromo-1,3-dihydroxytetrahydropyranbenzene

[1741]



[1742] To 4-bromo-benzene-1,3-diol (Compound Z8, 20 g, 105.8 mmol) and 3,4-dihydro-2H-pyran (38.6 mL), pyridium paratoluenesulfonate (266 mg) was added, and the mixture was stirred at 50°C for 1 hr. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (31.82 mg, 84%).

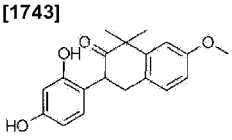
LCMS: m/z 358 $[M+H]^+$
HPLC retention time: 3.15 min (analysis condition C)

[Example 737]

Compound Z10

3-(2,4-Dihydroxy-phenyl)-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1743]



[1744] To 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 10 g), 2-bromo-1,3-dihydroxytetrahydropyranbenzene (Compound Z9, 20.98 g), sodium t-butoxide (5.88 g), palladium acetate (550 mg) and tri-t-butylphosphonium tetrafluoroborate (710 mg), toluene (40 mL) was added and the mixture was stirred and heated at 70°C under nitrogen atmosphere for 6 hr. After cooling, the reaction mixture was added with methanol (38 mL) and trifluoroacetic acid (14.54 mL) at room temperature, and then stirred at room temperature overnight. To the resulting residues, methylene chloride and saturated dipotassium hydrogen phosphate were added and the organic layer was washed with saturated brine. Thereafter, the organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (5.53 g, 36%).

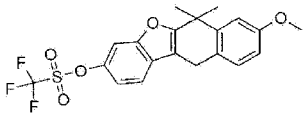
LCMS: m/z 312 $[M+H]^+$
HPLC retention time: 2.39 min (analysis condition F)

[Example 738]

Compound Z11

Trifluoromethanesulfonic acid 8-methoxy-6,6-dimethyl-6,11-dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester

[1745]



[1746] 3-(2,4-Dihydroxy-phenyl)-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound Z10, 5.53 g) was dissolved in methylene chloride (40 mL), and added with trifluoromethanesulfonic anhydride (2.98 mL) at room temperature. After cooling to 5°C, diisopropylethylamine (9.25 mL) and trifluoromethanesulfonic anhydride (4.47 mL) were added thereto. To the reaction mixture, methylene chloride and saturated dipotassium hydrogen phosphate were added and the organic layer was washed with saturated brine. Thereafter, the organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (4.82 g, 64%).

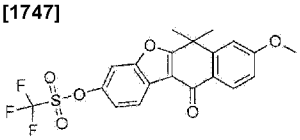
LCMS: m/z 427 $[M+H]^+$
HPLC retention time: 8.95 min (analysis condition H)

[Example 739]

Compound Z12

Trifluoromethanesulfonic acid 8-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester

[1747]



[1748] Trifluoromethanesulfonic acid 8-methoxy-6,6-dimethyl-6,11-dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester (Compound Z11, 4.82 g) was dissolved in acetonitrile (48 mL) and water (24 mL), added with sodium chlorite (2.55 g) and N-hydroxyphthalimide (369 mg), and then the mixture was stirred at 40°C for 1 hr. The reaction mixture was added with methylene chloride and the organic layer was washed with saturated brine. Thereafter, the organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (2.80 g, 56%).

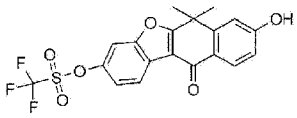
LCMS: m/z 441 $[M+H]^+$
HPLC retention time: 8.02 min (analysis condition H)

[Example 740]

Compound Z13

Trifluoromethanesulfonic acid 8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester

[1749]



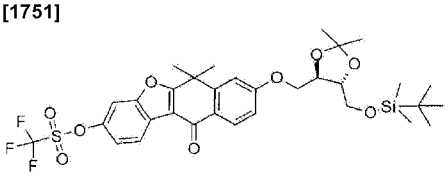
[1750] Under the same conditions as Compound A6, the title compound was prepared as a crude product from Compound Z12.

[Example 741]

Compound Z14

Trifluoro-methanesulfonic acid 8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6 dimethyl-11-oxo-6,11-dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester

[1751]



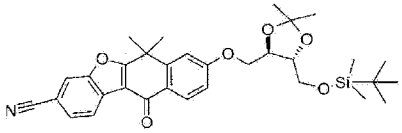
[1752] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was obtained as a crude product from Compound Z13 and [5-(tert-butyldimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (Compound T22-0).

[Example 742]

Compound Z15

8-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphth[2,3-d]furane-3-carbonitrile

[1753]



[1754] Trifluoro-methanesulfonic acid 8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6 dimethyl-11 -oxo-6,11 - dihydro-benzo[b]naphth[2,3-d]furan-3-yl ester (Compound Z14, 24 mg) was dissolved in DMF (0.5 mL), added with zinc (II) cyanide (8.2 mg) and palladium tetrakistriphenylphosphine (2.0 mg), and the mixture was stirred under heating at 200°C for 20 min with microwave irradiation. To the reaction mixture, ethyl acetate was added and the organic layer was washed with saturated brine. Thereafter, the organic layer was dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (15 mg).

LCMS: m/z 562 $[M+H]^+$

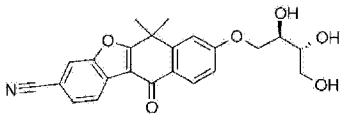
HPLC retention time: 4.14 min (analysis condition F)

[Example 743]

Compound Z16

6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[b]naphth[2,3-d]furane-3-carbonitrile

[1755]



[1756] Under the same conditions as Compound S7-2, the title compound was prepared from Compound Z15.

LCMS: m/z 408 $[M+H]^+$

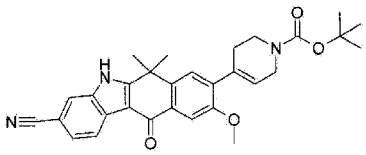
HPLC retention time: 4.51 min (analysis condition H)

[Example 744]

Compound K7-5

4-(3-Cyano-9-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester

[1757]



[1758] Under the same conditions as the method for synthesizing Compound B2-22-1, the title compound was prepared from Compound K6 and 4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-3,6-dihydro-2H-pyridine-1-carboxylic acid tert-butyl ester.

LCMS: m/z 498 $[M+H]^+$

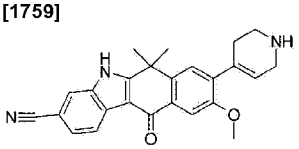
HPLC retention time: 4.24 min (analysis condition W)

[Example 745]

Compound K7-6

9-Methoxy-6,6-dimethyl-11-oxo-8-(1,2,3,6-tetrahydro-pyridin-4-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1759]



[1760] Under the same conditions as the method for synthesizing Compound A8-1, the title compound was prepared from K7-5.

LCMS: m/z 398 $[M+H]^+$

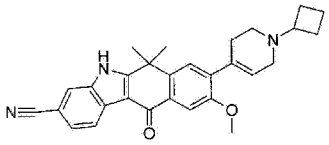
HPLC retention time: 2.57 min (analysis condition W)

[Example 746]

Compound K8-1

8-(1-Cyclobutyl-1,2,3,6-tetrahydro-pyridin-4-yl)-9-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1761]



[1762] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound K7-6 and cyclobutanone.

LCMS: m/z 452 $[M+H]^+$

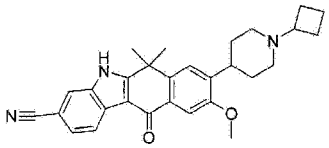
HPLC retention time: 2.72 min (analysis condition W)

[Example 747]

Compound K8-2

8-(1-Cyclobutyl-piperidin-4-yl)-9-methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1763]



[1764] Under the same conditions as the method for synthesizing Compound B3-13-1, the title compound was prepared from Compound K8-1.

LCMS: m/z 454 $[M+H]^+$

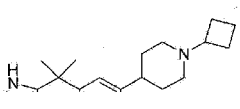
HPLC retention time: 2.76 min (analysis condition W)

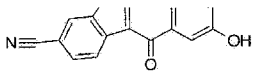
[Example 748]

Compound K9-5

8-(1-Cyclobutyl-piperidin-4-yl)-9-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1765]





[1766] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound K8-2.

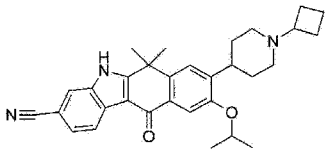
LCMS: m/z 440 $[M+H]^+$
HPLC retention time: 2.57 min (analysis condition W)

[Example 749]

Compound K10-8

8-(1-Cyclobutyl-piperidin-4-yl)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1767]

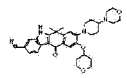
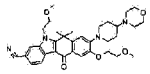
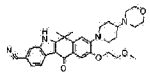
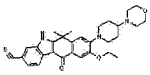
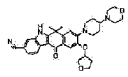
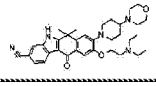


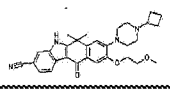
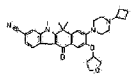
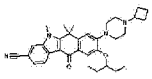
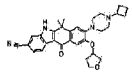
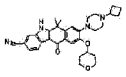
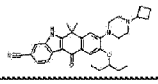
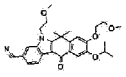
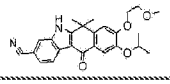
[1768] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound K9-5 and isopropyl iodide.

LCMS: m/z 482 $[M+H]^+$
HPLC retention time: 1.74 min (analysis condition S)

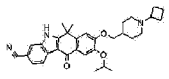
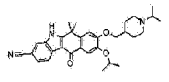
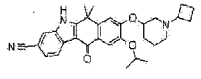
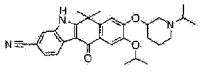
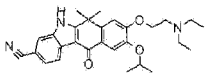
[1769] The compounds described in the following Tables 2-3 were synthesized from the intermediates of Compound K or Compound L by alkylation of hydroxyl group according to Mitsunobu reaction used for preparing Compound A7-1 or the method used for the synthesis of Compound A7-17 (described in the Table).

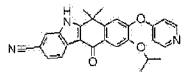
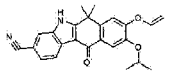
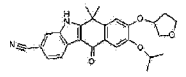
[Table 2]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
750	K10-9		6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-(tetrahydropyran-4-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.85	555	A7-1
751	K10-10		9-(2-Methoxy-ethoxy)-5-(2-methoxyethyl)-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.50	587	A7-17
752	K10-11		9-(2-Methoxy-ethoxy)-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.37	529	A7-17
753	K10-12		9-Ethoxy-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.95	499	A7-1 7
754	K10-13		6,6-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-(tetrahydrofuran-3-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.40	541	A7-1
755	K10-14		9-(2-Diethylamino-ethoxy)-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.13	570	A7-17

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
756	K10-15		8-(4-Cyclobutyl-piperazin-1-yl)-9-(2-methoxy-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.45	499	A7-17
757	K10-16		8-(4-Cyclobutyl-piperazin-1-yl)-5,6,6-trimethyl-11-oxo-9-(tetrahydro-furan-3-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.98	525	A7-1
758	K10-17		8-(4-Cyclobutyl-piperazin-1-yl)-9-(1-ethyl-propoxy)-5,6,6-trimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	243	525	A7-1
759	K10-18		8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-(tetrahydro-furan-3-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.92	511	A7-1
760	K10-19		8-(4-Cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-(tetrahydro-pyran-4-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.97	525	A7-1
761	K10-20		8-(4-Cyclobutyl-piperazin-1-yl)-9-(1-ethyl-propoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.82	511	A7-1
762	L10-3		9-Isopropoxy-8-(2-methoxy-ethoxy)-5-(2-methoxy-ethyl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	2.68	477	A7-17
763	L10-4		9-Isopropoxy-8-(2-methoxy-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	2.68	419	A7-17

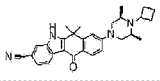
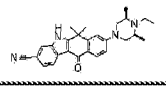
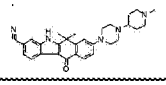
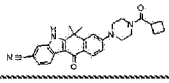
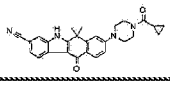
[Table 3]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
764	L10-5		8-(1-Cyclobutyl-piperidin-4-ylmethoxy)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazole-3-carbonitrile	S	1.65	512	A7-1
765	L10-6		9-Isopropoxy-8-(1-isopropyl-piperidin-4-ylmethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.62	500	A7-1
766	L10-7		8-(1-Cyclobutyl-piperidin-3-yloxy)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.65	498	A7-1
767	L10-8		9-isopropoxy-9-(1-isopropyl-piperidin-3-yloxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.59	486	A7-1
768	L10-9		8-(2-Diethylamino-ethoxy)-9-isopropoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.07	460	A7-17

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
769	L10-10		9-Isopropoxy-6,6-dimethyl-11-oxo-8-(pyridin-4-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.07	438	A7-17
770	L10-11		9-Isopropoxy-6,6-dimethyl-11-oxo-8-vinyloxy-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.77	387	A7-17
771	L10-12		9-Isopropoxy-6,6-dimethyl-11-oxo-8-(tetrahydro-furan-3-yloxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	2.45	431	A7-1

[1770] The compounds described in the following Table 4 were synthesized from the intermediates of Compound B according to the method described in the Table.

[Table 4]

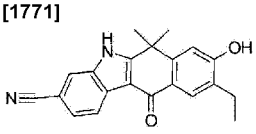
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
772	B3-39		8-((3R,5S)-4-Cyclobutyl-3,5-dimethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.90	453	B3-32
773	B3-40		8-((3R,5S)-4-Ethyl-3,5-dimethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.82	427	B3-32
774	B2-30		6,6-Dimethyl-8-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.58	468	B2-1
775	B3-41		8-(4-Cyclobutanecarbonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.35	453	A9-10
776	B3-42		8-(4-Cyclopropanecarbonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.22	439	A9-10

[Example 777]

Compound E6-4

9-Ethyl-8-hydroxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1771]



[1772] Under the same conditions as the method for synthesizing Compound E3-2, the title compound was prepared from Compound E5-1.

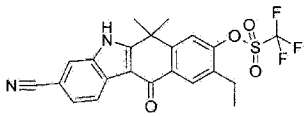
LCMS: m/z 331 $[M+H]^+$
HPLC retention time: 3.42 min (analysis condition W)

[Example 778]

Compound E7

Trifuloro-methanesulfonic acid 3-cyano-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-8-yl ester

[1773]



[1774] Under the same conditions as the method for synthesizing Compound B1, the title compound was prepared from Compound E6-4.

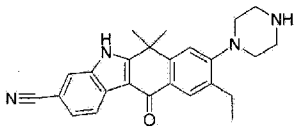
LCMS: m/z 463 $[M+H]^+$
HPLC retention time: 4.39 min (analysis condition W)

[Example 779]

Compound E8-1

9-Ethyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[*b*]carbazole-3-carbonitrile

[1775]



[1776] The title compound was prepared from Compound E7 and piperazine in the same manner as the method for synthesizing Compound B2-1.

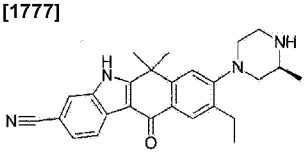
LCMS: m/z 399 $[M+H]^+$
HPLC retention time: 1.88 min (analysis condition U)

[Example 780]

Compound E8-2

9-Ethyl-6,6-dimethyl-8-((S)-3-methyl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1777]



[1778] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound E7 and 2-(S)-methylpiperazine.

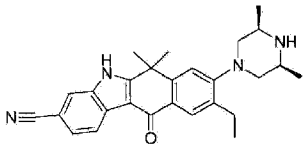
LCMS: m/z 413 $[M+H]^+$
HPLC retention time: 2.76 min (analysis condition W)

[Example 781]

Compound E8-3

8-((3R,5S)-3,5-Dimethyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1779]



[1780] Under the same conditions as the method for synthesizing Compound B2-1, the title compound was prepared from Compound E7 and cis-2,6-dimethylpiperazine.

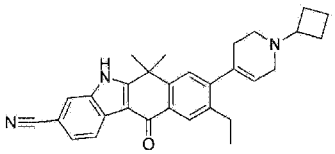
LCMS: m/z 427 $[M+H]^+$
HPLC retention time: 2.00 min (analysis condition U)

[Example 782]

Compound E8-4

8-(1-Cyclobutyl-1,2,3,6-tetrahydro-pyridin-4-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1781] Compound 7 was converted in the same manner as Compound B2-22-1 and Compound 2, and subsequently subjected to reductive amination in the same manner as Compound B3-32 to obtain the title compound.



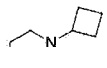
LCMS: m/z 450 $[M+H]^+$
HPLC retention time: 2.12 min (analysis condition U)

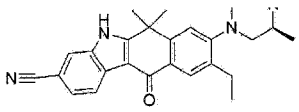
[Example 783]

Compound E9-1

8-((S)-4-Cyclobutyl-3-methyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1782]





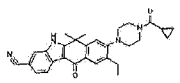
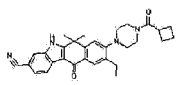
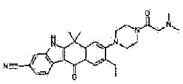
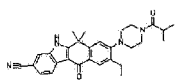
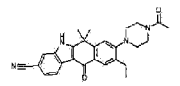
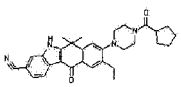
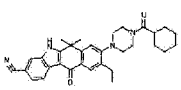
[1783] Under the same conditions as the method for synthesizing Compound B3-32, the title compound was prepared from Compound E8-2 and cyclobutanone.

LCMS: m/z 467 $[M+H]^+$

HPLC retention time: 2.90 min (analysis condition W)

[1784] The compounds described in the following Table 5 were prepared by acylation from Compound E8-1 in the same manner as the method for synthesizing Compound A9-10.

[Table 5]

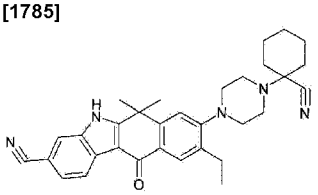
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
784	E9-2		8-(4-Cyclopropanecarbonyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	258	467
785	E9-3		8-(4-Cyclobutanecarbonyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.74	481
786	E9-4		8-[4-(2-Dimethylamino-acetyl)-piperazin-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.98	484
787	E9-5		9-Ethyl-8-(4-isobutyryl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.67	469
788	E9-6		8-(4-Acetyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.35	441
789	E9-7		8-(4-Cyclopentanecarbonyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	287	495
790	E9-8		8-(4-Cyclohexanecarbonyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	2.97	509

[Example 791]

Compound E9-9

8-[4-(1-Cyano-cyclohexyl)-piperazin-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1785]



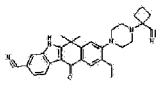
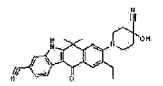
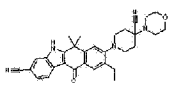
[1786] 9-Ethyl-6,6-dimethyl-11-oxo-8-piperazin-1-yl-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (45 mg) and cyclohexanone (25 mg) were suspended in chloroform (2 ml), added with trimethylsilyl cyanide (30 mg) and zinc iodide (5 mg), and the mixture was stirred at 60°C for 17 hrs. The reaction mixture was diluted with ethyl acetate (20 ml) and the organic layer was washed with 10% brine solution and concentrated under reduced pressure. The resulting residues were purified by silica gel column (dichloromethane/methanol (= 99/1)) to obtain the title compound (12 mg, yield 30%).

LCMS: m/z 506 $[M+H]^+$

HPLC retention time: 3.00 min (analysis condition U)

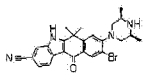
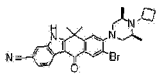
[1787] The compounds described in the following Table 6 were synthesized from Compound E8-1 or Compound PR10-1 in the same manner as the method for Compound E9-9.

[Table 6]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
792	E9-10		8-[4-(1-Cyano-cyclobutyl)-piperazin-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	288	478
793	PR11-20		8-(4-Cyano-4-hydroxy-piperidine-1-dihydro-5H-benzo[b]carbazole-3-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-carbonitrile	Y	3.05	439
794	PR11-21		6-(4-Cyano-4-morpholine-4-yl-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	3.35	508

[1788] With respect to the compounds described in the following Table 7, Compound F2 was subjected to amination in the same manner as Compound B2-1. Subsequently, the preparation was carried out by reductive amination in the same manner as the method for Compound B3-32.

[Table 7]

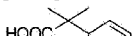
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
795	F3-12		9-Bromo-8-((3R,5S)-3,5-dimethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.05	477,479	B2-1
796	F4-11		9-Bromo-8-((3R,5S)-4-cyclobutyl-3,5-dimethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	228	531,533	B3-32

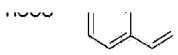
[Example 797]

Compound PR1

2-(4-Vinylphenyl)-2-methylpropanoic acid

[1789]





[1790] 2-(4-Bromophenyl)-2-methylpropanoic acid (30 g), PPh_3 (5.0 g), potassium vinyltrifluoroborate (24.8 g), potassium carbonate (51.2 g), and palladium acetate (1.43 g) were dissolved in 1-propanol (198 ml) and distilled water (99 ml). After deaeration, the mixture was stirred under reflux for 6 hrs under nitrogen atmosphere. Insoluble matters were removed by filtration and washed with 1-propanol (210 ml). The filtrate was then concentrated under reduced pressure. Concentrated residues were partitioned between CPME (300 ml) and distilled water (150 ml, comprising 4.17 ml of ethylenediamine). The organic layer was removed and the aqueous layer was adjusted to pH 5 by using 2 N hydrochloric acid. The aqueous layer was extracted with a mixture of isopropyl acetate (240 ml) and heptane (240 ml). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Ethanol (300 ml) was added thereto for suspending and washing the resultant. The solid was removed by Celite filtration, and the filtrate was concentrated under reduced pressure to obtain the title compound (21.7 g, 93%).

^{1}H-NMR (400 MHz $CDCl_3$) δ ppm 7.49-7. 34(4 H, m), 6.69(1 H, dd, J = 17.6, 11.0 Hz), 5.72(1 H, d, J = 17.6 Hz), 5. 23(1 H, d, 11.0 Hz), 1. 59(s, 6 H)

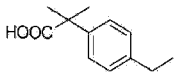
HPLC retention time: 2.05 min (analysis condition S)

[Example 798]

Compound PR2

2-(4-Ethylphenyl)-2-methylpropanoic acid

[1791]



[1792] 2-(4-Vinylphenyl)-2-methylpropanoic acid (58 g) was dissolved in ethanol, and then stirred for 3 hrs under atmospheric hydrogen pressure in the presence of 10% palladium carbon (5.8 g). The catalyst was removed by filtration, and the filtrate was concentrated to obtain a crude product, which was then suspended and washed with hexane to give the title compound (56.5 g, 94.8%).

^{1}H-NMR (270 MHz DMSO-d_6) δ ppm 12.28(1 H, s), 7.27-7.22(2 H, m), 7. 18-7.14(2 H, m), 2.56(2 H, q, J = 7.6 Hz), 1.45(6 H, s), 1.16(3 H, t, J = 7.6 Hz)

LCMS: m/z 193 $[M+H]^+$

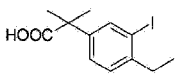
HPLC retention time: 2.18 min (analysis condition S)

[Example 799]

Compound PR3

2-(4-Ethyl-3-iodophenyl)-2-methylpropanoic acid

[1793]



[1794] 2-(4-Ethylphenyl)-2-methylpropanoic acid (58.1 g, 302.2 mmol) was dissolved in acetic acid (175 ml), added with N-iodosuccinimide (71.4 g, 317.3 mmol, 1.05 eq.) and conc. sulfuric acid (75 ml) at 0°C. Thereafter, the mixture was stirred at room temperature for 2 hrs. After cooling the reaction solution to 0°C, 10% aqueous solution of sodium hydrogen sulfite (100 ml) was added and the mixture was stirred for 1 hr. H_2O (450 ml) was added to the mixture and the precipitated solid was filtered to obtain the title compound as a crude product. Ethanol (150 ml) and 10% aqueous solution of sodium hydrogen sulfite (50 ml) were added to the

crude product, and the mixture was dissolved under heating at 50°C. After confirming the dissolution, the solution was cooled to room temperature, added with H_2O (300 ml), and then stirred at 0°C for 1 hr. The precipitated solid was filtered to obtain the title compound (95.8 g, 99%).

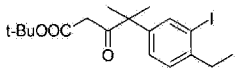
^{1}H-NMR (270 MHz DMSO-d_6) δ ppm 12.46(1 H, s), 7.70(1 H, d, J = 1.8 Hz), 7.32(1 H, dd, J = 8.1, 1.8 Hz), 7.26(1 H, d, J = 8.1 Hz), 2.64(2 H, q, J = 7.5 Hz), 1. 43(6 H, s), 1.12(3 H, t, J = 7. 5 Hz)
HPLC retention time: 2.53 min (analysis condition S)

[Example 800]

Compound PR4

Tert-butyl 4-(4-ethyl-3-iodophenyl)-4-methyl-3-oxopentanoic acid

[1795]



[1796] Mono-tert-butyl malonic acid (72.5 g) was dissolved in DME (360 ml), added with TEA (189 ml) and magnesium chloride (29.63 g) and the mixture was stirred for 2 hrs. In a separate vessel, CDI (52.75 g) was added to the DME (360 ml) solution of 2-(4-ethyl-3-iodophenyl)-2-methylpropanoic acid (90 g) and stirred at room temperature for 1 hr to prepare a solution. This solution was then added dropwise to the aforementioned mixture, and the resulting solution was washed with DME (90 ml) and stirred at 70°C for 3 hrs. The reaction mixture was diluted with isopropyl acetate (225 ml) and heptane (225 ml), and the organic layer was washed with 2 N hydrochloric acid (684 ml), 0.17 N hydrochloric acid (540 ml), 15% aqueous solution of ammonium chloride (540 ml), 1 N aqueous solution of sodium hydroxide (540 ml) and 15% brine (540 ml) in order. The organic layer was concentrated under reduced pressure to obtain the title compound as a crude product, which was used for the next step without further purification.

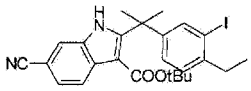
^{1}H-NMR (270 MHz DMSO-d_6) δ : 7.64(1 H, d, J = 2.0 Hz), 7.30(1 H, d, J = 8.1 Hz), 7.24(1 H, d, J = 8.0, 2. 0 Hz), 3.32(2 H, s), 2.65(2 H, q, J = 7.4 Hz), 1.40(6 H, s), 1.34(9 H, s), 1.13(3 H, t, J = 7.4 Hz)

[Example 801]

Compound PR5-1

Tert-butyl 6-cyano-2-(2-(4-ethyl-3-iodophenyl)propan-2-yl)-1H-indole-3-carboxylic acid

[1797]



[1798] 4-(4-Ethyl-3-iodophenyl)-4-methyl-3-oxopentanoic acid tert-butyl (117.76 g) was dissolved in DMF (471 ml) and added with cesium carbonate (276.5 g). DMF solution (176.6 ml) of 4-chloro-3-nitrobenzonitrile (63.9 g) was added dropwise thereto (washed with DMF 58.8 ml), and the mixture was stirred at 35°C for 6 hrs. To the mixture, THF (588.8 ml), ethyl acetate (588.8 ml), acetic acid (72.87 ml) and distilled water (588.8 ml) were added for distribution, and the aqueous layer was removed. The organic layer was added with THF (588.8 ml) and water (588.8 ml), and under stirring sodium hydrosulfite (80%, 147.76 g) was added in small portions and the mixture was stirred at room temperature for 3 hrs. After removing the aqueous layer, the organic layer was washed with 15% brine (588.8 ml). The organic layer was added with 1 N hydrochloric acid (94.2 ml), stirred for 1 hr, and then added with 1 N aqueous solution of sodium hydroxide (329.7 ml). The aqueous layer was removed and the organic layer was concentrated under reduced pressure. The concentrated residues were dissolved in ethanol (824.3 ml) and added dropwise with distilled water (247.3 ml). The resulting precipitated crystals were filtered and collected, washed with water : ethanol (= 1 : 2 mixture solution, 588.8 ml), and then dried to obtain the title compound (98.12 g, two-step 63.5%).

^{1}H-NMR (270 MHz DMSO-d_6) δ : 12.04(1 H, br. s), 8.01(1 H, d, J = 8. 4 Hz), 7.91(1 H, d, J = 0.8 Hz), 7.55(1 H, d, J = 1.8 Hz), 7. 49(1

H, dd, J = 1.5, 8.4 Hz), 7.16(1 H, d, J = 8.1 Hz), 7.07(1 H, dd, J = 2.0, 8.1 Hz), 2.58(2 H, q, J = 7.4 Hz), 1.79(6 H, s), 1.23(9 H, s), 1.06(3 H, t, J = 7.4 Hz)

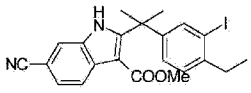
LCMS: m/z 459, 515 $[M+H]^+$

[Example 802]

Compound PR5-2

Methyl 6-cyano-2-(2-(4-ethyl-3-iodophenyl)propan-2-yl)-1H-indole-3-carboxylic acid

[1799]



[1800] The title compound was prepared from monomethyl malonate and 2-(4-ethyl-3-iodophenyl)-2-methylpropanoic acid in the same manner as the method for Compound PR4 and Compound PR5-1.

^{1}H-NMR (270 MHz DMSO-D_6) δ : 12. 20(s, 1 H), 8. 06-8. 03(m, 1 H), 7.95-7.94(m, 1 H), 7.58-7. 57(m, 1 H), 7.53-7. 49(m, 1 H), 7.17-7.14(m, 1 H), 7.06-7. 02(m, 1 H), 3.46(s, 3 H), 2. 65-2. 56(q, 2 H, J = 7.5 Hz), 1.78(s, 6 H), 1.12-1.07(t, 3 H, J = 7.5 Hz)

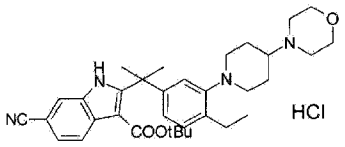
LCMS: m/z 473 $[M+H]^+$

[Example 803]

Compound PR6

Tert-butyl 6-cyano-2-(2-(4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)phenyl)propan-2-yl)-1H-indole-3-carboxylic acid hydrochloric acid salt

[1801]



[1802] Tert-butyl 6-cyano-2-(2-(4-ethyl-3-iodophenyl)propan-2-yl)-1H-indole-3-carboxylic acid (390.5 g), 4-morpholin-4-yl piperidine (158 g), and 1,3-bis-(2,6-diisopropylphenyl)-imidazoyl-2-ylidene (allyl) palladium (II) chloride (8.83 g) were dissolved in a mixture of NaHMDS (1.9 M, THF solution 1.32 L) and DME (1.95L) under nitrogen stream, and the mixture was stirred at 40°C for 1 hr. The reaction mixture was then partitioned between isopropyl acetate (1.95 L) and 20% aqueous solution of ammonium chloride (1.95 L). The organic layer was washed twice with 10% brine (1.56 L), and then concentrated under reduced pressure. The resulting residues were dissolved in a mixture of DME (3.9 L) and water (78.1 ml), added with N-acetylcysteine (12.39 g), and stirred at 45°C for 1 hr. After that, the insoluble matters were filtered and washed with DME (1.95 L). The filtrate was concentrated under reduced pressure. The resulting residues were dissolved in acetone (5.5 L) and added with the solution in which pyridinium chloride (96.5 g) is dissolved in acetone (195 ml) and ethanol (78 ml). The precipitated solid was filtered, collected, washed with acetone (1.95 L) and dried to obtain the title compound (373 g, 83%).

^{1}H-NMR (400 MHz DMSO-D_6) δ : 12.03(1 H, s), 10. 75-10. 88(1 H, m), 7. 99(1 H, d, J = 8.3 Hz), 7.93(1 H, d, J = 1.3 Hz), 7.46(1 H, dd, J = 1.3, 8.1 Hz), 7. 10(1 H, d, J = 7.9 Hz), 6.88(1 H, dd, J = 1.7, 7.9 Hz), 6.79(1 H, d, J = 1.7 Hz), 3.91-4.01(2 H, m), 3.76-3.87(2 H, m), 3.37-3. 46(2 H, m), 3.22(1 H, m), 2.94-3.11(4 H, m), 2.57(2 H, q, J = 7.5 Hz), 2.45-2.53(2 H, m), 2.09-2.16(2 H, m), 1.80(6 H, s), 1. 71-1.77(2 H, m), 1.19(9 H, s), 1.14(3 H, t, J = 7.5 Hz)

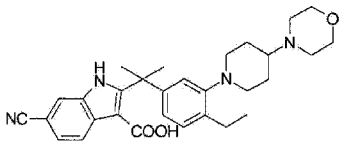
LCMS: m/z 557 $[M+H]^+$

[Example 804]

Compound PR7

6-Cyano-2-(2-(4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)phenyl)propan-2-yl)-1H-indole-3-carboxylic acid

[1803]



[1804] Tert-butyl 6-cyano-2-(2-(4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)phenyl)propan-2-yl)-1H-indole-3-carboxylic acid hydrochloric acid salt (1400 g) was suspended in TFE (7 L) under nitrogen stream, and added dropwise with TMSCl (554 ml) at 8°C. After stirring for 3 hrs, the reaction solution was added with acetone (5.6 L) and aqueous solution of NaOH (1 N, 4.39L), and 10% aqueous solution of K_2HPO_4 (1.4 L) was added thereto for neutralization. The precipitated solid was filtered and collected, washed twice with a mixture solution of water : acetone (= 1 : 1, 2.8 L), and dried to obtain the title compound (1061 g, 96.6%).

^{1}H-NMR (270 MHz DMSO-D_6) δ : 11.95 (1 H, s), 11.92(1 H, bs), 8.04 (1 H, d, J = 8.4 Hz), 7.89 (1 H, d, J = 1.3 Hz), 7.44 (1 H, J = dd, 1.3, 8.4 Hz), 7.00 (1 H, d, J = 8.4 Hz), 6.88 (1 H, d, J = 1.8 Hz), 6.71(1 H, dd, J = 2.2, 7.9 Hz), 3.50-3.55 (4 H, m), 2.92-2.96(2 H, m), 2.54(2 H, q, 7.5 Hz), 2.39-2.50 (6 H, m), 2.15-2.22 (1 H, m), 1.74-1.85 (8 H, m), 1.43-1.52 (2 H, m), 1.13 (3 H, t, J = 7.5 Hz)

LCMS: m/z 501 $[M+H]^+$

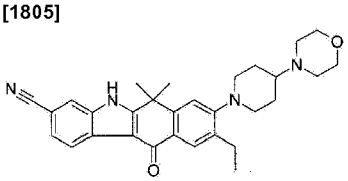
HPLC retention time: 1.53 min (analysis condition U)

[Example 805]

Compound F6-20

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1805]



[1806] 6-Cyano-2-(2-(4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)phenyl)propan-2-yl)-1H-indole-3-carboxylic acid (500 g) was dissolved in a mixture of DMA (9.4 L), acetic anhydride (270 ml) and DIPEA (1170 ml) under nitrogen stream. The mixture was stirred at 90°C for 1 hr. After cooling to room temperature, the mixture was added with methanol (3.525 L) and subsequently with distilled water (5.875 L). The precipitated solid was filtered, collected, washed twice with the mixture solution (methanol: water = 3 : 5, 1.41 L), and then dried to obtain the title compound (389.6 g, 85%).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.70 (1 H, s), 8.32 (1 H, d, J = 7.9 Hz), 8.04 (1 H, s), 8.00 (1 H, s), 7.61 (1 H, d, J = 8.5 Hz), 7.34 (1 H, s), 3.64-3.57 (4 H, m), 3.27-3.18(2 H, m), 2.82-2.66 (4 H, m), 2.39-2.28 (1 H, m), 1.96-1.87 (2 H, m), 1.76 (6 H, s), 1.69-1.53 (2 H, m), 1.29 (3 H, t, J = 7.3 Hz)

LCMS: m/z 483 $[M+H]^+$

HPLC retention time: 1.98 min (analysis condition U)

Hydrochloric acid salt of Compound F6-20

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (400 g) was dissolved in a mixture solvent of methylethyl ketone (4.8 L), acetic acid (1.44 L) and distilled water (1.68 L) at room temperature. The resulting solution was added dropwise to the mixture of ethanol (12 L) and 2 N hydrochloric acid (0.8 L). The precipitated solid was filtered, washed with ethanol (2 L), and dried to obtain hydrochloric acid salt of Compound F6-20 (357 g).

^{1}H-NMR (400 MHz, DMSO-d_6) δ : 12.83 (1 H, s), 10.78 (1 H, s), 8.32 (1 H, d, J = 8.1 Hz), 8.06 (1 H, s), 8.01(1 H, s), 7.61 (1 H, d, J = 8.1 Hz), 7.37 (1 H, s), 4. 02(2 H, m), 3.85(2 H, m), 3.51(2 H, m), 3.34(1 H, m), 3.32(2 H,m), 3.15(2 H, m), 2. 81(2 H, dd, J = 11.98, 11.7 Hz), 2. 72(2 H, q, J = 7.5 Hz), 2. 23(2 H, m), 1.89(2 H, m), 1.77(6 H, s), 1.29(3 H, t, J = 7.5 Hz)

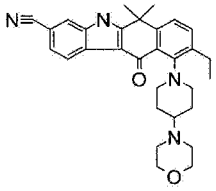
FABMS : m/z 483.4 $[M+H]^+$

[Example 806]

Compound F6-22

9-Ethyl-6,6-dimethyl-10-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1807]



[1808] From the filtrate solution obtained from the synthesis of Compound F6-20, the title compound was obtained.

^{1}H-NMR (400 MHz DMSO-D_6) δ : 12.56(1 H, s), 8.32 (1 H, d, J = 7.9 Hz), 7.96 (1 H, s), 7.45-7.59 (3 H, m), 3.55-3.62 (4 H, m), 3.36-3.50 (2 H, m), 2.75-2. 86 (2 H, m), 2.71 (2 H, q, J = 7.5 Hz), 2.45-2.56 (4 H, m), 2.27-2.38 (1 H, m), 1.73-1.84 (2 H, m), 1.69 (6 H, s), 1.43-1.58 (2 H, m), 1. 21 (3 H, t, J = 7.5 Hz).

LCMS: m/z 483 $[M+H]^+$

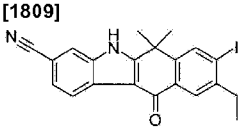
HPLC retention time: 1.52 min (analysis condition U)

[Example 807]

Compound PR8

9-Ethyl-6,6-dimethyl-8-iodo-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1809]



[1810] Tert-butyl 6-cyano-2-(2-(4-ethyl-3-iodophenyl)propan-2-yl)-1H-indole-3-carboxylic acid (11 g) was dissolved in Eaton's reagent (200 g) and stirred at room temperature for 30 min. The reaction solution was diluted with acetonitrile (200 ml) and distilled water (400 ml). The precipitated solid was collected by filtration, washed with distilled water, and then dried. The crude product was dissolved in DMA (45 ml), diluted with acetonitrile (20 ml) and distilled water (18 ml), and re-precipitated to obtain the title compound (6.62 g, 70%).

^{1}H-NMR (400 MHz DMSO-D_6) δ : 12.79(1 H, s), 8.32-8.29(2 H, m), 8. 06(1 H, s), 8.01(1 H, s), 7.62(1 H, dd, J = 1.3, 7.9 Hz), 2.78(2 H, q, J = 7.5 Hz), 1. 75(6 H, s), 1.20(3 H, t, J = 7.5 Hz)

LCMS: m/z 441 $[M+H]^+$

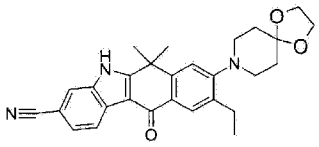
HPLC retention time: 3.17 min (analysis condition U)

[Example 808]

Compound PR9-1

8-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1811]



[1812] The dioxane solution (50 ml) of 9-ethyl-6,6-dimethyl-8-iodo-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (5.0 g), 1,4-dioxa-8-aza-spiro[4.5]decane (2.08 ml), $Pd_2(dba)_3$ (520 mg), and S-Phos (963 mg) was flushed with nitrogen gas, added with NaHMDS (1M, THF solution 40 ml), and stirred at 60°C for 1 hr. The resulting mixture was diluted with ethyl acetate (200 ml). The organic layer was washed three times with 10% brine, and then concentrated under reduced pressure to obtain the title compound as a crude product. This crude product was used for the next step without further purification.

LCMS: m/z 456 $[M+H]^+$

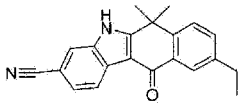
HPLC retention time: 2.78 min (analysis condition U)

[Example 809]

Compound PR9-2

9-Ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1813]



[1814] As a by-product of Compound PR9-1, the target compound was obtained according to silica gel column separation of Example 810.

LCMS: m/z 315 $[M+H]^+$

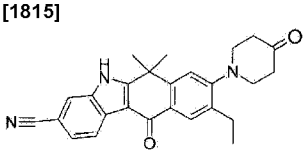
HPLC retention time: 2.77 min (analysis condition U)

[Example 810]

Compound PR10-1

9-Ethyl-6,6-dimethyl-11-oxo-8-(4-oxopiperidin-1-yl)-6,11-dihydro-5H-benzo[*b*]carbazole-3-carbonitrile

[1815]



[1816] 8-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile, which had been prepared in Example 809, was dissolved in THF (10 ml), added with 5 N hydrochloric acid (50 ml), and the mixture was

stirred for 17 hrs. The reaction mixture was neutralized with 5 N aqueous solution of sodium hydroxide and diluted with ethyl acetate (200 ml). The organic layer was washed with 10% brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (dichloromethane/methanol = 99/1 to 90/10) to obtain the title compound (2.9 g, two step yield 64%).

^{1}H-NMR (400 MHz DMSO-D_6) δ : 12.70(1 H, s), 8.32(1 H, d, J = 8.4), 8. 07(1 H, s), 7.99(1 H, s), 7.60(1 H, dd, J = 1.3, 7.9 Hz), 7.42(1 H, s), 3.28(4 H, t, J = 5.7), 2.80(q, 2 H, J = 7.5 Hz), 2.55(4 H, t, J = 5.7), 1.75(6 H, s), 1.31(3 H, t, J = 7.5 Hz)

LCMS: m/z 412 $[M+H]^+$

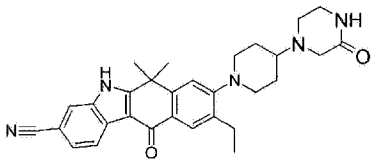
HPLC retention time: 2.57 min (analysis condition U)

[Example 811]

Compound PR11-1

9-Ethyl-6,6-dimethyl-11-oxo-8-[4-(3-oxo-piperazin-1-yl)-piperidin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1817]



[1818] 9-Ethyl-6,6-dimethyl-11-oxo-8-(4-oxopiperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (30 mg) and 2-ketopiperazine (10 mg) were dissolved in THF (2 ml), added with sodium triacetoxy borohydride (30 mg), and the mixture was stirred at 30°C for 6 hrs. The reaction mixture was diluted with ethyl acetate (20 ml). The organic layer was washed with 10% brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (dichloromethane/methanol = 99/1 to 90/10) to obtain the title compound (11.5 mg, yield 32%).

LCMS: m/z 496 $[M+H]^+$

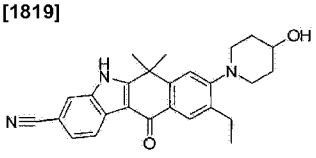
HPLC retention time: 1.90 min (analysis condition U)

[Example 812]

Compound PR11-2

9-Ethyl-8-(4-hydroxy-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1819]



[1820] As a by-product of Compound PR11-1, the target compound was obtained.

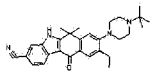
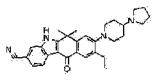
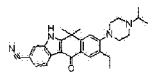
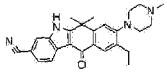
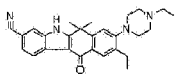
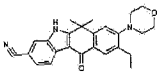
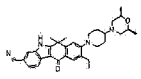
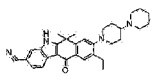
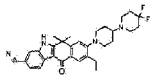
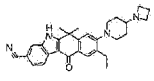
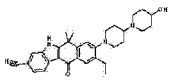
LCMS: m/z 414 $[M+H]^+$

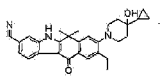
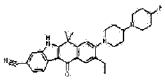
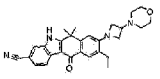
HPLC retention time: 2.13 min (analysis condition S)

[1821] The compounds described in the following Tables 8-10 were synthesized by introducing a corresponding amine to 9-ethyl-6,6-dimethyl-8-iodo-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile according to the method used for the synthesis of Compound PR9-1. Although the relevant literatures are not entirely known, some amines in which a tertiary alkyl group is attached to the nitrogen atom were prepared according to the method described in Journal of Medicinal Chemistry, 45 (14), 3143-3160, 2002. Alternatively, the preparation was carried out by introducing a corresponding amine to 9-ethyl-6,6-dimethyl-11-oxo-8-(4-oxopiperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile based on the method that is used for the synthesis of Compound PR11-1 (i.e.,

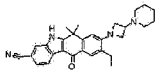
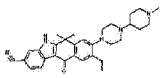
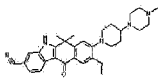
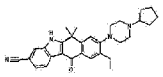
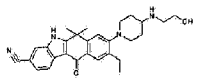
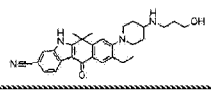
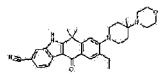
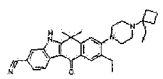
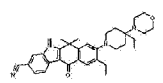
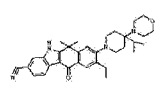
reductive amination).

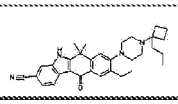
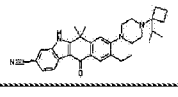
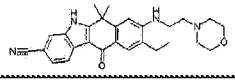
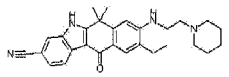
[Table 8]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
813	PR9-3		8-(4-*tert*-Butyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.63	455
814	PR9-4		9-Ethyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.13	467
815	PR9-5		9-Ethyl-8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.08	441
816	PR9-6		9-Ethyl-6,6-dimethyl-8-(4-methyl-piperazin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.97	413
817	PR9-7		9-Ethyl-8-(4-ethyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.03	427
818	PR9-8		9-Ethyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.65	400
819	PR11 -3		8-[4-((2R,6S)-2,6-Dimethyl-morpholin-4-yl)-piperidin-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.65	511
820	PR11-4		8-[1,4']Bipiperidinyl-1'-yl-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[*b*]carbazole-3-carbonitrile	S	1.63	481
821	PR11-5		8-(4,4-Difluoro-[1,4']bipiperidinyl-1'-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	S	1.70	517
822	PR11-6		8-(4-Azetidin-1-yl-piperidin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.55	453
823	PR11-7		9-Ethyl-8-(4-hydroxy-[1,4']bipiperidinyl-1'-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-	U	1.95	497

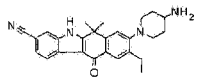
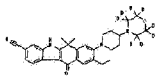
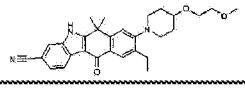
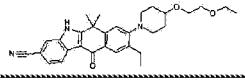
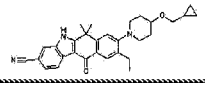
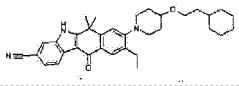
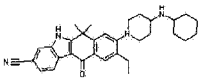
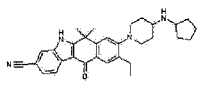
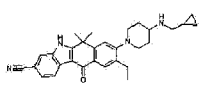
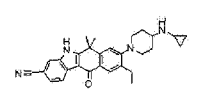
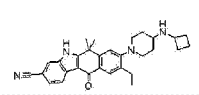
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
			carbonitrile			
824	PR9-9		8-(4-Cyclopropyl-4-hydroxy-piperidin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.53	454
825	PR11-8		9-Ethyl-8-(4-fluoro-[1,4']bipiperidinyl-1'-yl)-6,8-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	2.13	499
826	PR9-10		9-Ethyl-6,6-dimethyl-8-(3-morpholin-4-yl-azetidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.48	455

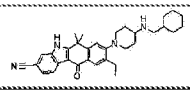
[Table 9]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
827	PR9 - 11		9-Ethyl-6,6-dimethyl-11-oxo-8-(3-piperidin-1-yl-azetidin-1-yl)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.57	453
828	PR9 - 12		9-Ethyl-6,6-dimethyl-8-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.70	496
829	PR9 - 13		9-Ethyl-6,6-dimethyl-8-[4-(4-methyl-piperazin-1-yl)-piperidin-1-yl]-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.73	496
830	PR11 - 9		8-(4-Cyclopentyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	2.12	467
831	PR11 - 10		9-Ethyl-8-[4-(2-hydroxy-ethylamino)-piperidin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	U	1.90	457
832	PR11 - 11		9-Ethyl-8-[4-(3-hydroxy-propylamino)-piperidin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	S	1.90	471
833	PR9 - 14		9-Ethyl-6,6-dimethyl-8-(4-methyl-4-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	2.00	497
834	PR9 - 15		9-Ethyl-8-[4-(1-ethyl-cyclobutyl)-piperazine-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	2.25	481
835	PR9 - 16		9-Ethyl-8-(4-ethyl-4-morpholine-4-yl-piperidine-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	2.17	511
836	PR9 - 17		9-Ethyl-8-(4-iso propyl-4-mo rpholine-4-yl-piperidine-1-yl)-6,6-dimethyl-11-oxo-6,11 -dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	2.12	525

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
837	PR9 - 18		9-Ethyl-6,6-dimethyl-11-oxo-8-[4-(1-propyl-cyclobutyl)-piperazine-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	2.28	495
838	PR9 - 19		9-Ethyl-8-[4-(1-isopropyl-cyclobutyl)-piperazine-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	2.25	495
839	PR9 - 20		9-Ethyl-6,6-dimethyl-8-(2-morpholine-4-yl-ethylamino)-11-oxo-6,11 -dihydro-5H-benzo[b]carbazole-3-carbo nitrile	Y	1.85	443
840	PR9 - 21		9-Ethyl-6,6-dimethyl-11-oxo-8-(2-piperidine-1-yl-ethylamino)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	1.85	441

[Table 10]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
841	PR11 - 12		8-(4-Amino-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	1.92	413
842	PR1 1 - 1 3		9-Ethyl-6,6-dimethyl-8-(4-2,2,3,3,5,5,6,6-d8-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11 -dihydro-5H-benzo[b]carbazole-3-carbonitrile	U	1.98	491
843	PR9 - 22		9-Ethyl-8-[4-(2-methoxy-ethoxy)-piperidine-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	3.23	472
844	PR9 - 23		8-[4-(2-Ethoxy-ethoxy)-piperidine-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	3.35	486
845	PR9 - 24		8-(4-Cyclopropylmethoxy-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbo nitrile	Y	3.50	468
846	PR9 - 25		8-[4-(2-Cyclohexyl-ethoxy)-piperidine-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	4.00	524
847	PR11 - 14		8-(4-Cyclohexylamino-piperidine-1 - yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5 H-be nzo[b]carbazole-3-carbo nitrile	Y	2.33	495
848	PR11 - 15		8-(4-Cyclopentylamino-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	2.15	481
849	PR11 - 16		8-[4-(Cyclopropylmethyl-amino)-piperidine-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	2.15	467
850	PR11 -1 7		8-(4-Cyclopropylamino-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbo nitrile	Y	2.08	453
851	PR11 - 18		8-(4-Cyclobutylamino-piperidine-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbo nitrile	Y	2.13	467
			8-[4-(Cyclohexylmethyl-amino)-piperidine-			

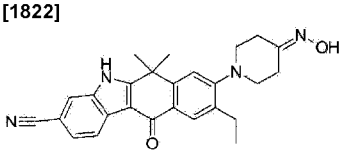
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
852	PR11 - 19		1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile	Y	2.42	509

[Example 853]

Compound PR11-22

9-Ethyl-8-(4-hydroxyimino-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1822]



[1823] 9-Ethyl-6,6-dimethyl-11-oxo-8-(4-oxopiperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (30 mg) and hydroxylamine hydrochloric acid salt (10 mg) were dissolved in ethanol (5 ml) and stirred at 60°C for 6 hrs. The reaction mixture was diluted with ethyl acetate (20 ml). The organic layer was washed with 10% brine and concentrated under reduced pressure. The resulting residues were purified by silica gel column (dichloromethane/methanol = 99/1 to 90/10) to obtain the title compound (23.5 mg, yield 74%).

LCMS: m/z 427 $[M+H]^+$

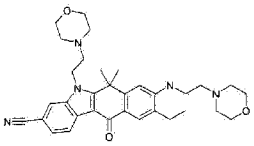
HPLC retention time: 3.08 min (analysis condition Y)

[Example 854]

Compound PR10-2

9-Ethyl-6,6-dimethyl-5-(2-morpholin-4-yl-ethyl)-8-(2-morpholin-4-yl-ethylamino)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1824]



[1825] 9-Ethyl-6,6-dimethyl-8-(2-morpholin-4-yl-ethylamino)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (10 mg) was dissolved in DMF (1 ml), added with K_2CO_3 (10 mg) and 1-(2-chloroethyl)morpholine (8 mg), and then stirred at 90°C for 17 hrs. The reaction mixture was diluted with ethyl acetate (10 ml). The organic layer was washed with 10% brine and concentrated under reduced pressure. The resulting residues were purified by silica gel column (dichloromethane/methanol = 99/1 to 90/10) to obtain the title compound (6.4 mg, yield 58%).

LCMS: m/z 556 $[M+H]^+$

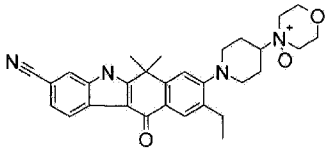
HPLC retention time: 1.78 min (analysis condition Y)

[Example 855]

Compound F7

9-Ethyl-6,6-dimethyl-11-oxo-8-[4-(4-oxy-morpholin-4-yl)-piperidin-1-yl]-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile

[1826]



[1827] 9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (400 mg) was dissolved in trifuloroethanol (80 ml), added with 30% hydrogen peroxide solution (0.8 ml), and the mixture was stirred at 60°C for 17 hrs. The reaction mixture was concentrated to 30 ml and diluted with water (20 ml). The precipitated matter was collected by filtration and dried to obtain the title compound (375 mg, yield 90%).

LCMS: m/z 499 $[M+H]^+$

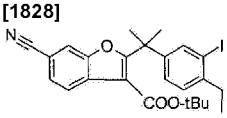
HPLC retention time: 2.05 min (analysis condition U)

[Example 856]

Compound FR1

6-Cyano-2-[1-(4-ethyl-3-iodophenyl)-1-methyl-ethyl]-benzofuran-3-carboxylic acid tert-butyl ester

[1828]



[1829] 4-(4-Ethyl-3-iodo-phenyl)-4-methyl-3-oxo-pentanoic acid tert-butyl ester (1.00 g, 2.40 mmol) was dissolved in NMP (4 ml), added with cesium carbonate (1.56 g, 4.80 mmol, 2.0 eq.), and the mixture was stirred for 5 min. The NMP solution (2 ml) of 4-chloro-3-nitro-benzonitrile (542 mg, 2.88 mmol, 1.2 eq.) was added thereto, and the mixture was stirred at 50°C for 64 hrs under nitrogen atmosphere. After cooling to room temperature, ethyl acetate (20 ml) was added and the organic layer was washed with saturated aqueous solution of ammonium chloride (20 ml). The organic layer was further washed with saturated brine and dried over sodium sulfate. The drying agent was removed by filtration and the residues obtained after concentration under reduced pressure were purified by silica gel column chromatography (ethyl acetate/hexane) to obtain the title compound (white amorphous, 320 mg, 26%).

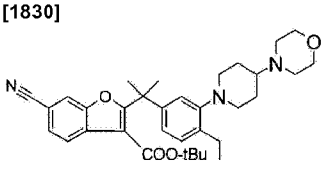
LCMS: m/z 516 $[M+H]^+$

[Example 857]

Compound FR2

6-Cyano-2-{1-[4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methylethyl}-benzofuran-3-carboxylic acid tert-butyl ester

[1830]



[1831] 6-Cyano-2-[1-(4-ethyl-3-iodophenyl)-1-methyl-ethyl]-benzofuran-3 -carboxylic acid tert-butyl ester was converted to obtain the title compound in the same manner as the method for Compound PR6.

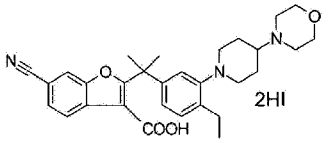
LCMS: m/z 558 $[M+H]^+$

[Example 858]

Compound FR3

6-Cyano-2-{1-[4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methylethyl}-benzofuran-3-carboxylic acid hydroiodic acid salt

[1832]



[1833] To obtain the title compound, 6-Cyano-2-{1-[4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methyl-ethyl}-benzofuran-3-carboxylic acid tert-butyl ester was deprotected by using trimethylsilyl iodide in the same manner as the method for Compound PR7.

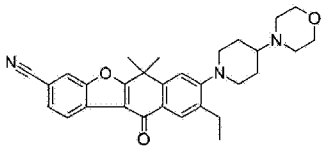
LCMS: m/z 502 $[M+H]^+$

[Example 859]

Compound FR4

9-Ethyl-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-3-carbonitrile

[1834]



[1835] 6-Cyano-2-{1-[4-ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methylethyl}-benzofuran-3-carboxylic acid hydroiodic acid salt was converted in the same method as Example 805 to obtain the target compound.

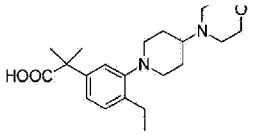
LCMS: m/z 484 $[M+H]^+$

[Example 860]

Compound LB1

2-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-2-methyl-propionic acid

[1836]



[1837] The title compound was prepared from 2-(4-ethyl-3-iodophenyl)-2-methylpropanoic acid by carrying out amination in the same manner as the method for synthesizing Compound PR6.

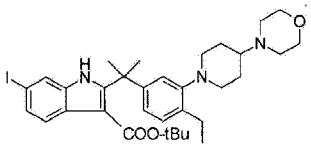
LCMS: m/z 361 $[M+H]^+$

[Example 861]

Compound LB2

2-{1-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methyl-ethyl}-6-iodo-1H-indole-3-carboxylic acid tert-butyl ester

[1838]



[1839] 2-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-2-methyl-propionic acid was converted in the same manner as the method for synthesizing Compound PR5-1 to obtain the title compound.

LCMS: m/z 658 $[M+H]^+$

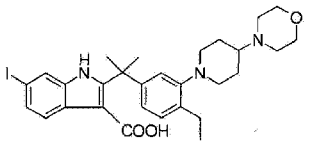
HPLC retention time: 2.76 min (analysis condition U)

[Example 862]

Compound LB3

2-{1-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methyl-ethyl}-6-iodo-1H-indole-3-carboxylic acid

[1840]



[1841] 2-{1-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methyl-ethyl}-6-iodo-1H-indole-3-carboxylic acid tert-butyl ester was deprotected in the same manner as the method for preparing Compound PR7 to obtain the title compound.

LCMS: m/z 602 $[M+H]^+$

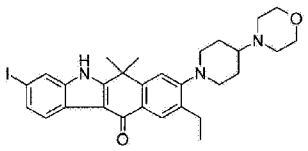
HPLC retention time: 2.17 min (analysis condition U)

[Example 863]

Compound LB4

9-Ethyl-3-iodo-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-5,6-dihydro-benzo[b]carbazol-11-one

[1842]



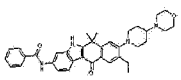
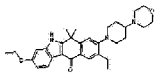
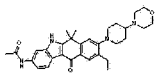
[1843] 2-{1-[4-Ethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-phenyl]-1-methyl-ethyl}-6-iodo-1H-indole-3-carboxylic acid was converted in the same manner as Example 805 to obtain the title compound.

LCMS: m/z 584 $[M+H]^+$

HPLC retention time: 2.25 min (analysis condition U)

[1844] The compounds described in the following Table 11 were converted and prepared from 9-ethyl-3-iodo-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-5,6-dihydro-benzo[b]carbazol-11-one according to the method described in the Table.

[Table 11]

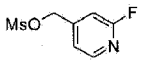
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
864	LB5 - 1		N-[9-Ethyl-6,6-dimethyl-8-(4-morpholine-4-yl-piperidine-1 -yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-yl]-benzamide	Y	1.78	577	B2-10
865	LB5 - 2		9-Ethyl-3-ethylsulfanyl-6,6-dimethyl-8-(4-morpholine-4-yl-pireridine-1-yl)-5,6-dihydro-benzo[b]carbazole-11-one	Y	2.28	518	B2-17
866	LB5 - 3		N-[9-Ethyl-6,6-dimethyl-8-(4-morpholine-4-yl-piperidine-1-yl)-11-oxo-6.11-dihydro-5H-benzo[b]carbazole-3-yl]-acetamide	Y	1.50	515	B2-10

[Example 867]

Compound AZ1

Methanesulfonic acid (2-fluoropyridin-4-yl)methyl ester

[1845]



[1846] (2-Fluoropyridin-4-yl) methanol (1 g) was dissolved in DCM (40 ml), added with TEA (3.3 ml) and mesyl chloride (0.67 ml), and the mixture was stirred at 0°C for 1 hr. The mixture was concentrated and then purified by silica gel column (n-hexane/ethyl acetate = 4/1) to obtain the title compound (1.18 g, 77%).

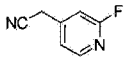
^{1}H-NMR(270 MHz DMSO-d_6) δ : 3.21(3 H, s), 5.38(2 H, s), 7.22(1 H, s), 7. 39(1 H, d, J = 5.0), 8.29(1 H, d, J = 5.0)

[Example 868]

Compound AZ2

(2-Fluoropyridin-4-yl)acetonitrile

[1847]



[1848] To the DMF (28 ml) solution of methanesulfonic acid (2-fluoropyridin-4-yl)methyl ester (1.16 g), sodium cyanide (0.42 g) was added and the mixture was stirred at 80 °C for 1 hr. The mixture was diluted with ethyl acetate (100 ml), and washed with 15% brine and distilled water in order. The organic layer was concentrated and purified by silica gel column (n-hexane/ethyl acetate = 5/1) to obtain the title compound (278 mg, 36%).

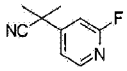
^{1}H-NMR(270 MHz DMSO-d_6) δ : 4.22(2 H, s), 7.18 (1 H, s), 7.36(1 H, d, J = 5.0), 8.27(1 H, d, J = 5.0)

[Example 869]

Compound AZ3

(2-Fluoropyridin-4-yl)2-methylpropionitrile

[1849]



[1850] The title compound was prepared from (2-fluoropyridin-4-yl) acetonitrile in the same manner as the method for Compound K2.

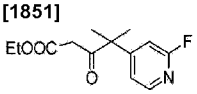
^{1}H-NMR(270 MHz DMSO-d_6) δ : 1.72(6 H, s), 7.34 (1 H, s), 7.53(1 H, d, J = 5.3), 8.31(1 H, d, J = 5.3)

[Example 870]

Compound AZ4

4-(2-Fluoropyridin-4-yl)-4-methyl-3-oxopentanoic acid ethyl ester

[1851]



[1852] The title compound was prepared from (2-fluoropyridin-4-yl) 2-methylpropionitrile in the same manner as the method for Compound K3.

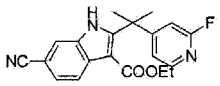
^{1}H-NMR(270 MHz DMSO-d_6) δ : 1.13(3 H, t, J = 7.3), 1.48(6 H, s), 3.57(2 H, s), 4.01(2 H, q, J = 7.3), 7. 12(1 H, s), 7.25(1 H, d, J = 5.3), 8.22(1 H, d, J = 5.3)

[Example 871]

Compound AZ5

6-Cyano-2-[1-(2-fluoropyridin-4-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid ethyl ester

[1853]



[1854] The title compound was prepared from 4-(2-fluoropyridin-4-yl)-4-methyl-3-oxopentanoic acid ethyl ester in the same manner as the method for Compound K4 and Compound K5.

LCMS: m/z 352 $[M+H]^+$

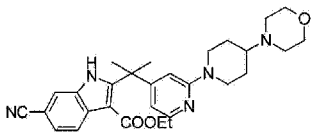
^{1}H-NMR(270 MHz DMSO-d_6) δ : 1.05(3 H, t, J = 7.3), 1.82(6 H, s), 3.98(2 H, q, J = 7.3), 6.99-7.02(2 H, m), 7.16(1 H, dd, J = 8.4, 1.5), 7.97(1 H, s), 8.05-8. 11(2 H, m)

[Example 872]

Compound AZ6

6-Cyano-2-[1-(2-(4-morpholin-4-yl-piperidin-1-yl))pyridin-4-yl)-1-methylethyl]-1H-indole-3-carboxylic acid ethyl ester

[1855]



[1856] 6-Cyano-2-[1-(2-fluoropyridin-4-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid ethyl ester (110 mg) was dissolved in NMP (3.3 ml), added with 4-morpholin-4-yl-piperidine (319 mg), and stirred in a sealing tube at 120°C for 1 hr. The reaction mixture was diluted with ethyl acetate (50 ml) and washed with 15% brine and distilled water in order. The organic layer was concentrated and purified by silica gel column (DCM/methanol = 20/1) to obtain the title compound (120 mg, 76%).

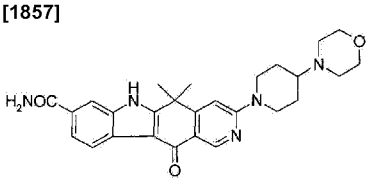
LCMS: m/z 502 $[M+H]^+$

[Example 873]

Compound AZ7-1

5,5-Dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide

[1857]



[1858] 6-Cyano-2-[1-(2-(4-morpholin-4-yl-piperidin-1-yl))pyridin-4-yl)-1-methylethyl]-1H-indole-3-carboxylic acid ethyl ester (110 mg) was dissolved in Eaton's reagent (2.5 ml) and stirred at 55°C for 17 hrs. The reaction mixture was neutralized with saturated aqueous solution of sodium bicarbonate. The precipitated matters were collected by filtration, and then washed with water to obtain the title compound (72 mg, 70%).

LCMS: m/z 474 $[M+H]^+$

HPLC retention time: 1.17 min (analysis condition U)

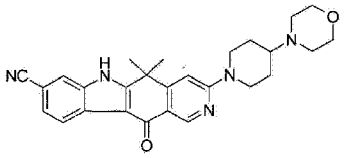
^{1}H-NMR(270 MHz DMSO-d_6) δ : 1.38(2 H, m), 1.75(6 H, s), 1.88(2 H, m), 2. 44(5 H, m), 2.94(2 H, m), 3.57(4 H, m), 4.58(2 H, m), 7.10(1 H, s), 7.32(1 H, s), 7. 75(1 H, d, J = 8.4), 8.00(2 H, m), 8.15(1 H, d, J = 8.4), 8.85 (1 H, s), 12.3(1 H, s)

[Example 874]

Compound AZ7-2

5,5-Dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile

[1859]



[1860] 5,5-Dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide (54 mg) was dissolved in DMF (1 ml), added with thionyl chloride (25 µL), and the mixture was stirred at room temperature for 1 hr. The reaction mixture was diluted with water. The precipitated matters were collected by filtration to obtain the title compound (25 mg, 49%).

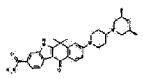
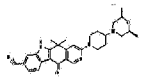
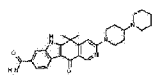
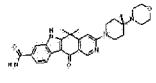
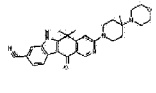
LCMS: m/z 456 $[M+H]^+$

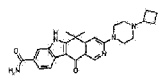
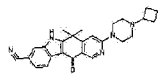
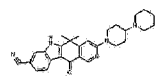
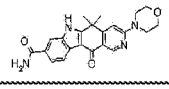
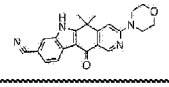
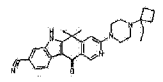
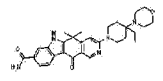
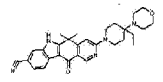
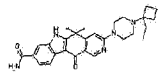
HPLC retention time: 1.55 min (analysis condition U)

^{1}H-NMR(270 MHz DMSO-d_6) δ : 1.36(2 H, m), 1.76(6 H, s), 1.89(2 H, m), 2. 44(5 H, m), 2.95(2 H, m), 3.57(4 H, m) 4.58(2 H, m), 7.10(1 H, s), 7.59(1 H, d, J = 8. 0), 7.99(1 H, s), 8.29(1 H, d, J = 8.0), 8.86(1 H, s), 12.7(1 H, s)

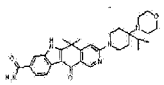
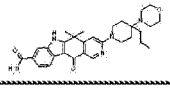
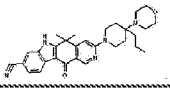
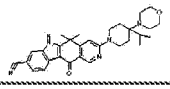
[1861] The compounds described in the following Tables 12-13 were synthesized by introducing a corresponding amino group to 6-cyano-2-[1-(2-fluoropyridin-4-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid ethyl ester and forming a ring according to the method that is used for the synthesis of Compound AZ7-1. Furthermore, the preparation was carried out by converting the substituent group at position 3 from a carboxamide group to a cyano group according to the method that is used for the synthesis of Compound AZ7-2.

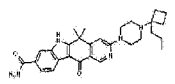
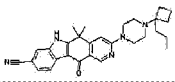
[Table 12]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
875	AZ7 - 3		3-[4-((2R,6S)-2,6-Dimethylmorpholine-4-yl)-piperidine-1-yl]-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.32	502
876	AZ7 - 4		3-[4-((2R,6S)-2,6-Dimethylmorpholine-4-yl)-piperidine-1-yl]-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	U	1.70	484
877	AZ7 - 5		3-[1,4']Bipiperidinyl-1'-yl-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.30	472
878	AZ7 - 6		5,5-Dimethyl-3-(4-methyl-4-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	Y	1.00	488
879	AZ7 - 7		5,5-Dimethyl-3-(4-methyl-4-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	Y	1.62	470

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
880	AZ7 - 8		3-(4-Cyclobutyl-piperazine-1-yl)-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	Y	1.22	444
881	AZ7 - 9		3-(4-Cyclobutyl-piperazine-1-yl)-5,5-dimethyl-11-oxo-6.11-dihydro-5H-pyrido [4,3-b]carbazole-8-carbonitrile	Y	1.55	426
882	AZ7 - 10		3-[1,4']Bipiperidinyl-1'-yl-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	Y	1.73	454
883	AZ7 - 11		5,5-Dimethyl-3-morpholine-4-yl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.33	391
884	AZ7 - 12		5,5-Dimethyl-3-morpholine-4-yl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	U	1.77	373
885	AZ7 - 13		3-[4-(1 -Ethyl-cyclobutyl)-piperazine-1-yl]-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	Y	1.93	464
886	AZ7 - 14		3-(4-Ethyl-4-morpholine-4-yl-piperidine-1-yl)-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	Y	1.18	502
887	AZ7 - 15		3-(4-Ethyl-4-morpholine-4-yl-piperidine-1-yl)-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	Y	1.78	484
888	AZ7 - 16		3-[4-(1 -Ethyl-cyclobutyl)-piperaz ine-1-yl]-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazo le-6-carboxylic acid amide	Y	1.25	472

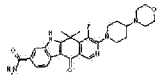
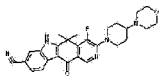
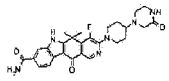
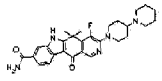
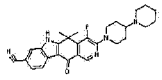
[Table 13]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
889	AZ7 - 17		3-(4-Iso pro pyl-4-mo rpho line-4-yl-piperidine-1 -yl)-5,5-dimethyl-11-oxo-6,11 -dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.27	516
890	AZ7 - 18		5,5-Dimethyl-3-(4-morpholine-4-yl-4-propyl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.36	516
891	AZ7 - 19		5,5-Dimethyl-3-(4-morpholine-4-yl-4-propyl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	U	1.68	498
892	AZ7 - 20		3-(4-Iso pro pyl-4-mo rpho line-4-yl-piperldine-1 -yl)-5,5-dimethyl-11-oxo-6,11 -dihydro-5H-pyrido[4,3-b]carbazole-8-carbo nitrile	U	1.60	498

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
893	AZ7 - 21		5,5-Dimethyl-11-oxo-3-[4-(1-propylcyclobutyl)-piperazine-1-yl]-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.58	486
894	AZ7 - 22		5,5-Dimethyl-11-oxo-3-[4-(1-propylcyclobutyl)-piperazine-1-yl]-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	U	1.97	468

[1862] The compounds described in the following Table 14 were synthesized from (2-chloro-3-fluoropyridin-4-yl)methanol according to the method that is used for the synthesis of Compound AZ1 to AZ7-2.

[Table 14]

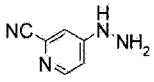
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
895	AZ7 - 23		4-Fluo ro-5,5-dime thyl-3-(4-morpholine-4-yl-piperidine-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.37	492
896	AZ7 - 24		4-Fluoro-5,5-dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-pyrido[4,3-*b*]carbazole-8-carbonitrile	U	1.74	474
897	AZ7 - 25		4-Fluoro-5,5-dimethyl-11-oxo-3-[4-(3-oxo-piperazin-1-yl)-piperidin-1-yl]-6,11-dihydro-5*H*-pyrido[4,3-*b*]carbazole-8-carboxylic acid amide	U	1.32	505
898	AZ7 - 26		3-[1,4']Bipiperidinyl-1'-yl-4-fluoro-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carboxylic acid amide	U	1.45	490
899	AZ7 - 27		3-[1,4']Bipiperidinyl-1'-yl-4-fluoro-5,5-dimethyl-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazole-8-carbonitrile	U	1.87	472

[Example 900]

Compound BZ1

2-Cyano-4-hydrazinopyridine

[1863]



[1864] 4-Chloro-2-cyanopyridine (1 g) was dissolved in hydrazine monohydrate (1 ml) and 1,4-dioxane (10 ml), and stirred overnight under reflux. The reaction solution was diluted with water (30 ml) and extracted repeatedly with ethyl acetate. The organic layer was concentrated to obtain the title compound as a crude product, which was used for the next step without further purification.

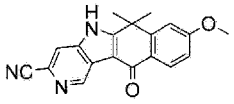
LCMS: m/z 135 $[M+H]^+$

[Example 901]

Compound BZ2-1

8-Methoxy-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[f]pyrido[4,3-b]indol-3-carbonitrile

[1865]



[1866] According to the method used for synthesizing Compound A3-1, the intermediate was prepared from 2-cyano-4-hydrazinopyridine and 7-methoxy-1,1-dimethyl-3,4 dihydro-1H-naphthalen-2-one. Without any purification, the intermediate was subjected to oxidation according to the method used for synthesizing Compound A4 to obtain the title compound.

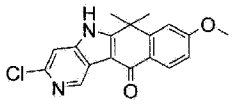
LCMS: m/z 318 $[M+H]^+$
HPLC retention time: 2.10 min (analysis condition U)

[Example 902]

Compound BZ2-2

3-Chloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[f]pyrido[4,3-b]indol-11-one

[1867]



[1868] According to the method used for synthesizing Compound A3-1, the intermediate was prepared from 2-chloro-4-hydrazinopyridine and 7-methoxy-1,1-dimethyl-3,4 dihydro-1H-naphthalen-2-one. Without any purification, the intermediate was subjected to oxidation according to the method used for synthesizing Compound A4 to obtain the title compound.

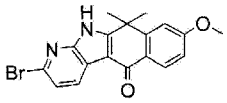
LCMS: m/z 327, 329 $[M+H]^+$
HPLC retention time: 1.80 min (analysis condition S)

[Example 903]

Compound CZ1

2-Bromo-8-methoxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one

[1869]



[1870] According to the method used for synthesizing Compound A3-1, the intermediate was prepared from 2-bromo-6-hydrazinopyridine and 7-methoxy-1,1-dimethyl-3,4 dihydro-1H-naphthalen-2-one. Without any purification, the intermediate was subjected to oxidation according to the method used for synthesizing Compound A4 to obtain the title compound.

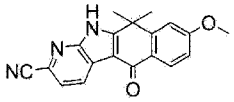
LCMS: m/z 371, 373 $[M+H]^+$
HPLC retention time: 2.85 min (analysis condition U)

[Example 904]

Compound CZ2

8-Methoxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1871]



[1872] According to the method 1 for Compound A5-2, 2-bromo-8-methoxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one was subjected to cyanation to obtain the title compound.

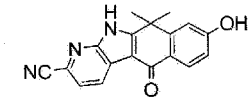
LCMS: m/z 318 $[M+H]^+$
HPLC retention time: 2.35 min (analysis condition U)

[Example 905]

Compound CZ3

8-Hydroxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1873]



[1874] According to the method used for synthesizing Compound A6, 8-methoxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was subjected to demethylation to obtain the title compound.

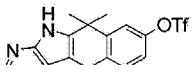
LCMS: m/z 304 $[M+H]^+$
HPLC retention time: 1.72 min (analysis condition S)

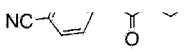
[Example 906]

Compound CZ4

Trifuloromethanesulfonic acid 2-cyano-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester

[1875]





[1876] According to the method used for synthesizing Compound B1, 8-hydroxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was subjected to trifluoromethanesulfone esterification to obtain the title compound.

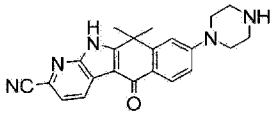
LCMS: m/z 436 $[M+H]^+$
HPLC retention time: 3.32 min (analysis condition Y)

[Example 907]

Compound CZ5-1

10,10-Dimethyl-5-oxo-8-piperazin-1-yl-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1877]



[1878] According to the method used for synthesizing Compound B2-1, trifuloromethanesulfonic acid 2-cyano-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester was introduced with piperazine to obtain the title compound.

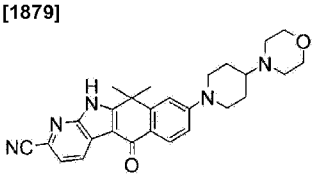
LCMS: m/z 372 $[M+H]^+$
HPLC retention time: 1.17 min (analysis condition S)

[Example 908]

Compound CZ5-2

10,10-Dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1879]



[1880] According to the method used for synthesizing Compound B2-1, trifuloromethanesulfonic acid 2-cyano-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester was introduced with 4-morpholin-4-yl piperidine to obtain the title compound.

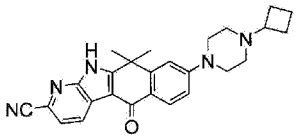
LCMS: m/z 456 $[M+H]^+$
HPLC retention time: 1.68 min (analysis condition U)

[Example 909]

Compound CZ6

8-(4-Cyclobutyl-piperazin-1-yl)-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1881]



[1882] According to the method used for synthesizing Compound B3-32, 10,10-dimethyl-5-oxo-8-piperazin-1-yl-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was subjected to reductive amination with cyclobutanone to obtain the title compound.

LCMS: m/z 426 $[M+H]^+$

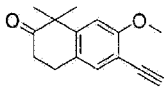
HPLC retention time: 1.60 min (analysis condition U)

[Example 910]

Compound DZ1

6-Ethynyl-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1883]



[1884] 6-Bromo-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (1 g) was dissolved in acetonitrile (50 ml), added with $PdCh(CH_3CN)_2$ (45 mg), X-phos (168 mg), $CsCO_3$ (1.2 g) and trimethylsilylacetylene (0.9 ml), and the mixture was stirred at 85°C for 2 hrs. The reaction mixture was diluted with ethyl acetate (100 ml). The organic layer was washed twice with 10% brine and concentrated under reduced pressure. The resulting residues were dissolved in THF (10 ml), added with the THF solution (4 ml) comprising tetrabutylammonium fluoride and stirred at room temperature for 1 hr. The reaction mixture was diluted with ethyl acetate (100 ml). The organic layer was washed twice with 10% brine and concentrated under reduced pressure. The resulting residues were purified by silica gel column (n-hexane/ethyl acetate = 9/1) to obtain the title compound (346 mg, two step yield 43%).

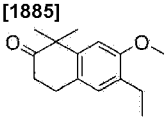
LCMS: m/z 229 $[M+H]^+$

[Example 911]

Compound DZ2

6-Ethyl-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1885]



[1886] 6-Ethynyl-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (346 mg) was dissolved in ethanol: THF (= 2 : 1 mixture solvent, 20 ml), added with 10% Pd/C (170 mg), and then the mixture was stirred at room temperature for 1 hr under hydrogen atmosphere. The catalyst was removed by filtration and the organic layer was concentrated under reduced pressure to obtain the title compound (322 mg, yield 91%).

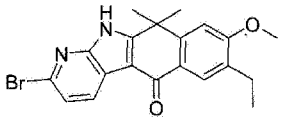
LCMS: m/z 233 $[M+H]^+$

[Example 912]

Compound DZ3

2-Bromo-7-ethyl-8-methoxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one

[1887]



[1888] According to the method used for synthesizing Compound A3-1, the intermediate was prepared from 2-bromo-6-hydrazinopyridine and 6-ethyl-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one. Without any purification, the intermediate was subjected to oxidation according to the method used for synthesizing Compound A4 to obtain the title compound.

LCMS: m/z 399, 401 $[M+H]^+$

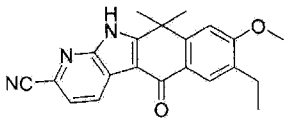
HPLC retention time: 3.35 min (analysis condition Y)

[Example 913]

Compound DZ4

7-Ethyl-8-methoxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1889]



[1890] According to the method 1 for Compound A5-2, 2-bromo-7-ethyl-8-methoxy-10,10-dimethyl-10,11-dihydro-1,11-diaza-benzo[b]fluoren-5-one was subjected to cyanation to obtain the title compound.

LCMS: m/z 346 $[M+H]^+$

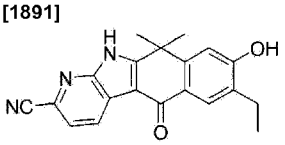
HPLC retention time: 3.05 min (analysis condition Y)

[Example 914]

Compound DZ5

7-Ethyl-8-hydroxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1891]



[1892] According to the method used for synthesizing Compound A5, 7-ethyl-8-methoxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was subjected to demethylation to obtain the title compound.

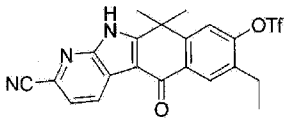
LCMS: m/z 332 $[M+H]^+$
HPLC retention time: 2.60 min (analysis condition Y)

[Example 915]

Compound DZ6-1

Trifuloro-methanesulfonic acid 2-cyano-7-ethyl-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester

[1893]

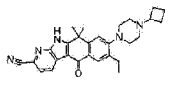
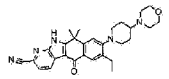
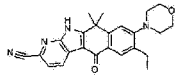
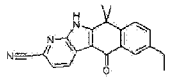
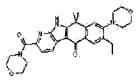


[1894] According to the method used for synthesizing Compound B1, 7-ethyl-8-hydroxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was subjected to trifluoromethanesulfone esterification to obtain the title compound.

LCMS: m/z 464 $[M+H]^+$
HPLC retention time: 3.50 min (analysis condition Y)

[1895] The compounds described in the following Table 15 were prepared from trifuloro-methanesulfonic acid 2-cyano-7-ethyl-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluoren-8-yl ester and corresponding amine according to the method that is used for the synthesis of Compound B2-10. The compounds of Example 919 and Example 920 were obtained as a by-product of the reaction.

[Table 15]

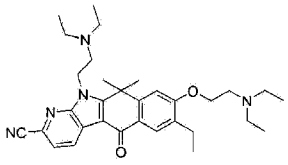
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
916	DZ7-1		8-(4-Cyclobutyl-pipe raz ine-1-yl)-7-ethyl-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluo re ne-2-carbonit rile	Y	1.83	454
917	DZ7-2		7-Ethyl-10,10-dimethyl-8-(4-morpholine-4-yl-piperidine-1-yl)-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile	Y	1.85	484
918	DZ7-3		7-Ethyl-1 0,10-dimethyl-8-morpholine-4-yl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile	Y	3.02	401
919	DZ7-4		7-Ethyl-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo [b]fluo re ne-2-carbonitrile	Y	3.07	316
920	DZ7-5		7-Ethyl-10,10-dimethyl-2-(morpholine-4-carbonyl)-8-morpholine-4-yl-10,11-dihydro-1,1 1 -diaza-benzo [b]fluo rene-5-one	Y	2.70	489

[Example 921]

Compound DZ6-2

8-(2-Diethylamino-ethoxy)-11-(2-diethylamino-ethyl)-7-ethyl-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile

[1896]



[1897] According to the method used for synthesizing Compound A7-17, 7-ethyl-8-hydroxy-10,10-dimethyl-5-oxo-10,11-dihydro-5H-1,11-diaza-benzo[b]fluorene-2-carbonitrile was alkylated to obtain the title compound.

LCMS: m/z 530 $[M+H]^+$

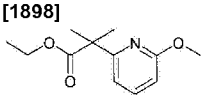
HPLC retention time: 1.38 min (analysis condition Y)

[Example 922]

Compound EZ1

2-(6-Methoxy-pyridin-2-yl)-2-methyl-propionic acid ethyl ester

[1898]



[1899] 2-Bromo-6-methoxypyridine (7.0 g), ethyl isobutyrate (4.75 g), tri t-butylphosphine (300 mg) and Pd2(dba)3 (680 mg) were dissolved in toluene (200 ml) under nitrogen atmosphere, added with THF solution of LiHMDS (1.6 M, 24 ml), and the mixture was stirred at 100°C for 6 hrs. The reaction mixture was diluted with ethyl acetate (300 ml), and washed three times with 15% brine (200 ml). The organic layer was concentrated under reduced pressure and the resulting residues were purified by silica gel column (n-hexane/ethyl acetate = 4/1) to obtain the title compound (5.353 g, yield 60%).

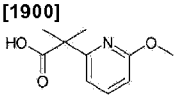
LCMS: m/z 224 $[M+H]^+$

[Example 923]

Compound EZ2

2-(6-Methoxy-pyridin-2-yl)-2-methyl-propionic acid

[1900]



[1901] 2-(6-Methoxy-pyridin-2-yl)-2-methyl-propionic acid ethyl ester (5.33 g) was dissolved in methanol (200 ml), added with 5 N aqueous solution of potassium hydroxide (25 ml), and then stirred under reflux. The reaction mixture was concentrated and neutralized with 2 N hydrochloric acid. The precipitated matters were collected by filtration and dried to obtain the title compound (3.55

g).

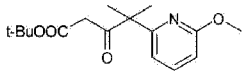
LCMS: m/z 196 $[M+H]^+$

[Example 924]

Compound EZ3

4-(6-Methoxy-pyridin-2-yl)-4-methyl-3-oxo-pentanoic acid tert-butyl ester

[1902]



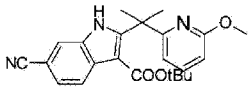
[1903] The title compound was synthesized from 2-(6-methoxy-pyridin-2-yl)-2-methyl-propionic acid and mono-tert-butyl malonic acid according to the method used for the synthesis of Compound PR4. The resultant was used for the next step without further purification.

[Example 925]

Compound EZ4-1

6-Cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid tert-butyl ester

[1904]



[1905] According to the method that is used for the preparation of Compound PR5-1, the title compound was synthesized from 4-(6-methoxy-pyridin-2-yl)-4-methyl-3-oxo-pentanoic acid tert-butyl ester and 4-chloro-3-nitrobenzonitrile

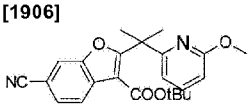
LCMS: m/z 392 $[M+H]^+$

[Example 926]

Compound EZ4-2

6-Cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-benzofuran-3-carboxylic acid tert-butyl ester

[1906]



[1907] According to the method that is used for the preparation of Compound FR1, the title compound was synthesized from 4-(6-methoxy-pyridin-2-yl)-4-methyl-3-oxo-pentanoic acid tert-butyl ester and 4-chloro-3-nitrobenzonitrile.

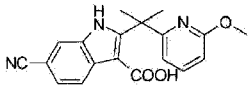
LCMS: m/z 393 $[M+H]^+$

[Example 927]

Compound EZ5-1

6-Cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid

[1908]



[1909] According to the method that is used for the preparation of Compound PR7, the title compound was synthesized from 6-cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid tert-butyl ester.

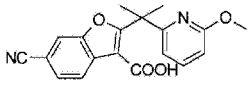
LCMS: m/z 336 $[M+H]^+$

[Example 928]

Compound EZ5-2

6-Cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-benzofuran-3-carboxylic acid

[1910]



[1911] According to the method that is used for the preparation of Compound PR7, the title compound was synthesized from 6-cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-benzofuran-3-carboxylic acid tert-butyl ester.

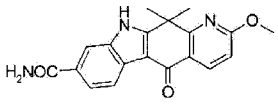
LCMS: m/z 337 $[M+H]^+$

[Example 929]

Compound EZ6-1

2-Methoxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carboxylic acid amide

[1912]



[1913] According to the method that is used for the preparation of Compound AZ7-1, the title compound was synthesized from 6-cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-1H-indole-3-carboxylic acid.

LCMS: m/z 336 $[M+H]^+$

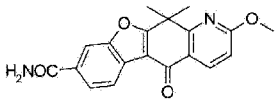
HPLC retention time: 1.98 min (analysis condition S)

[Example 930]

Compound EZ6-2

2-Methoxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carboxylic acid amide

[1914]



[1915] According to the method that is used for the preparation of Compound AZ7-1, the title compound was synthesized from 6-cyano-2-[1-(6-methoxy-pyridin-2-yl)-1-methyl-ethyl]-benzofuran-3-carboxylic acid.

LCMS: m/z 337 $[M+H]^+$

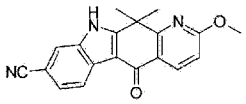
HPLC retention time: 2.38 min (analysis condition S)

[Example 931]

Compound EZ7-1

2-Methoxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carbonitrile

[1916]



[1917] According to the method that is used for the preparation of Compound AZ7-2, the title compound was synthesized from 2-methoxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carboxylic acid amide.

LCMS: m/z 318 $[M+H]^+$

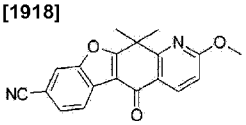
HPLC retention time: 2.60 min (analysis condition S)

[Example 932]

Compound EZ7-2

2-Methoxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carbonitrile

[1918]



[1919] According to the method that is used for the preparation of Compound AZ7-2, the title compound was synthesized from 2-methoxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carboxylic acid amide.

LCMS: m/z 319 $[M+H]^+$

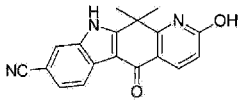
HPLC retention time: 3.18 min (analysis condition S)

[Example 933]

Compound EZ8-1

2-Hydroxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carbonitrile

[1920]



[1921] According to the method that is used for the preparation of Compound A5, 2-methoxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carbonitrile was demethylated to synthesize the title compound.

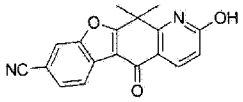
LCMS: m/z 304 $[M+H]^+$
HPLC retention time: 1.70 min (analysis condition U)

[Example 934]

Compound EZ8-2

2-Hydroxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carbonitrile

[1922]

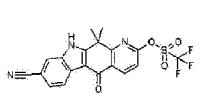
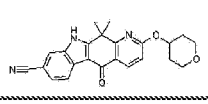
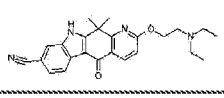


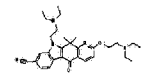
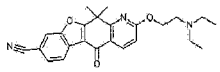
[1923] According to the method that is used for the preparation of Compound A5, 2-methoxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carbonitrile was demethylated to synthesize the title compound.

LCMS: m/z 305 $[M+H]^+$
HPLC retention time: 2.17 min (analysis condition U)

[1924] The compounds described in the following Table 16 were synthesized from 2-hydroxy-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carbonitrile or from 2-hydroxy-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3,2-g]quinoline-8-carbonitrile according to the method described in the Table.

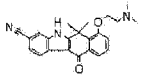
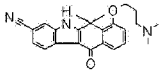
[Table 16]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
935	EZ9-1		Trifluoro-methariesulfonic acid 8-cyano-11,11-dimethyl-5-oxo-10,11-dihydro-5*H*-pyrido[2,3-*b*]carbazol-2-yl ester	U	2.93	436	B1
936	EZ9-2		11,11-Dimethyl-5-oxo-2-(tetrahydropyran-4-yloxy)-10,11-dihydro-5*H*-pyrido[2,3-*b*]carbazole-8-carbonitrile	U	2.57	388	A7-1
937	EZ9-3		2-(2-Diethylamino-ethoxy)-11,11 -dimethyl-5-oxo-1 0,11 -dihydro-5H-pyrido[2,3-b]carbazole-8-carbo nitrite	Y	1.63	403	A7-17
			2-(2-Diethylamino-ethoxy)-10-(2-				

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
938	EZ9-4		diethylamino-ethyl)-11,11-dimethyl-5-oxo-10,11-dihydro-5H-pyrido[2,3-b]carbazole-8-carbonitrile	Y	1.82	502	A7-17
939	EZ9-5		2-(2-Diethylamino-ethoxy)-11,11-dimethyl-5-oxo-5,11-dihydro-benzo[4,5]furo[3.2-g]quinoline-8-carbo nitrile	Y	1.77	404	A7-17

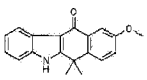
[1925] The compounds described in the following Table 17 were synthesized from Compound W3 and corresponding halide by alkylation of hydroxyl group according to the method that is used for the synthesis of Compound A7-17.

[Table 17]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
940	**W4-3**		7-(2-Dimethylami no-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[*b*]]carbazole-3-carbonitrile	I	0.96	374.0
941	**W4-4**		7-(3-Dimethylamino-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonitrile	I	0.92	388.0

[1926] The compounds described in the following Table 18 were synthesized according to the method shown below. Specifically, Compound GT1-1 was prepared from Compound J2 and phenylhydrazine according to the method that is used for the synthesis of Compound A3 and Compound A4. Subsequently, in accordance with the methylation carried out in the same manner as Compound A10-1, Compound GT1-2 was prepared.

[Table 18]

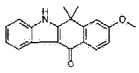
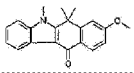
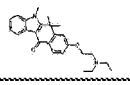
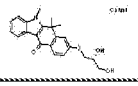
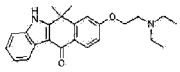
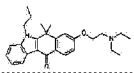
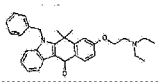
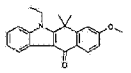
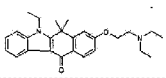
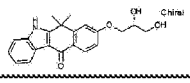
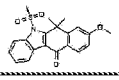
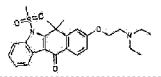
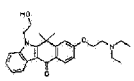
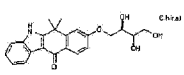
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
942	**GT1-1**		9-Methoxy-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.36	292.0	A3 A4
943	**GT1-2**		9-Methoxy-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.53	306.0	A10-1

[1927] The compounds described in the following Table 19 were synthesized according to the method shown below. Specifically, Compound GT2-1 was prepared from Compound A2 and phenylhydrazine according to the method that is used for the synthesis of Compound A3 and Compound A4.

[1928] Subsequently, by carrying out the alkylation in the same manner as Compound A10-1, Compound GT2-2 and Compound GT2-8 were prepared.

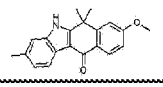
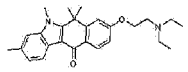
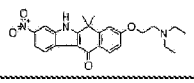
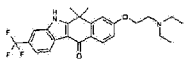
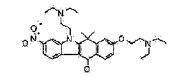
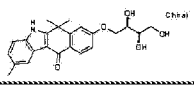
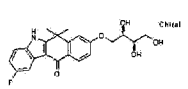
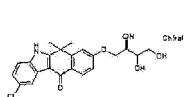
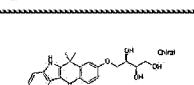
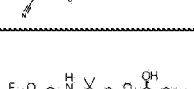
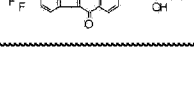
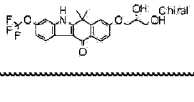
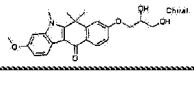
[1929] To obtain the compounds of the Table, chemical conversion of Compound GT2-1 or the 5-alkylate of Compound GT2-1 was achieved by using in combination the functional group modifications (e.g., demethylation according to the method used for the preparation of Compound A6 and subsequent introduction of a functional group, etc.) as explained before and described in the Table.

[Table 19]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
944	GT2-1		8-Methoxy-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.30	292.0	A3 A4
945	GT2-2		8-Methoxy-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.55	306.0	A1 0-1
946	GT2-3		8-(2-Diethylamino-ethoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	1.90	391.0	A6 A7-17 A10-1
947	GT2-4		8-((R)-2,3-Dihydroxy-propoxy)-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	1.90	366.0	A6 A7-17 A10-1
948	GT2-5		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	F	1.93	377.3	A7-17
949	GT2-6		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-5-propyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.09	419.0	A6 A7-17 A10-1
950	GT2-7		5-Benzyl-8-(2-diethylamino-ethoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	B	4.83	467.3	A6 A7-17 A10-1
951	GT2-8		5-Ethyl-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.94	320.0	A10-1
952	GT2-9		8-(2-Diethylamino-ethoxy)-5-ethyl-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.16	405.0	A6 A7-17 A10-1
953	GT2-10		8-(2-Diethylamino-ethoxy)-5-isopropyl-6,6-dimethyl-5,6-dihydro-benzo[*b*] carbazol-11-one	A	2.02	419.0	A6 A7-17 A1 0-1
954	GT2-11		8-((R)-2.3-Dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	2.17	352.2	A6 A7-17 A7-14-2
955	GT2-12		5-Methanesulfonyl-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	2.87	370.1	A9-1
956	GT2-13		8-(2-Diethylamino-ethoxy)-5-methanesulfonyl-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.20	455.1	A6 A7-17 A9-1
957	GT2-14		8-(2-Diethylamino-ethoxy)-5-(2-hydroxy-ethyl)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	H	3.73	421.0	A6 A7-17 A10-1
958	GT2-15		6,6-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	H	3.73	382.4	A7-1 A7-14-2

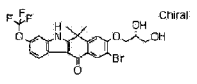
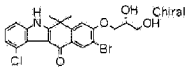
[1930] The compounds described in the following Table 20 were synthesized according to the method shown below. Specifically, by using Compound A2 and phenylhydrazine having a corresponding substituent group, 2 (or 3)-substituted-8-methoxy-6,6-dimethyl-6,11-dihydro-5H-benzo[b]carbazol-11-one was prepared according to the method that is used for the synthesis of Compound A3 and Compound A4. Subsequently, to obtain the compounds of the Table, chemical conversion of the above compounds was achieved by using in combination the functional group modifications as explained before and described in the Table.

[Table 20]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
959	GT3-1		8-Methoxy-3,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.39	306.0	A3 A4
960	GT3-2		8-(2-Diethylamino-ethoxy)-3,5,6,6-tetramethyl-5,6-dihydro-benzo[*b*]]carbazol-11-one	A	1.97	405.0	A6 A7-17 A10-1
961	GT3-3		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-nitro-5,6-dihydro-benzo[*b*]carbazol-11-one	B	3.86	422.2	A6 A7-17
962	GT3-4		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-trifluoromethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	2.03	445.0	A6 A7-17
963	GT3-5		8-(2-Diethylamino-ethoxy)-5-(2-diethylamino-ethyl)-6,6-dimethyl-3-nitro-5,6-dihydro-benzo[*b*]carbazol-11-one	F	1.74	521.3	A6 A7-17 A10-1
964	GT3-6		2,6,6-Trimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.03	396.0	A6 A7-17 A7-14-2
965	GT3-7		2-Fluoro-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	F	1.99	400.0	A6 A7-17 A7-14-2
966	GT3-8		2-Chloro-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.14	416.0	A6 A7-17 A7-14-2
967	GT3-9		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-2-carbonitrile	F	1.90	407.4	A6 A7-17 A7-14-2
96B	GT3-10		6,6-Dimettiyl-3-trifluoromethoxy-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.31	466.4	A6 A7-17 A7-14-2
969	GT3-11		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-trifluoromethoxy-5,6-dihydro-benzo[*b*]carbazol-11-one	F	2.43	436.4	A6 A7-17 A7-14-2
970	GT3-12		8-((R)-2,3-Dihydroxy-propoxy)-3-methoxy-5,6,6-trimethyl-5,6-dihydro-benzo[b]carbazol-11-one	B	3.79	396.5	A6 A7-17 A10-1 A7-14-2
971	GT3-13		8-((R)-2,3-Di hydroxy-propoxy)-3-methoxy-6,6-dimethyl-5,6-di hydro-benzo[*b*]carbazol-11-one	B	3.40	382.4	A6 A7-17 A7-14-2

[1931] The compounds described in the following Table 21 were synthesized according to the method shown below. Specifically, by using Compound E1 and phenylhydrazine having a corresponding substituent group, 9-bromo-1-chloro-8-methoxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one or 9-bromo-8-methoxy-6,6-dimethyl-3-trifuloromethoxy-5,6-dihydro-benzo[b]carbazol-11-one was prepared according to the method used for the synthesis of Compound A3 and Compound A4. Subsequently, to obtain the compounds of the Table, chemical conversion of the above compounds was achieved by using in combination the functional group modifications as explained before and described in the Table.

[Table 21]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
972	GT4-1		9-Bromo-8-((R)-2,3-di hydroxy-propoxy)-6.6-dimethyl-3-trifluoromethoxy-5,6-dihydro-benzo[*b*] carbazol-11-one	C	2.68	514.0	A6 A7-17 A7-14-2
973	GT4-2		9-Bromo-1-chloro-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	2.58	464.0	A6 A7-17 A7-14-2

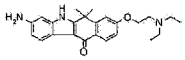
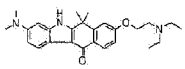
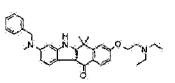
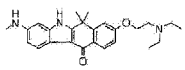
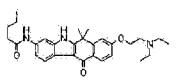
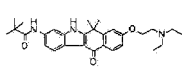
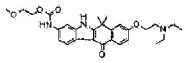
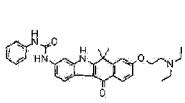
[1932] The compounds described in the following Tables 22-23 were synthesized according to the method shown below. Specifically, catalytic reduction of Compound GT3-3 was carried out according to the method used for the preparation of Compound D2 to prepare Compound GT5-1.

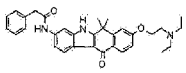
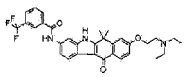
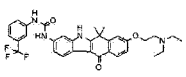
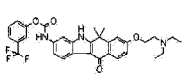
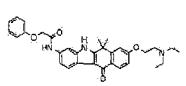
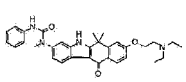
[1933] Reductive alkylation of Compound GT5-1 was carried out according to the method used for the preparation of Compound B3-32 for the introduction of a methyl group or a benzyl group (Compound GT5-2, Compound GT5-3).

[1934] Catalytic reduction of Compound GT5-3 was carried out according to the method used for the preparation of Compound D2, and then processed to prepare Compound GT5-4.

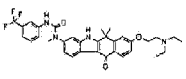
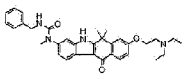
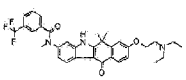
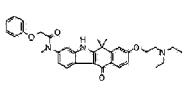
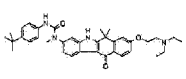
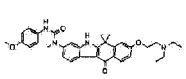
[1935] The resulting amino derivatives of Compound GT5-1 to 4 were reacted with corresponding acyl chloride, isocynate, or chloroformate according to the method used for the preparation of Compound A9-1 to obtain the compounds of the Table.

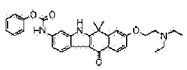
[Table 22]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
974	GT5-1		3-Amino-8-(2-diethylamino-ethoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	1.15	392.3	D2
975	GT5-2		8-(2-Diethylamino-ethoxy)-3-dimethylamino-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	A	1.18	420.2	B3-32
976	GT5-3		3-(Benzyl-methyl-amino)-8-(2-diethylamino-ethoxy)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	B	3.05	496.4	B3-32
977	GT5-4		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-methylamino-5,6-dihydro-benzo[*b*]carbazol-11-one	B	2.46	406.3	83-32 D2
978	GT5-5		Pentanoic acid [8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-amide	C	2.52	476.5	A9-1
979	GT5-6		*N*-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-2,2-dimethyl-propionamide	A	1.74	476.4	A9-1
980	GT5-7		[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-carbamic acid 2-methoxy-ethyl ester	A	1.55	494.3	A9-1
981	GT5-8		1-[8-(2-Diethylami no-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-3-phenyl-urea	B	3.79	511.3	A9-1
			N-[8-(2-Diethylamino-				

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
982	GT5-9		ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-2-phenyl-acetamide	B	3.81	510.4	A9-1
983	GT5-10		N -[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*] carbazol-3-yl]-3-trifluoromethyl-benzami de	B	4.47	564.4	A9-1
984	GT5-11		1-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-3-(3-trifluoromethyl-phenyl)-urea	B	4.55	579.4	A9-1
985	GT5-12		[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-carbamic acid 3-trifluoromethyl-phenyl ester	H	5.17	580.1	A9-1
986	GT5-13		*N*-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-2-phenoxy-acetamide	C	2.57	526.1	A9-1
987	GT5-14		1-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-5,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-1-methyl-3-phenyl-urea	B	3.83	525.6	A9-1

[Table 23]

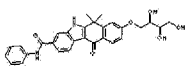
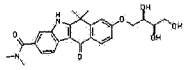
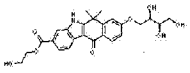
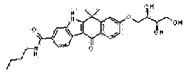
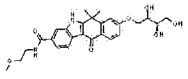
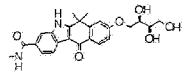
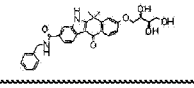
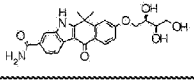
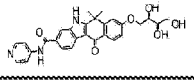
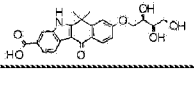
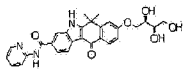
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
988	GT5-15		1-[8-(2-Diethytamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-1-methyl-3-(3-trifluoromethyl-phenyl)-urea	B	4.58	593.4	A9-1
989	GT5-16		3-Benzyl-1-[8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-1-methyl-urea	B	3.81	539.4	A9-1
990	GT5-1 7		*N*-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-*N*-methyl-3-trifluoromethyl-benzamide	B	4.15	578.3	A9-1
991	GT5-18		*N*-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-*N*-methyl-2-phenoxy-acetamide	C	2.62	540.4	A9-1
992	GT5-19		3-(4-*tert*-Butyl-phenyl)-1-[8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-1-methyl-urea	F	2.45	581.6	A9-1
993	GT5-20		1-[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-3-(4-methoxyphenyl)-1-methyl-	B	3.77	555.4	A9-1

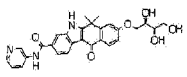
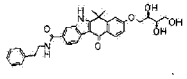
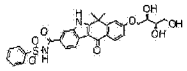
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
			urea				
994	GT5-21		[8-(2-Diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl]-carbamic acid phenyl ester	A	1.89	512.2	A9-1

[1936] The compounds described in the following Table 24 were synthesized according to the method shown below. Specifically, having Compound T22-1 as a starting material, 8-[(4R,5R)-5-(tert-butyl-dimethylsilanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-5,6-dihydro-11-oxo-benzo[b]carbazole-3-carboxylic acid was prepared according to the method that is used for the preparation of Compound B2-28.

[1937] The resulting carboxylic acid was subjected to dehydrating condensation with corresponding amine, alcohol according to the method that is used for the preparation of Compound A9-10. Subsequently, deprotection was carried out according to the method used for the preparation of Compound T22-1-1 and Compound T22-1-2 to obtain the compounds described in the Table.

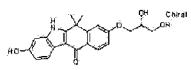
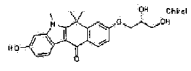
[Table 24]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
995	GT6-1		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid phenylamide	A	1.79	501.0	A9-10
996	GT6-2		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid dimethylamide	D	1.33	453.0	A9-10
997	GT6-3		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid 2-hydroxy-ethyl ester	A	1.40	470.0	A9-10
998	GT6-4		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid butylamide	D	1.55	481.0	A9-10
999	GT6-5		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid (2-methoxy-ethyl)-amide	D	1.30	483.0	A9-10
1000	GT6-6		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid methylamide	D	1.24	439.0	A9-10
1001	GT6-7		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid benzylamide	D	1.58	515.0	A9-1 0
1002	GT6-8		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid amide	D	1.18	425.0	A9-10
1003	GT6-9		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-tri hydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid pyridin-4-ylamide	D	1.40	502.0	A9-10
1004	GT6-10		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid	D	1.01	426.0	B2-28
1005	GT6-11		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid pyridin-2-ylamide	D	1.52	502.0	A9-10

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1006	GT6-12		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid pyridin-3-ylamide	D	1.34	502.0	A9-10
1007	GT6-13		6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carboxylic acid phenethyl-amide	D	1.67	529.0	A9-10
1008	GT6-14		*N*-[6,6-Dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-5*H*-benzo[*b*]carbazole-3-carbonyl]-benzenesulfonamide	D	1.23	565.0	A9-10

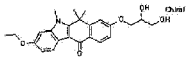
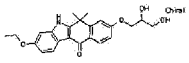
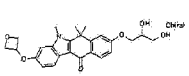
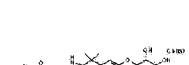
[1938] To the compounds described in the following Table 25, a hydroxyl group was introduced from Compound T17-3 according to the method described in JACS 2006, Vol. 128, page 10964. Subsequently, deprotection was carried out according to the method used for Compound A7-14-2 and Compound T22-2 to obtain the compounds shown below.

[Table 25]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1009	GT7-1		8-((R)-2,3-Dihydroxy-propoxy)-3-hydroxy-5,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	B	2.59	368.4
1010	GT7-2		8-((R)-2,3-Dihydroxy-propoxy)-3-hydroxy-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	1.90	382.4

[1939] The compounds described in the following Table 26 were prepared by alkylation according to the method used for the preparation of Compound A7-1 from Compound GT7-1 or Compound GT7-2, or by carbamation according to the method used for the preparation of A9-1.

[Table 26]

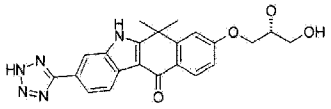
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1011	GT8-1		8-((R)-2,3-Dihydroxy-propoxy)-3-ethoxy-5,6,6-trimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	2.43	410.5	A7-1
1012	GT8-2		8-((R)-2,3-Dihydroxy-propoxy)-3-ethoxy-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	C	2.30	396.5	A7-1
1013	GT8-3		8-((R)-2,3-Dihydroxy-propoxy)-5,6,6-trimethyl-3-(oxetan-3-yloxy)-5,6-dihydro-benzo[*b*]carbazol-11-one	B	1.72	438.5	A7-1
1014	GT8-4		Phenyl-carbamic acid 8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[*b*]carbazol-3-yl ester	B	4.23	487.0	A9-1

[Example 1015]

Compound GT9-1

8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-(2H-tetrazol-5-yl)-5,6-dihydro-benzo[b]carbazol-11-one

[1940]



[1941] 8-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazole-3-carbonitrile (20.0 mg, 0.048 mmol), ammonium chloride (1.28 mg, 0.024 mmol) and NaN_3 (6.24 mg, 0.096 mmol) were dissolved in DMF, and the mixture was stirred at 120°C for 14 hrs. NaN_3 (6.24 mg, 0.096 mmol) was further added to the mixture, which was then stirred at 120°C for 30 hrs. The reaction solution was added with 1 N aqueous solution of hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with saturated brine and concentrated under reduced pressure. The resultant solid obtained after concentration was washed with hexane : ethyl acetate = 1 : 1 to obtain 8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-3-(2H-tetrazol-5-yl)-5,6-dihydro-benzo[b]carbazol-11-one as a white solid.

[1942] The product was suspended in MeOH (1.0 ml), added with 1 N aqueous solution of hydrochloric acid, and then stirred at 60°C for 1 hr and 30 min. After cooling to room temperature, the reaction solution was concentrated under reduced pressure, and the resulting solid was washed with DCM to obtain the title compound as a pale yellow solid (13.4 mg, 66.3%).

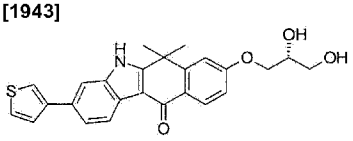
LCMS: m/z 420 $[M+H]^+$

[Example 1016]

Compound GT9-2

8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-thiophen-3-yl-5,6-dihydro-benzo[b]carbazol-11-one

[1943]



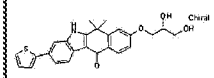
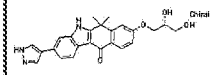
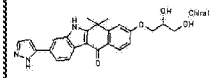
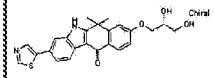
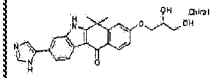
[1944] 3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-ll-one (20.0 mg, 0.043 mmol), thiophene-3-boronic acid (10.9 mg, 0.085 mmol), K_3PO_4 (40 mg) and Pd $(PPh_3)_4$ (9.9 mg, 0.0086 mmol) were dissolved in DMA(0.8 ml) and water (0.2 ml), and stirred at 140°C for 10 min under microwave irradiation. The reaction solution was diluted with ethyl acetate and washed with saturated brine. The organic layer was concentrated under reduced pressure, and the resulting residues were purified by column chromatography (hexane/ethyl acetate) to obtain 8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-3-thiphen-3-yl-5,6-dihydro-benzo[b]carbazol-11-one.

[1945] This product was suspended in MeOH (1.0 ml), added with 1 N hydrochloric acid, and then stirred at 60°C for 1 hr and 30 min. The reaction solution was concentrated under reduced pressure, and the resulting solid was washed with DCM to obtain the title compound as a yellow solid (12.6 mg, 67.1%).

LCMS: m/z 434 $[M+H]^+$

[1946] Using the combination of Compound T18-1 and corresponding boronic acid or the combination of (S)-8-((2,2-dimethyl-1,3-dioxolan-4-yl)methoxy)-6,6-dimethyl-3-(4,4,5,5-tetramethyl-l,3,2-dioxaborolan-2-yl)-5H-benzo[b]carbazol-11(6H)-one and corresponding bromide, the reaction was carried out in the same manner as Compound GT9-2 to obtain the compounds of the following Table 27.

[Table 27]

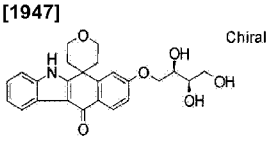
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1017	GT9-3		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-thiophen-2-yl-5,6-dihydro-benzo[*b*]carbazol-11-one	B	4.59	434.0
1018	GT9-4		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-(1*H*-pyrazol-4-yl)-5,6-dihydro-benzo[*b*]carbazol-11-one	B	4.04	418.0
1019	GT9-5		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-(2*H*-pyrazol-3-yl)-5,6-dihydro-benzo[*b*]carbazol-11-one	A	1.51	418.0
1020	GT9-6		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-thiazol-5-yl-5,6-dihydro-benzo[*b*]carbazol-11-one	F	1.97	435.0
1021	GT9-7		8-((R)-2,3-Dihydroxy-propoxy)-3-(3*H*-imidazol-4-yl)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	H	2.91	418.0

[Example 1022]

Compound GT10-1

8-((2R,3R)-2,3,4-Trihydroxybutoxy)-2',3',5',6'-tetrahydrospiro[benzo[b]carbazole-6,4'-pyran]-11(5H)-one

[1947]



[1948] Preparation was carried out in the same manner as Compound N6-1-2.

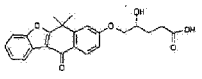
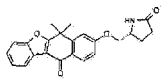
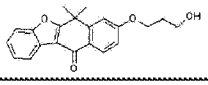
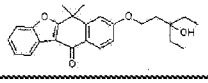
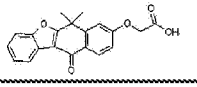
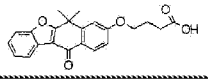
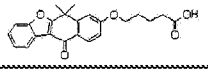
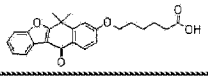
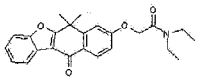
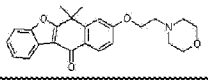
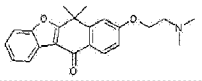
LCMS: m/z 434 $[M+H]^+$

HPLC retention time: 1.56 min (analysis condition A)

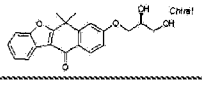
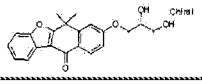
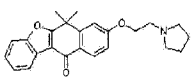
[1949] The compounds described in the following Table 28- were synthesized according to the method shown below. Specifically, by using the method for the preparation of Compound Z10, Z11, Z12 and Z13, 8-hydroxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-

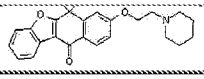
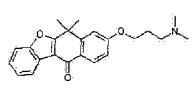
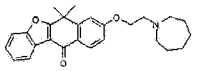
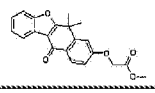
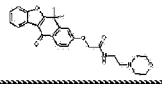
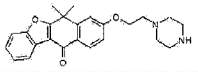
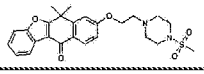
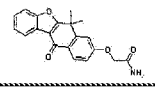
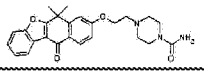
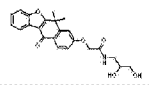
11-one was prepared from Compound A2 and bromophenol. To the resulting compound, a side chain or a synthetic equivalent thereof was introduced according to Mitsunobu reaction that is used for the preparation of Compound A7-1 or the method that is used for A7-17, etc. After that, if necessary, functional group modification such as deprotection, etc. was carried out to prepare the compounds listed below.

[Table 28]

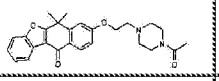
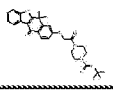
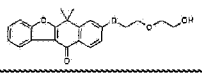
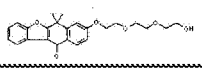
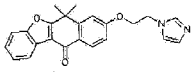
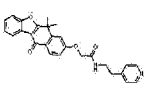
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1023	GT11-1		(R)-5-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-4-hydroxy-pentanoic acid	H	5.37	395.0
1024	GT11-2		(R)-5-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxymethyl)-pyrrolidin-2-one	H	5.50	376.0
1025	GT11-3		8-(3-Hydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.97	337.0
1026	GT11-4		8-(3-Ethyl-3-hydroxy-pentyloxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-d]furan-11-one	H	9.29	393.0
1027	GT11-5		(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetic acid	H	5.65	336.0
1028	GT11-6		4-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-butyric acid	H	6.15	365.0
1029	GT11-7		5-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-pentanoic acid	H	6.44	379.0
1030	GT11-8		6-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-hexanoic acid	H	6.77	393.0
1031	GT11-9		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N,N*-diethyl-acetamide	H	6.39	392.0
1032	GT11-10		6,6-Dimethyl-8-(2-morpholin-4-yl-ethoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.45	392.0
1033	GT11-11		8-(2-Di methylami no-ethoxy)- 6 ,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.59	350.0

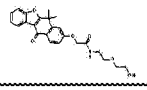
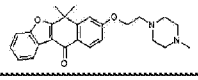
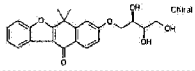
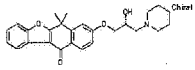
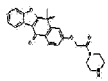
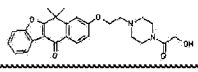
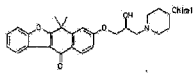
[Table 29]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1034	GT11-12		8-((S)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.40	353.0
1035	GT11-13		8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.07	353.0
1036	GT11-14		6,6-Dimethyl-8-(2-pyrrolidin-1-yl-ethoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.03	375.9
			6,6-Dimethyl-8-(2-piperidin-1-yl-			

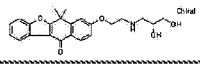
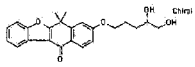
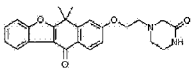
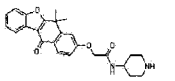
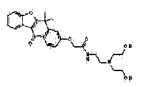
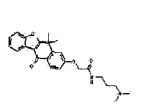
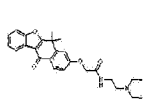
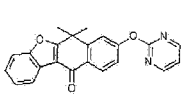
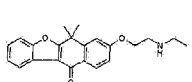
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1037	GT11-15		ethoxy)-6*H*-benzo[*b*]naphtho[2,3-d]furan-11-one	C	3.15	389.9
1038	GT11-16		8-(3-Dimethylamino-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.30	364.2
1039	GT11-17		8-(2-Azepan-1-yl-ethoxy)-6,6-di methyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.35	404.3
1040	GT11-18		(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetic acid methyl ester	D	2.38	351.0
1041	GT11-19		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N*-(2-morpholin-4-yl-ethyl)-acetamide	D	2.03	450.0
1042	GT11-20		6,6-Dimethyl-8-(2-piperazin-1-yl-ethoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.81	391.2
1043	GT11-21		8-[2-(4-Methanesulfonyl-piperazin-1-yl)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.21	469.1
1044	GT11-22		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetamide	D	1.95	336.0
1045	GT11-23		4-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-piperazine-1-carboxylic acid amide	F	2.04	434.0
1046	GT11-24		*N*-(2,3-Dihydroxy-propyl)-2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetamide	D	1.82	410.0

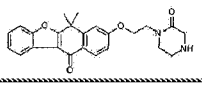
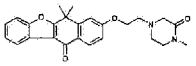
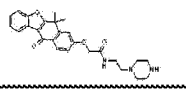
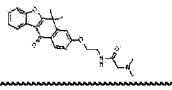
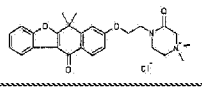
[Table 30]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1047	GT11-25		8-[2-(4-Acetyl-piperazin-1-yl)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.10	433.1
1048	GT11-26		4-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetyl]-piperazine-1-carboxylic acid *tert*-butyl ester	D	2.53	505.0
1049	GT11-27		8-[2-(2-Hydroxy-ethoxy)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.62	367.0
1050	GT11-28		8-{2-[2-(2-Hydroxy-ethoxy)-ethoxy]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.64	411.0
1051	GT11-29		8-(2-Imidazol-1-yl-ethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.05	373.1
1052	GT11-30		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N*-(2-pyridin-4-yl-ethyl)-acetamide	D	2.10	441.0
1053	GT11-31		*N*-(2-Dimethylamino-ethyl)-2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-	D	2.01	407.0

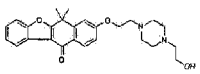
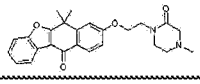
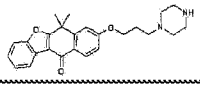
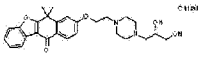
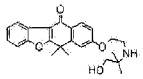
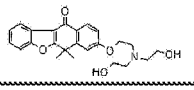
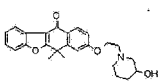
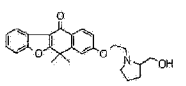
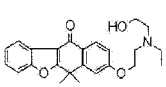
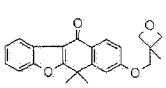
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
			d]furan-8-yloxy)-acetamide			
1054	GT11-32		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N*-[2-(2-hydroxy-ethoxy)-ethyl]-acetamide	D	1.88	424.0
1055	GT11-33		6,6-Dimethyl-8-[2-(4-methyl-piperazin-1-yl)-ethoxy]-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	1.99	405.2
1056	GT11-34		6,6-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.21	383.0
1057	GT11-35		8-((R)-2-Hydroxy-3-piperidin-1-yl-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.25	420.0
1058	GT11-36		6,6-Dimethyl-8-(2-oxo-2-piperazin-1-yl-ethoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	D	1.92	405.0
1059	GT11-37		8-{2-[4-(2-Hydroxy-acetyl)-piperazin-1-yl]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.06	449.1
1060	GT11-38		8-((S)-2-Hydroxy-3-piperidin-1-yl-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.24	420.0

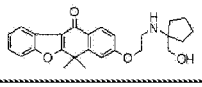
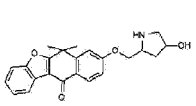
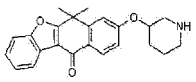
[Table 31]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1061	GT11-39		8-[2-((R)-2,3-Dihydroxy-propylamino)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.18	396.0
1062	GT11-40		8-((S)-4,5-Dihydroxy-pentyloxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.56	381.0
1063	GT11-41		4-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-piperazin-2-one	F	2.06	405.0
1064	GT11-42		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N*-piperidin-4-yl-acetamide	D	1.92	419.0
1065	GT11-43		*N*-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethyl}-2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetamide	D	1.83	467.0
1066	GT11-44		*N*-(3-Dimethylamino-propyl)-2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetamide	D	2.08	422.0
1067	GT11-45		*N*-(2-Diethylamino-ethyl)-2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-acetamide	D	2.10	436.0
1068	GT11-46		6,6-Dimethyl-8-(pyrimidin-2-yloxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	6.35	357.0
1069	GT11-47		8-(2-Ethylamino-ethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.15	350.0

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1070	GT11-48		1-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-piperazin-2-one	H	4.42	405.0
1071	GT11-49		4-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-1-methyl-piperazin-2-one	H	4.33	419.0
1072	GT11-50		2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-*N*-(2-piperazin-1-yl-ethyl)-acetamide	A	3.99	448.0
1073	GT11-51		2-Dimethylamino-*N*-[2-(6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-acetamide	D	2.13	408.0
1074	GT11-52		4-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-1,1-dimethyl-3-oxo-piperazin-1-ium; chloride	H	4.47	433.0

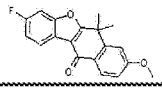
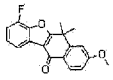
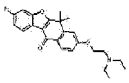
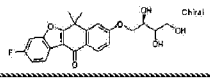
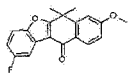
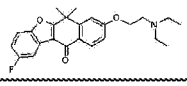
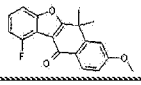
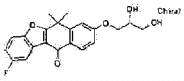
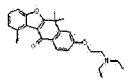
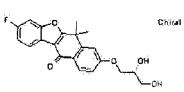
[Table 32]

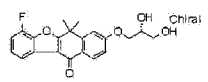
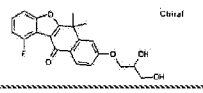
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1075	GT11-53		8-{2-[4-(2-Hydroxy-ethyl)-piperazin-1-yl]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	A	1.75	435.0
1076	GT11-54		1-[2-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-8-yloxy)-ethyl]-4-methyl-piperazin-2-one	B	4.09	419.0
1077	GT11-55		6,6-Dimethyl-8-(3-piperazin-1-yl-propoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	A	1.75	405.0
1078	GT11-56		8-{2-[4-((S)-2,3-Dihydroxy-propyl)-piperazin-1-yl]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	A	1.72	465.0
1079	GT11-57		8-[2-(2-Hydroxy-1,1-dimethyl-ethylamino)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.57	394.0
1080	GT11-58		8-{2-[Bis-(2-hydroxy-ethyl)-amino]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.77	410.0
1081	GT11-59		8-[2-(3-Hydroxy-piperidin-1-yl)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.88	406.0
1082	GT11-60		8-[2-(2-Hydroxymethyl-pyrrolidin-1-yl)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.82	406.0
1083	GT11-61		8-{2-[Ethyl-(2-hydroxy-ethyl)-amino]-ethoxy}-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.85	394.0
1084	GT11-62		6,6-Dimethyl-8-(3-methyl-oxetan-3-ylmethoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.03	363.0
			8-[2-(1-Hydroxymethyl-			

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1085	GT11-63		cyclopentylamino)-ethoxy]-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.72	420.0
1086	GT11-64		8-(4-Hydroxy-pyrrolidin-2-ylmethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	Y	2.96	378.0
1087	GT11-65		6,6-Dimethyl-8-(piperidin-3-yloxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	Y	3.03	362.0

[1950] The compounds described in the following Table 33 were synthesized according to the method shown below. From Compound A2 and 2-bromophenol having a fluorine atom at corresponding position, 8-methoxy-6H-benzo[b]naphtho[2,3-d]furan-11-one having a fluorine atom at corresponding position (Compound GT12-1, GT12-2, GT12-5 and GT12-7) was prepared according to the method used for the preparation of Compound Z10, Z11 and Z12. Further, demethylation was carried out according to the method used for the preparation of Compound A6 to obtain 8-hydroxy-6H-benzo[b]naphtho[2,3-d]furan-11-one which has a fluorine atom at corresponding position. Thereafter, according to Mitsunobu reaction used for the preparation of Compound A7-1 or the alkylation method used for the preparation of Compound A7-17, a corresponding side chain was introduced and, if necessary, functional group modification such as deprotection, etc. was carried out to prepare the compounds listed below.

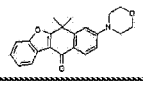
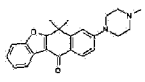
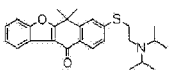
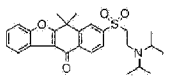
[Table 33]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1088	GT12-1		3-Fluoro-8-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	A	3.02	311.0
1089	GT12-2		4-Fluoro-8-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	A	3.00	311.0
1090	GT12-3		8-(2-Diethylamino-ethoxy)-3-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	4.48	396.0
1091	GT12-4		3-Fluoro-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.91	401.4
1092	GT12-5		2-Fluoro-8-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.01	311.0
1093	GT1 2-6		8-(2-Diethylamino-ethoxy)-2-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	209	395.0
1094	GT12-7		1-Fluoro-8-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	6.26	311.0
1095	GT12-8		8-((R)-2,3-Dihydroxy-propoxy)-2-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	2.22	371.0
1096	GT12-9		8-(2-Diethylamino-ethoxy)-1-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	4.20	396.0
1097	GT12-10		8-((R)-2,3-Dihydroxy-propoxy)-3-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	4.82	371.0

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1098	GT12-11		8-((R)-2,3-Dihydroxy-propoxy)-4-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	D	1.80	371.0
1099	GT12-12		8-((R)-2,3-Dihydroxy-propoxy)-1-fluoro-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	D	1.85	371.0

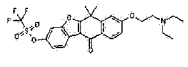
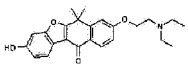
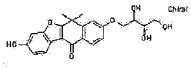
[1951] The compounds described in the following Table 34 were synthesized according to the method shown below. 8-Hydroxy-6H-benzo[b]naphtho[2,3-d]furan-11-one was transformed into trifuloromethanesulfonic acid ester according to the method used for the preparation of Compound B 1. Subsequently, by carrying out the method used for the preparation of Compound B2-1 or Compound B2-18, Compound GT13-1, Compound GT13-2 and Compound GT13-3 were prepared. Compound GT13-3 was oxidized according to the method used for the preparation of Compound B3-8 to prepare Compound 13-4.

[Table 34]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1100	GT13-1		6,6-Dimethyl-8-morpholin-4-yl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	3.04	348.2	B1, B2-1
1101	GT13-2		6,6-Dimethyl-8-(4-methyl-piperazin-1-yl)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.13	361.3	B1, B2-1
1102	GT13-3		8-(2-Diisopropylamino-ethylsulfanyl)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.45	422.0	B1, B2-18
1103	GT13-4		8-(2-Diisopropylamino-ethanesulfonyl)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	C	3.23	454.0	B3-8

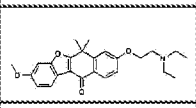
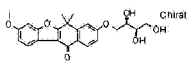
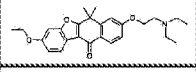
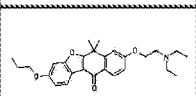
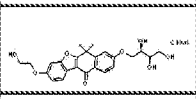
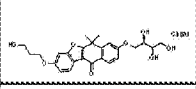
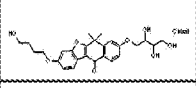
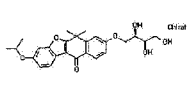
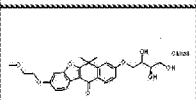
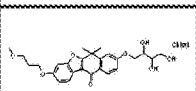
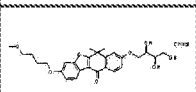
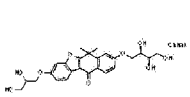
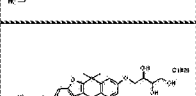
[1952] The compounds described in the following Table 35 were synthesized according to the method shown below. Specifically, a side chain was introduced to Compound Z13 to prepare Compound GT13-5 according to the method that is used for the preparation of Compound A7-17. Further Compound GT13-5 or trifuloromethanesulfonic acid ester of Compound Z14 was hydrolyzed to prepare Compound GT13-6 and Compound GT13-7 according to the method used for the preparation of Compound T20.

[Table 35]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1104	GT13-5		Trifluoro-methanesulfonic acid 8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	H	5.37	526.0	A7-17
1105	GT13-6		8-(2-Diethylamino-ethoxy)-3-hydroxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	3.40	394.0	T20
1106	GT13-7		3-Hydroxy-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	1.87	399.0	T20

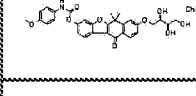
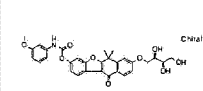
[1953] The compounds described in the following Table 36 were prepared by subjecting Compound GT13-6 or GT13-7 to Mitsunobu reaction that is used for the preparation of Compound A7-1 to introduce a corresponding side chain or a synthetic equivalent. After that, by carrying out deprotection, if necessary, the compounds listed below were prepared.

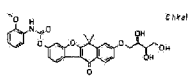
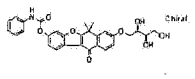
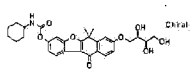
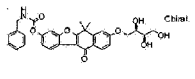
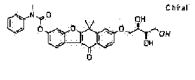
[Table 36]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1107	GT13-8		8-(2-Diethylamino-ethoxy)-3-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.72	408.0	A7-1
1108	GT1 3-9		3-Methoxy-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	B	4.23	413.2	A7-1
1109	GT13-10		8-(2-Diethylamino-ethoxy)-3-ethoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.10	422.0	A7-1
1110	GT13-11		8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-propoxy-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.63	436.0	A7-1
1111	GT13-12		3-(2-Hydroxy-ethoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	1.83	443.0	A7-1
1112	GT13-13		3-(3-Hydroxy-propoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	1.94	457.0	A7-1
1113	GT13-14		3-(4-Hydroxy-butoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.01	471.0	A7-1
1114	GT13-15		3-Isopropoxy-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.40	441.0	A7-1
1115	GT13-16		3-(2-Methoxy-ethoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.17	457.0	A7-1
1116	GT13-17		3-(3-Methoxy-propoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.34	471.0	A7-1
1117	GT13-18		3-(4-Methoxy-butoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.45	485.0	A7-1
1118	GT13-19		3-((S)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	1.69	473.0	A7-1 A7-14-11
1119	GT13-20		3-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	169	473.0	A7-1 A7-14-1

[1954] The compounds described in the following Table 37 were prepared from Compound GT13-7 according to carbamation that is used for the preparation of Compound A9-1.

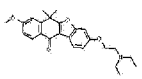
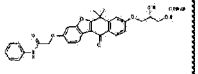
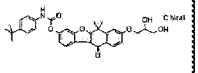
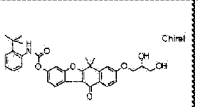
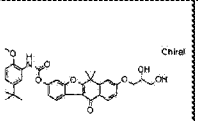
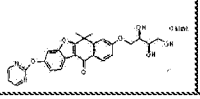
[Table 37]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1120	GT13-21		(4-Methoxy-phenyl)-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.34	548.2	A9-1
1121	GT13-22		(3-Methoxy-phenyl)-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.69	548.2	A9-1
			(2-Methoxy-phenyl)-carbamic acid				

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1122	GT13-23		6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.99	548.3	A9-1
1123	GT13-24		Phenyl-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.67	518.2	A9-1
1124	GT13-25		Cyclohexyl-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.94	524.2	A9-1
1125	GT13-26		Benzyl-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	A	2.09	532.3	A9-1
1126	GT13-27		Methyl-phenyl-carbamic acid 6,6-dimethyl-11-oxo-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	4.88	532.3	A9-1

[1955] The compounds described in the following Table 38 were prepared from corresponding intermediates by alkylation and carbamation based on the method described in the Table.

[Table 38]

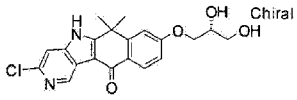
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1127	GT13-28		3-(2-Diethylamino-ethoxy)-8-methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.65	408.0	A7-17
1128	GT1 3-29		2-[8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yloxy]-*N*-phenyl-acetamide	B	4.70	502.0	A7-17 A8-1 T13-3
1129	GT13-30		(4-*tert*-Butyl-phenyl)-carbamic acid 8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	6.19	544.3	A9-1
1130	GT13-31		(2-*tert*-Butyl-phenyl)-carbamic acid 8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	5.74	544.3	A9-1
1131	GT13-32		(5-*tert*-Butyl-2-methoxy-phenyl)-carbamic acid 8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[*b*]naphtho[2,3-*d*]furan-3-yl ester	B	6.52	574.3	A9-1
1132	GT13-33		6,6-Dimethyl-3-(pyrimidin-2-yloxy)-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	4.14	477.0	A7-17

[Example 1133]

Compound GT14-1

3-Chloro-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-5,6-dihydro-benzo[f]pyrid[4,3-b]indol-11-one

[1956]



[1957] Compound BZ2-2 was demethylated according to the method used for the preparation of Compound A6, and subsequently introduced with a substituent group and deprotected according to the method used for the preparation of Compound A7-14-1 and A7-14-2.

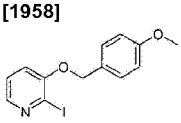
LCMS: m/z 386 $[M+H]^+$
HPLC retention time: 3.02 min (analysis condition B)

[Example 1134]

Compound GT15-1

2-Iodo-3-(4-methoxy-benzyloxy)-pyridine

[1958]



[1959] 2-Iodo-pyridin-3-ol (50 mg, 0.226 mmol), K_2CO_3 (62 mg, 0.452 mmol) and DMF (2 ml) were added with para-methoxybenzyl chloride (46 µL, 0.339 mmol), and the mixture was stirred overnight at 45°C. The resultant was added with water, and then extracted with ethyl acetate. The organic layer was washed with saturated brine, and the resulting residues obtained after concentration under reduced pressure were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (21 mg, 27%).

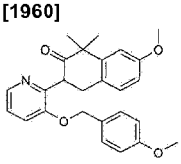
LCMS: m/z 342 $[M+H]^+$
HPLC retention time: 3.44 min (analysis condition Y)

[Example 1135]

Compound GT15-2

7-Methoxy-3-[3-(4-methoxy-benzyloxy)-pyridin-2-yl]-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1960]



[1961] Toluene (0.5 ml) was added to 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 36 mg), 2-iodo-3-(4-methoxy-benzyloxy)-pyridine (Compound GT15-1, 50 mg), sodium t-butoxide (35.3 mg), Pd_2dba_3 (13.5 mg) and Xantphos (17 mg), and the mixture was stirred and heated at 80°C for 2.5 hrs under nitrogen atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate and subjected to Celite filtration. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel

column (ethyl acetate/hexane) to obtain the title compound (27 mg, 44%).

LCMS: m/z 419 $[M+H]^+$

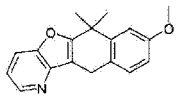
HPLC retention time: 3.31 min (analysis condition Y)

[Example 1136]

Compound GT15-3

8-Methoxy-10,10-dimethyl-5,10-dihydro-11-oxa-4-aza-benzo[b]fluorene

[1962]



[1963] To the mixture of 7-methoxy-3-[3-(4-methoxy-benzyloxy)-pyridin-2-yl]-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound GT15-2, 21 mg) and ethyl acetate (0.8 ml), sulfuric acid (0.2 ml) was added. The mixture was stirred and heated at 70°C for 5 hrs. After cooling, the reaction mixture was neutralized with 2 N aqueous solution of sodium hydroxide. The mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (7 mg, 50%).

LCMS: m/z 280 $[M+H]^+$

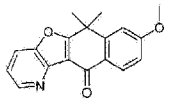
HPLC retention time: 2.71 min (analysis condition Y)

[Example 1137]

Compound GT15-4

8-Methoxy-10,10-dimethyl-10H-11-oxa-4-aza-benzo[b]fluoren-5-one

[1964]



[1965] 8-Methoxy-10,10-dimethyl-5,10-dihydro-11-oxa-4-aza-benzo[b]fluorene (Compound GT15-3, 22 mg) was dissolved in MeCN (0.26 ml) and water (0.13 ml), added with sodium chlorite (14 mg) and N-hydroxyphthalimide (2.6 mg), and the mixture was stirred at 40°C for 1 hr. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (16 mg, 70%).

LCMS: m/z 294 $[M+H]^+$

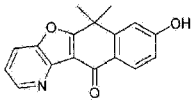
HPLC retention time: 2.85 min (analysis condition Y)

[Example 1138]

Compound GT15-5

8-Hydroxy-10,10-dimethyl-10H-11-oxa-4-aza-benzo[b]fluoren-5-one

[1966]



[1967] Mixture of 8-methoxy-10,10-dimethyl-10H-11-oxa-4-aza-benzo[b]fluoren-5-one (Compound GT15-4, 25 mg) and pyridine hydrochloric acid salt (492 mg) was stirred and heated at 178°C overnight. The reaction mixture was cooled, and added with water. The mixture was neutralized with saturated aqueous solution of sodium bicarbonate and extracted with DCM. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (DCM/MeOH) to obtain the title compound (13 mg, 54%).

LCMS: m/z 280 $[M+H]^+$

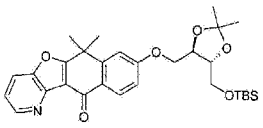
HPLC retention time: 2.30 min (analysis condition Y)

[Example 1139]

Compound GT15-6

8-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-10,10-dimethyl-10H-11-oxa-4-aza-benzo[b]fluoren-5-one

[1968]



[1969] In the same manner as Compound A7-1, the title compound was synthesized from Compound GT15-5 and Compound T22-0 (29 mg, 50%).

LCMS: m/z 538 $[M+H]^+$

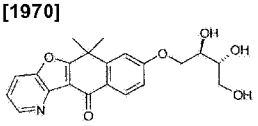
HPLC retention time: 3.64 min (analysis condition Y)

[Example 1140]

Compound GT15-7

10,10-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-10H-11-oxa-4-aza-benzo[b]fluoren-5-one

[1970]



[1971] To the mixture of 8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy]-10,10-dimethyl-10H-11-oxa-4-aza-benzo[b]fluoren-5-one (Compound GT15-6, 27 mg), MeOH (0.1 ml) and THF (0.3 ml), 0.5 N sulfuric acid (0.1 ml) was added, and the mixture was stirred and heated at 55 to 60°C for 4 hrs. The reaction mixture was neutralized with saturated aqueous solution of sodium bicarbonate. The resulting solid was filtered and washed with diethyl ether. The filtrate was extracted with the mixture solution of DCM and MeOH (DCM : MeOH = 10 : 1). The organic layer was washed with saturated brine, and dried over magnesium sulfate. The filtered solid and the residues obtained after concentration under reduced pressure were combined and purified by silica gel column (DCM/MeOH) to obtain the title compound (5.4 mg, 28%).

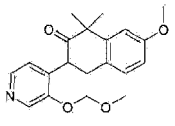
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 2.02 min (analysis condition Y)

[Example 1141]

Compound GT15-8

7-Methoxy-3-(3-methoxymethoxy-pyridin-4-yl)-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1972]



[1973] To 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 924 mg), 4-iodo-3-methoxymethoxy-pyridine (1 g), sodium t-butoxide (906 mg), Pd_2dba_3 (173 mg) and S-Phos (185 mg), toluene (19 ml) was added, and the mixture was stirred and heated at 70°C for 2 hrs under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate and filtered through Celite. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (610 mg, 47%).

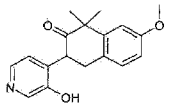
LCMS: m/z 342 $[M+H]^+$
HPLC retention time: 2.60 min (analysis condition Y)

[Example 1142]

Compound GT15-9

3-(3-Hydroxy-pyridin-4-yl)-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1974]



[1975] Mixture of 7-methoxy-3-(3-methoxymethoxy-pyridin-4-yl)-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound GT15-8, 430 mg) and 4 N hydrochloric acid dioxane solution (5 ml) was heated and stirred at room temperature for 1.5 hrs. The reaction mixture was neutralized with 2 N aqueous solution of sodium hydroxide. The resulting mixture was extracted with the mixture of DCM and MeOH (DCM : MeOH = 9 : 1). The residues obtained after concentration under reduced pressure were purified by silica gel column (DCM/MeOH) to obtain the title compound (280 mg, 75%).

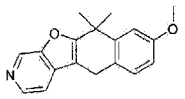
LCMS: m/z 298 $[M+H]^+$
HPLC retention time: 2.41 min (analysis condition Y)

[Example 1143]

Compound GT15-10

8-Methoxy-10,10-dimethyl-5,10-dihydro-11-oxa-2-aza-benzo[b]fluorene

[1976]



[1977] Mixture of 3-(3-hydroxy-pyridin-4-yl)-7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound GT15-9, 270 mg) and methanesulfonic acid (1 ml) was stirred and heated at 110°C for 0.5 hrs. After cooling, the reaction mixture was neutralized with 2 N aqueous solution of sodium hydroxide. The resulting mixture was extracted with the mixture of DCM and MeOH (DCM : MeOH = 9 : 1). The organic layer was concentrated under reduced pressure, and the resulting residues were purified by silica gel column (DCM/MeOH) to obtain the title compound (110 mg, 43%).

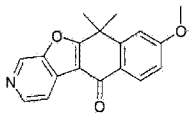
LCMS: m/z 280 $[M+H]^+$
HPLC retention time: 2.53 min (analysis condition Y)

[Example 1144]

Compound GT15-11

8-Methoxy-10,10-dimethyl-10H-11-oxa-2-aza-benzo[b]fluoren-5-one

[1978]



[1979] 8-Methoxy-10,10-dimethyl-5,10-dihydro-11-oxa-2-aza-benzo[b]fluorene (Compound GT15-10, 20 mg) was dissolved in acetonitrile (0.2 ml) and water (0.15 ml), added with sodium chlorite (16 mg) and N-hydroxyphthalimide (2.3 mg), and the mixture was stirred at 40°C for 40 min. To the reaction mixture, ethyl acetate was added. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (12 mg, 57%).

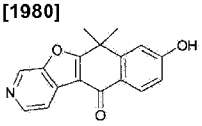
LCMS: m/z 294 $[M+H]^+$
HPLC retention time: 2.51 min (analysis condition Y)

[Example 1145]

Compound GT15-12

8-Hydroxy-10,10-dimethyl-10H-11-oxa-2-aza-benzo[b]fluoren-5-one

[1980]



[1981] DCM (0.34 ml) solution of 8-methoxy-10,10-dimethyl-10H-11-oxa-2-aza-benzo[b]fluoren-5-one (Compound GT15-11, 10 mg) was cooled to -78°C, added with the DCM solution (0.17 ml) of 1.0 M BBr_3, and the mixture was stirred at room temperature overnight. To the reaction mixture, water and saturated aqueous solution of sodium bicarbonate were added, and the solid produced therefrom was filtered off. The filtrate was extracted with the mixture solution of DCM and MeOH (DCM : MeOH = 9 : 1). The organic layer was washed with saturated brine. The filtered solid and the residues obtained after concentration under reduced pressure were combined to obtain the title compound (9.5 mg, 99%).

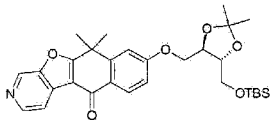
LCMS: m/z 280 $[M+H]^+$
HPLC retention time: 2.50 min (analysis condition Y)

[Example 1146]

Compound GT15-13

8-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-10,10-dimethyl-10H-11-oxa-2-aza-benzo[b]fluoren-5-one

[1982]



[1983] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound GT15-12 and Compound T22-0 (38 mg, 66%).

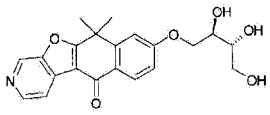
LCMS: m/z 538 $[M+H]^+$
HPLC retention time: 3.55 min (analysis condition Y)

[Example 1147]

Compound GT15-14

10,10-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-10H-11-oxa-2-aza-benzo[b]fluoren-5-one

[1984]



[1985] Under the same conditions as the method for synthesizing Compound GT15-7, the title compound was prepared from Compound GT15-13 (2.1 mg, 84%).

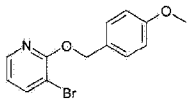
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 1.70 min (analysis condition Y)

[Example 1148]

Compound GT15-15

3-Bromo-2-(4-methoxy-benzyloxy)-pyridine

[1986]



[1987] Under the same conditions as the method for synthesizing Compound G15-1, the title compound was prepared from 3-bromo-pyridin-2-ol (740 mg, 88%).

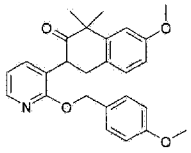
LCMS: m/z 295 $[M+H]^+$
HPLC retention time: 2.86 min (analysis condition Y)

[Example 1149]

Compound GT15-16

7-Methoxy-3-[2-(4-methoxy-benzyloxy)-pyridin-3-yl]-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one

[1988]



[1989] To 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 845 mg), 3-bromo-2-(4-methoxy-benzyloxy)-pyridine (Compound GT15-15, 1.46 g), sodium t-butoxide (597 mg), palladium acetate (18.6 mg) and tri-tert-butylphosphine tetrafluoroboric acid (21 mg), toluene (10 ml) and THF (2 ml) were added and the mixture was stirred and heated at 90°C for 2.5 hrs under nitrogen atmosphere. After cooling, the reaction mixture was added with saturated aqueous solution of ammonium chloride, and then extracted with ethyl acetate. The organic layer was washed with saturated brine, and the residues obtained after concentration under reduced pressure were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (140 mg, 8%).

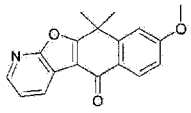
LCMS: m/z 419 $[M+H]^+$
HPLC retention time: 3.50 min (analysis condition Y)

[Example 1150]

Compound GT15-17

8-Methoxy-10,10-dimethyl-10H-11-oxa-1-aza-benzo[b]fluoren-5-one

[1990]



[1991] Under the same conditions as the method for synthesizing Compound GT15-3, the title compound was prepared from Compound GT15-16 (49 mg, 52%).

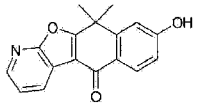
LCMS: m/z 294 $[M+H]^+$
HPLC retention time: 3.39 min (analysis condition Y)

[Example 1151]

Compound GT15-18

8-Hydroxy-10,10-dimethyl-10H-11-oxa-1-aza-benzo[b]fluoren-5-one

[1992]



[1993] Under the same conditions as the method for synthesizing Compound GT15-5, the title compound was prepared from Compound GT15-17 (6.5 mg, 51%).

LCMS: m/z 280 $[M+H]^+$

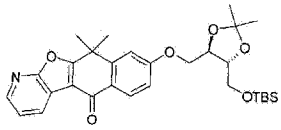
HPLC retention time: 3.10 min (analysis condition Y)

[Example 1152]

Compound GT15-19

8-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-10,10-dimethyl-10H-11-oxa-1-aza-benzo[b]fluoren-5-one

[1994]



[1995] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound GT15-18 and Compound T22-0 (4.5 mg, 11%).

LCMS: m/z 538 $[M+H]^+$

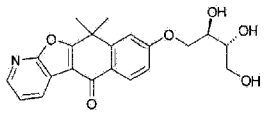
HPLC retention time: 3.88 min (analysis condition Y)

[Example 1153]

Compound GT15-20

10,10-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-10H-11-oxa-1-aza-benzo[b]fluoren-5-one

[1996]



[1997] Under the same conditions as the method for synthesizing Compound GT15-7, the title compound was prepared from Compound GT15-19 (7.9 mg, 51%).

LCMS: m/z 384 $[M+H]^+$

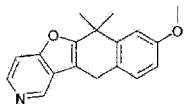
HPLC retention time: 2.57 min (analysis condition Y)

[Example 1154]

Compound GT15-21

8-Methoxy-10,10-dimethyl-5,10-dihydro-11-oxa-3-aza-benzo[b]fluorene

[1998]



[1999] To 7-methoxy-1,1-dimethyl-3,4-dihydro-1H-naphthalen-2-one (Compound A2, 2.5 g), 3-bromo-4-chloro-pyridine (2 g), sodium t-butoxide (3 g), Pd_2dba_3 (476 mg), and S-Phos (512 mg), toluene (20 ml) was added, and the mixture was stirred and heated at 100°C overnight under nitrogen atmosphere. After cooling, the reaction mixture was diluted with ethyl acetate and filtered through Celite. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine. Thereafter, the organic layer was dried over sodium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (112 mg, 4%).

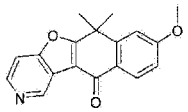
LCMS: m/z 280 $[M+H]^+$
HPLC retention time: 2.46 min (analysis condition Y)

[Example 1155]

Compound GT15-22

8-Methoxy-10,10-dimethyl-10H-11-oxa-3-aza-benzo[b]fluoren-5-one

[2000]



[2001] Under the same conditions as the method for synthesizing Compound GT15-3, the title compound was prepared from Compound GT15-21 (49 mg, 52%).

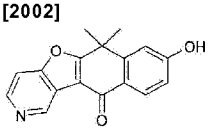
LCMS: m/z 294 $[M+H]^+$
HPLC retention time: 2.30 min (analysis condition Y)

[Example 1156]

Compound GT15-23

8-Hydroxy-10,10-dimethyl-10H-11-oxa-3-aza-benzo[b]fluoren-5-one

[2002]



[2003] Under the same conditions as the method for synthesizing Compound GT15-12, the title compound was prepared from

Compound GT15-22 (110 mg, 77%).

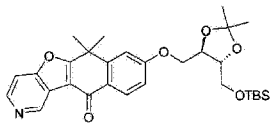
LCMS: m/z 280 $[M+H]^+$
HPLC retention time: 1.95 min (analysis condition Y)

[Example 1157]

Compound GT15-24

8-[(4R,5R)-5-(Tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-10,10-dimethyl-10H-11-oxa-3-aza-benzo[b]fluoren-5-one

[2004]



[2005] Under the same conditions as the method for synthesizing Compound A7-1, the title compound was prepared from Compound GT15-23 and Compound T22-0 (38 mg, 49%).

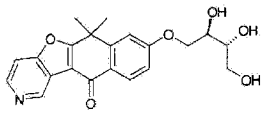
LCMS: m/z 538 $[M+H]^+$
HPLC retention time: 3.40 min (analysis condition Y)

[Example 1158]

Compound GT15-25

10,10-Dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-10H-11-oxa-3-aza-benzo[b]fluoren-5-one

[2006]



[2007] Under the same conditions as the method for synthesizing Compound GT15-7, the title compound was prepared from Compound GT15-24 (17 mg, 72%).

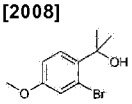
LCMS: m/z 384 $[M+H]^+$
HPLC retention time: 1.48 min (analysis condition Y)

[Example 1159]

Compound GT16-1

2-(2-Bromo-4-methoxy-phenyl)-propan-2-ol

[2008]



[2009] To the mixture of 1-(2-bromo-4-methoxyphenyl)-ethanone (300 mg) dissolved in THF solution (3 ml), MeMgBr (3 M THF solution, 0.52 ml) was added at 0°C under nitrogen atmosphere. Then, the mixture was stirred at room temperature for 6 hrs. The reaction mixture was added with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with saturated brine, and the residues obtained after concentration under reduced pressure were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (220 mg, 69%).

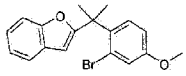
^{1}H-NMR ($CDCL_3$) δ : 7.55(1 H, d), 7. 14(1 H, d), 6. 83(1 H, dd), 3. 79(3 H, s), 2. 72(1 H, s), 1. 73(6 H, s)

[Example 1160]

Compound GT16-2

2-[1-(2-Bromo-4-methoxyphenyl)-1-methylethyl]benzofuran

[2010]



[2011] Mixture comprising 2-(2-bromo-4-methoxyphenyl)-propan-2-ol (100 mg), 2,3-benzofuran (0.19 ml) and polyphosphoric acid (1 g) was stirred and heated at 90°C for 30 min. The reaction mixture was added with water and extracted with DCM. The residues obtained after concentration under reduced pressure were purified by silica gel column (DCM/hexane) to obtain the title compound (143 mg, 51%).

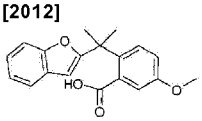
^{1}H-NMR ($CDCL_3$) δ : 7.4-7.5(1 H, m), 7. 3-7. 4(2 H, m), 7. 1-7. 25(3 H, m), 6. 87(1 H, dd), 6. 42(1 H, s) 3. 79(3 H, s), 1. 84(6 H, s)

[Example 1161]

Compound GT16-3

2-(1-Benzofuran-2-yl-1-methyl-ethyl)-5-methoxy-benzoic acid

[2012]



[2013] To the mixture comprising 2-[1-(2-bromo-4-methoxyphenyl)-1-methylethyl]benzofuran (140 mg) and THF (2 ml), n-butyl lithium (2.5 M solution, 0.17 ml) was added at -78°C under nitrogen atmosphere. The mixture was stirred for 20 min. The resulting reaction mixture was flushed with carbon dioxide gas for 15 min. Then, the reaction mixture was added with saturated aqueous solution of ammonium chloride and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and the residues obtained after concentration under reduced pressure were purified by silica gel column (DCM/MeOH) to obtain the title compound (68 mg, 54%).

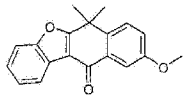
LCMS: m/z 311 $[M+H]^+$
HPLC retention time: 2.92 min (analysis condition Y)

[Example 1162]

Compound GT16-4

9-Methoxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2014]



[2015] To the DCM solution (1 ml) of 2-(1-benzofuran-2-yl-1-methylethyl)-5-methoxy benzoic acid (63 mg), trifuloroacetic anhydride (0.03 ml) was added at room temperature under nitrogen atmosphere. The mixture was stirred for 30 min. The reaction mixture was then added with water and extracted with DCM. The organic layer was dried over sodium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column (DCM) to obtain the title compound (50 mg, 84%).

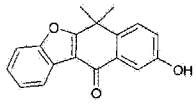
LCMS: m/z 293 $[M+H]^+$
HPLC retention time: 3.49 min (analysis condition Y)

[Example 1163]

Compound GT16-5

9-Hydroxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2016]



[2017] Under the same conditions as the method for synthesizing Compound A6, the title compound was prepared from Compound GT16-4.

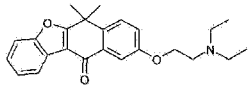
LCMS: m/z 279 $[M+H]^+$
HPLC retention time: 3.05 min (analysis condition Y)

[Example 1164]

Compound GT16-6

9-(2-Diethylamino-ethoxy)-6,6-dimethyl-6H-benzo[b]naphthor[2,3-d]furan-11-one

[2018]



[2019] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound GT16-5.

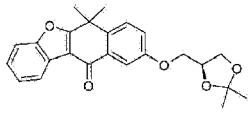
LCMS: m/z 378 $[M+H]^+$
HPLC retention time: 2.41 min (analysis condition Y)

[Example 1165]

Compound GT16-7

9-((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2020]



[2021] Under the same conditions as the method for synthesizing Compound A7-17, the title compound was prepared from Compound GT16-5 and toluene-4-sulfonic acid (R)-2,2-dimethyl-[1,3]dioxolan-4-yl methyl ester.

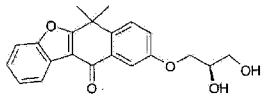
LCMS: m/z 393 $[M+H]^+$
HPLC retention time: 3.22 min (analysis condition Y)

[Example 1166]

Compound GT16-8

9-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2022]



[2023] Under the same conditions as the method for synthesizing Compound A7-14-2, the title compound was prepared from Compound GT16-7.

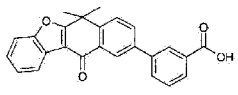
LCMS: m/z 353 $[M+H]^+$
HPLC retention time: 2.83 min (analysis condition Y)

[Example 1167]

Compound GT16-9

3-(6,6-Dimethyl-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-9-yl)-benzoic acid

[2024]



[2025] In the same manner as Compound GT9-2, the title compound was synthesized from Compound GT16-5.

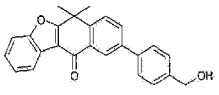
LCMS: m/z 383 $[M+H]^+$
HPLC retention time: 7.11 min (analysis condition H)

[Example 1168]

Compound GT16-10

9-(4-Hydroxyethyl-phenyl)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2026]



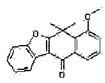
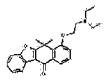
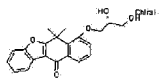
[2027] In the same manner as Compound GT9-2, the title compound was synthesized from Compound GT16-5.

LCMS: m/z 369 $[M+H]^+$

HPLC retention time: 6.97 min (analysis condition H)

[2028] The compounds described in the following Table 39 were synthesized according to the method shown below. Specifically, Compound GT17-1 was prepared from 8-methoxy-1,1-dimethyl-3,4-dihydro-1H naphthalen-2-one and bromophenol by following the method that is used for the preparation of Compound Z10, Z11 and Z12. Compound GT17-1 was demethylated according to the method used for the preparation of Compound A6, and as a result 7-hydroxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one was prepared. The resulting hydroxy compound was subjected to the alkylation according to the method used for the preparation of A7-1, or Mitsunobu reaction used for the preparation of Compound A7-17 for introducing a corresponding side chain or a synthetic equivalent thereof. Thereafter, if necessary, functional group modification was carried out to prepare Compound GT17-2 and Compound GT17-3.

[Table 39]

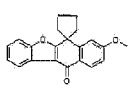
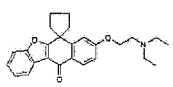
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1169	GT17-1		7-Methoxy-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	Y	13.42	293.0
1170	GT17-2		7-(2-Diethylamino-ethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	Y	9.92	378.0
1171	GT17-3		7-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	Y	11.68	353.0

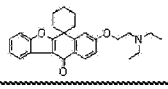
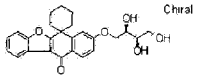
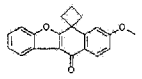
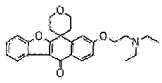
[2029] The compounds described in the following Table 40 were synthesized according to the method shown below.

[2030] By using the method used for the preparation of Compound Z10, Z11 and Z12, Compound GT18-1 was prepared from Compound M1 and bromophenol. Further, according to the method used for the preparation of Compound A6, Compound GT18-1 was demethyalted to prepare 8-hydroxy-11H-spiro[benzo[b]naphtho[2,3-d]furan-6,1'-cyclopentan]-11-one, which was then introduced with a side chain based on the alkylation that is used for the preparation of Compound A7-1. As a result, Compound GT18-2 was prepared.

[2031] The following spiro compounds were prepared from 7-methoxy-3,4-dihydro-1H-naphthalen-2-one and corresponding dibromide in the same manner as above.

[Table 40]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1172	GT18-1		8-methoxy-11H-spiro[benzo[b]naphtho[2,3-d]furan-6,1'-cyclo pentane]-11-one	Y	10.00	313.0
1173	GT18-2		8-(2-diethylarnirio-ethoxy)-11 H-spiro[benzo[b]niphtho[2,3-d]furan-6,1'-cyclopentane]-11-one	C	2.19	404.0

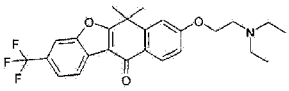
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1174	GT18-3		8-(2-diethylamino-ethoxy)-11H-spiro[beno[b]naphtho[2,3-d]furan-6,1'-cyclohexane]-11-one	C	3.28	418.2
1175	GT18-4		8- ((2R, 3R)-2, 3, 4-trihydroxybutoxy) -11 H-spiro[benzo[b]naphtho[2,3-d]furan-6,1'-cyclohexane]-11-one	A	2.26	423.2
1176	GT18-5		8-methoxy-11H-spiro[benzo[b]naphtho[2,3-d]furan-6,1'-cyclobutane]-11-one	Y	9.00	305.0
1177	GT18-6		8-(2-diethylamino-ethoxy)-2',3',5',6'-tetrahydro-11H-spiro[benzo[b]naphtho[2,3-d]furan-6,4'-pyran]-11-one	B	4.05	420.3

[Example 1178]

Compound GT19-1

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-trifuloromethyl-6H-benzo[B]naphtho[2,3-d]iuran-11-one

[2032]



[2033] According to the method described before, the preparation was carried out by using 7-methoxy-1,1-dimethyl-3,4-dihydro-1H naphthalen-2-one and 2-bromo-5-trifulorophenol.

LCMS: m/z 446 $[M+H]^+$

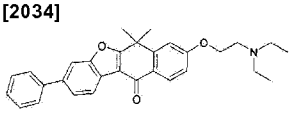
HPLC retention time: 3.25 min (analysis condition C)

[Example 1179]

Compound GT19-2

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-phenyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2034]



[2035] By carrying out Suzuki coupling of Compound GT23-5 and a corresponding boronic acid reagent based on the method that is used for the preparation of Compound GT9-2, the title compound was prepared.

LCMS: m/z 454 $[M+H]^+$

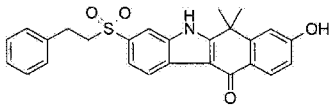
HPLC retention time: 2.67 min (analysis condition F)

[Example 1180]

Compound GT20-1

8-Hydroxy-6,6-dimethyl-3-(2-phenyl-ethanesulfonyl)-5,6-dihydro-benzo[b]carbazol-11-one

[2036]



[2037] 3-Bromo-8-hydroxy-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (72.2 mg, 0.203 mmol), 2-phenylethanethiol (0.0297 ml, 0.221 mmol), Pd_2dba_3 (9.3 mg, 0.0102 mmol), Xantphos (11.6 mg, 0.020 mmol) and ethyl diisopropylamine (0.068 ml, 0.40 mmol) were dissolved in dioxane (0.6 ml), and the mixture was stirred at 110°C for 16 hrs under nitrogen atmosphere. Water and ethyl acetate were added to the mixture to give a suspension, which was then filtered. The organic layer was washed with water and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane). The resulting residues were dissolved in THF (4 ml), and the supernatant liquid (2 ml) was taken and added with water (1 ml) and OXONE (99 mg). The resulting mixture was stirred at room temperature overnight. The reaction solution was partitioned between water and ethyl acetate. The organic layer was washed with brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (37.1 mg).

LCMS: m/z 446 $[M+H]^+$

HPLC retention time: 2.51 min (analysis condition F)

[Example 1181]

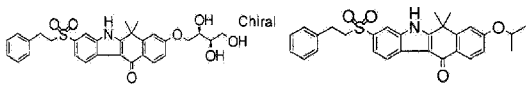
Compound GT20-2

6,6-Dimethyl-3-(2-phenyl-ethanesulfonyl)-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one and

Compound GT20-3

8-Isopropoxy-6,6-dimethyl-3-(2-phenyl-ethanesulfonyl)-5,6-dihydro-benzo[b]carbazol-11-one

[2038]



[2039] 8-Hydroxy-6,6-dimethyl-3-(2-phenyl-ethanesulfonyl)-5,6-dihydro-benzo[b]carbazol-11-one (30 mg, 0.0673 mmol), [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]methanol (22.3 mg, 0.0808 mmol), and PPh_3 (23 mg, 0.0875 mmol) were dissolved in THF (0.5 ml), added with DIAD (0.0169 ml, 0.0808 mmol), and the mixture was stirred at 50°C overnight. After cooling, the reaction solution was filtered and concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane). The resulting residues were dissolved in THF (0.4 ml) and water (0.13 ml), added with camphor sulfonic acid (28.1 mg, 0.121 mmol), and then subjected to microwave irradiation at 80°C for 15 min under nitrogen atmosphere. Ethyl acetate was added to the resultant. The organic layer was washed with saturated aqueous solution of sodium hydrocarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by thin layer chromatography (MeOH/DCM) to obtain Compound GT20-2 (10.5 mg) and Compound GT20-3 (2.4 mg).

Compound GT20-2

LCMS: m/z 550 $[M+H]^+$

HPLC retention time: 2.20 min (analysis condition F)

Compound GT20-3

LCMS: m/z 488 $[M+H]^+$

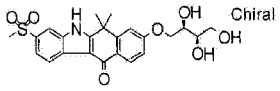
HPLC retention time: 3.13 min (analysis condition F)

[Example 1182]

Compound GT20-4

3-Methanesulfonyl-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-5,6-dihydro-benzo[b]carbazol-11-one

[2040]



[2041] The DMA solution (0.6 ml) comprising Compound GT23-2 (59.6 mg, 0.167 mmol), sodium methanethiolate (77 mg, 1.10 mmol), Pd_2dba_3 (23.7 mg, 0.0259 mmol) and Xantphos (29.7 mg, 0.0513 mmol) was subjected to microwave irradiation at 180°C for 30 min under nitrogen atmosphere. The reaction solution was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane and MeOH/DCM). The resulting solids were dissolved in THF (1 ml) and water (0.5 ml), and then added with OXONE (101.4 mg). The resulting mixture was stirred at room temperature for 2 hrs. The reaction solution was partitioned between water and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were suspended and washed with MTBE. The resulting solid was dissolved in THF (0.4 ml), and added with PPh_3 (37 mg, 0.141 mmol), [(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-methanol (39.0 mg, 0.141 mmol) and DEAD (2.2 M toluene solution, 0.064 ml, 0.141 mmol), and the mixture was stirred at 40°C for 4 hrs under nitrogen atmosphere. The reaction solution was partitioned between water and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (MeOH/DCM). Thus-obtained product was dissolved in THF (0.25 ml) and MeOH (0.05 ml), added with 0.5 M sulfuric acid (0.1 ml), and the mixture was stirred at 60°C for 5 hrs. After cooling, the mixture was added with diethyl ether and sodium hydrocarbonate (13 mg, 0.15 mmol). The separated aqueous layer was filtered, concentrated under reduced pressure, and suspended and purified with MeOH to obtain the title compound as a white solid (10.4 mg, 14%).

LCMS: m/z 460 $[M+H]^+$

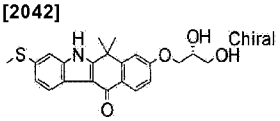
HPLC retention time: 1.71 min (analysis condition F)

[Example 1183]

Compound GT20-5

8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-methylsulfanyl-5,6-dihydro-benzo[b]carbazol-11-one

[2042]



[2043] 3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one (47.3 mg, 0.101 mmol), sodium methanethiolate (34.6 mg, 0.493 mmol), $Pd_2(dba)_3$ (13.1 mg, 0.0413 mmol), and Xantphos (17.9 mg, 0.0309 mmol) were dissolved in DMA (0.5 ml) and subjected to microwave irradiation at 200°C for 30 min under nitrogen atmosphere. The resultant was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by thin layer chromatography (ethyl acetate/ DCM). The resulting solid was dissolved in THF (0.23 ml) and MeOH (0.06 ml), and then added with 0.5 M sulfuric acid (0.12 ml). The resulting mixture was stirred at 60°C for 2 hrs. The reaction solution was diluted with diethyl ether and neutralized with

sodium hydrocarbonate (15.5 mg, 0.185 mmol). Thereafter, the solution was partitioned between brine and ethyl acetate. The organic layer was concentrated under reduced pressure. The resulting residues were added with diethyl ether. The precipitated solid was filtered to obtain the title compound as a white solid (15.8 mg, 39%).

LCMS: m/z 398 $[M+H]^+$

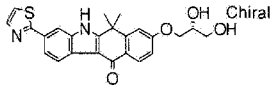
HPLC retention time: 4.46 min (analysis condition H)

[Example 1184]

Compound GT20-5

8-((R)-2,3-Dihydroxy-propoxy)-6,6-dimethyl-3-thiazol-2-yl-5,6-dihydro-benzo[b]carbazol-11-one

[2044]



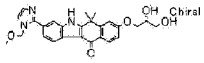
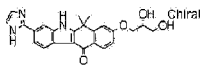
[2045] 3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-11-one (47 mg, 0.10 mmol), bis (pinacolate)diborone (33 mg, 0.13 mmol), Pd $(dppf)_2Cl_2 \cdot$ DCM (8.2 mg, 0.010 mmol) and potassium acetate (294 mg, 0.3 mmol) were dissolved in dioxane (0.6 ml), and the mixture was stirred at 100°C overnight under nitrogen atmosphere. The resultant was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/DCM) to obtain 8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-5,6-dihydro-benzo[b]carbazol-11-one (30.2 mg). The product (11 mg) was dissolved in DMA (0.4 ml), added with 2-bromothiazole (0.0038 ml, 0.0428 mmol), Pd $(PPh_3)_4$ (5.3 mg, 0.00459 mmol), potassium phosphate (27.4 mg, 0.129 mmol) and water (0.1 ml), and the mixture was subjected to microwave irradiation at 140°C for 7 min under nitrogen atmosphere. The resultant was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by thin layer chromatography (MeOH/DCM). The resulting solid was dissolved in MeOH (1 ml), and then added with 1 N HCl (3 drops). The resulting mixture was stirred at 60°C for 2 hrs. The reaction solution was concentrated under reduced pressure, and the residues obtained therefrom were suspended and washed with DCM/hexane (2/1) followed by drying to obtain the title compound as a yellow solid (8.7 mg).

LCMS: m/z 435 $[M+H]^+$

HPLC retention time: 1.76 min (analysis condition A)

[2046] The compounds described in the following Table 41 were also synthesized in the same manner.

[Table 41]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1185	GT20-6		8-((R)-2,3-Di hydroxy-propoxy)-3-(1-methoxymethyl-1*H*-imidazol-2-yl)-6,6-di methyl-5,6-di hydro-benzo[*b*]carbazol-11-one	B	2.63	462.0
1186	GT20-7		8-((R)-2,3-Dihydroxy-propoxy)-3-(1*H*-imidazol-2-yl)-6,6-dimethyl-5,6-dihydro-benzo[*b*]carbazol-11-one	B	2.45	418.5

[Example 1187]

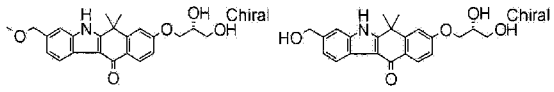
Compound GT20-8

8-((R)-2,3-Dihydroxy-propoxy)-3-methoxymethyl-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one and

Compound GT20-9

8-((R)-2,3-Dihydroxy-propoxy)-3-hydroxymethyl-6,6-dimethyl-5,6-dihydro-benzo[b]carbazol-11-one

[2047]



[2048] 3-Bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-5,6-dihydrobenzo[b]carbazol-ll-one (200.2 mg, 0.426 mmol), palladium acetate (II) (19 mg, 0.0848 mmol), hexacarbonyl molybdenum (115.5 mg, 0.438 mmol) and tris(o-tolyl)phosphine (52.5 mg, 0.172 mmol) were dissolved in THF (1.3 ml) and ethanol (0.075 ml), added with DBU (0.195 ml), and subjected to microwave irradiation at 160°C for 15 min under nitrogen atmosphere. The resulting reaction solution was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were dissolved in ethanol (10 ml) and THF (3 ml), added with 2 N KOH (2 ml), and stirred at room temperature for 2 hrs, at 50°C overnight and at 70°C for 2 hrs. The reaction solution was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were suspended and purified with MTBE/hexane (1/1) (155.4 mg). The THF solution (1.5 ml) of the product (109 mg) was added with TEA (0.052 ml, 0.373 mmol) and ethyl chloroformate (0.029 ml, 0.303 mmol) under ice cooling, and the mixture was stirred at 0°C for 2 hrs. Subsequently, ethanol (1 ml) and sodium borohydride (75.7 mg, 2.0 mmol) were added to the mixture, which was then stirred at room temperature for 2 hrs. The reaction solution was partitioned between aqueous solution of potassium dihydrophosphoric acid and ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (MeOH/DCM) (35.2 mg). Thus-obtained solid (9.6 mg) was dissolved in MeOH (1 ml), added with 1 N HCl (3 drops), and the mixture was stirred at 60°C for 90 min. After cooling and concentration under reduced pressure, the resultant was purified by TLC (MeOH/DCM) to obtain Compound GT20-8 (6.2 mg, white solid) and Compound GT20-9 (4.3 mg, white solid).
Compound GT20-8

LCMS: m/z 396 $[M+H]^+$
HPLC retention time: 1.66 min (analysis condition A)
Compound GT20-9

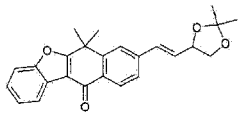
LCMS: m/z 382 $[M+H]^+$
HPLC retention time: 1.37 min (analysis condition A)

[Example 1188]

Compound GT21-1

8-[(E)-2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-vinyl]-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2049]



[2050] To the DMF solution (4 ml) of trifuloro-methanesulfonic acid 6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-8-yl ester (300 mg), 2,2-dimethyl-4-vinyl-[1,3]dioxolane (469 mg) and $PdCl_2(PPh_3)_2$ (103 mg), sodium hydrocarbonate (184 mg) was added, and the mixture was stirred at 100°C overnight under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (130 mg, 46%).

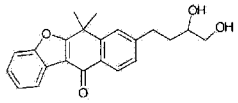
LCMS: m/z 389 $[M+H]^+$
HPLC retention time: 3.28 min (analysis condition Y)

[Example 1189]

Compound GT21-2

8-(3,4-Dihydroxy-butyl)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2051]



[2052] To the MeOH solution (5 ml) of 8-[(E)-2-(2,2-dimethyl-[1,3]dioxolan-4-yl)-vinyl]-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-ll-one (125 mg), 10% Pd-C (25 mg) was added and the mixture was stirred overnight at room temperature under hydrogen atmosphere. The catalyst was removed by filtration. The residues obtained after concentration under reduced pressure were purified by HPLC to obtain the title compound (35 mg, 31%).

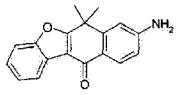
LCMS: m/z 351 $[M+H]^+$
HPLC retention time: 1.79 min (analysis condition Y)

[Example 1190]

Compound GT21-3

8-Amino-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2053]



[2054] To trifuloro-methanesulfonic acid 6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-8-yl ester (100 mg), benzhydrylideneamine (0.05 ml), cesium carbonate (110 mg), palladium acetate (2 mg) and BINAP (7 mg), THF (2 ml) was added. The mixture was stirred and heated at 65°C overnight under nitrogen atmosphere, and the reaction mixture was diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (16 mg, 23%).

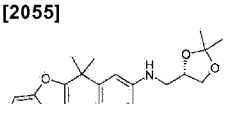
LCMS: m/z 278 $[M+H]^+$
HPLC retention time: 2.52 min (analysis condition Y)

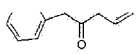
[Example 1191]

Compound GT21-4

8-[((S)-2,2-Dimethyl-[1,3]dioxolan-4-yl methyl)-aminol-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2055]





[2056] The mixture comprising 8-amino-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one (50 mg), (R)-4-iodomethyl-2,2-dimethyl-[1,3]dioxolane (104 mg), potassium carbonate (150 mg) and DMF (2 ml) was stirred and heated at 160°C for 2 days under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane). To the compound (71 mg) obtained therefrom, THF (1 ml) and conc. hydrochloric acid (8 drops) were added and the mixture was stirred at room temperature for 1 hr. The reaction mixture was added with saturated aqueous solution of sodium bicarbonate and then diluted with ethyl acetate. The organic layer was washed with saturated aqueous solution of sodium bicarbonate and saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (34 mg, 51%).

LCMS: m/z 392 $[M+H]^+$

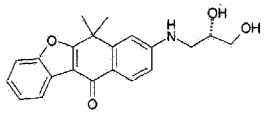
HPLC retention time: 3.11 min (analysis condition Y)

[Example 1192]

Compound GT21-5

8-((S)-2,3-Dihydroxy-propylamino)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2057]



[2058] In the same manner as Compound A7-14-2, Compound GT21-4 was deprotected to obtain the title compound.

LCMS: m/z 352 $[M+H]^+$

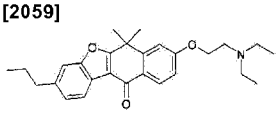
HPLC retention time: 2.26 min (analysis condition Y)

[Example 1193]

Compound GT22-1

8-(2-Diethylamino-ethoxy)-6,6-dimethyl-3-propyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2059]



[2060] To the mixture of trifluoro-methanesulfonic acid 8-(2-diethylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-3-yl ester (15 mg), which had been obtained in the same manner as Compound A7-25, tris(1-methyl-3-oxo-1-butenyloxy) iron (III) (1 mg), NMP (0.3 ml) and THF (0.3 ml), n-PrMgBr (0.88 M, THF solution, 0.291 ml) and zinc chloride (0.5 M THF solution, 0.114 ml) were added at 0°C under nitrogen atmosphere, and the mixture was stirred at 0°C for 10 min. The reaction mixture was added with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain the title compound (4.5 mg, 38%).

LCMS: m/z 420 $[M+H]^+$

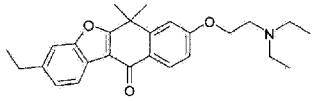
HPLC retention time: 5.77 min (analysis condition H)

[Example 1194]

Compound GT22-2

8-(2-Diethylamino-ethoxy)-3-ethyl-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2061]



[2062] In the same manner as Compound GT22-2, the title compound was synthesized.

LCMS: m/z 406 $[M+H]^+$

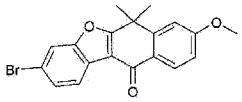
HPLC retention time: 5.12 min (analysis condition B)

[Example 1195]

Compound GT23-1

3-Bromo-8-methoxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2063]



[2064] 8-Methoxy-6,6-dimethyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-6H-benzo[b]naphtho[2,3-d]furan-11-one (10.3 mg), which had been synthesized from Compound Z12 under the same conditions as the method for synthesizing Compound GT20-5, was mixed with copper (II) bromide (16.5 mg), MeOH (0.5 ml) and water (0.25 ml), and the mixture was stirred and heated at 70°C for 2 hrs. DCM was added to the reaction solution for extraction. The organic layer was concentrated and purified by silica gel column to obtain the title compound (9.4 mg).

LCMS: m/z 371 $[M+H]^+$

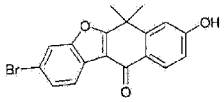
HPLC retention time: 7.55 min (analysis condition B)

[Example 1196]

Compound GT23-2

3-Bromo-8-hydroxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2065]



[2066] In the same manner as Compound GT15-5, 3-bromo-8-methoxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one was

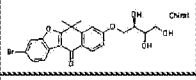
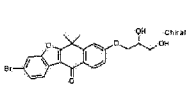
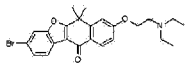
deprotected to obtain the title compound.

LCMS: m/z 357 $[M+H]^+$

HPLC retention time: 2.82 min (analysis condition A)

[2067] The compounds described in the following Table 42 were synthesized from Compound GT23-2 according to the method given in the Table.

[Table 42]

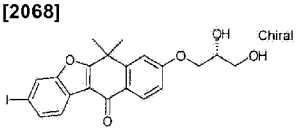
Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z	Method
1197	GT23-3		3-Bromo-6,6-dimethyl-8-((2R,3R)-2,3,4-tri hydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	D	2.30	461.0	T22-1-1 T22-2
1198	GT23-4		3-Bromo-8-((R)-2,3-dihydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furen-11-one	A	5.42	431.0	A7-14-1 A7614-2
1199	GT23-5		3-Bromo-8-(2-diethylamino-ethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.37	456.0	A7-17

[Example 1200]

Compound GT24-1

8-((R)-2,3-Dihydroxy-propoxy)-3-iodo-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2068]



[2069] To 3-bromo-8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one (15 mg, 0.032 mmol), CuI (6.2 mg, 0.032 mmol), NaI (9.6 mg, 0.064 mmol) and trans-N,N'-dimethylcyclohexane-1,2-diamine (0.01 ml) were added and the mixture was stirred for 48 hrs under nitrogen atmosphere. The reaction solution was diluted with ethyl acetate. The organic layer was washed with saturated brine, and then concentrated under reduced pressure. The resulting residues were purified by silica gel column (ethyl acetate/hexane) to obtain 8-((S)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy)-3-iodo-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one (16 mg, 97%), which was then deprotected according to the method of A-14-2 to give the title compound.

LCMS: m/z 479 $[M+H]^+$

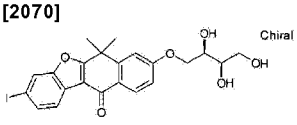
HPLC retention time: 4.26 min (analysis condition A)

[Example 1201]

Compound GT24-2

3-Iodo-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2070]



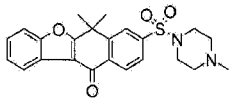
[2071] In the same manner as Compound GT24-1, 3-iodo-8-[(4R,5R)-5-(tert-butyldimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one was synthesized from 3-bromo-8-[(4R,5R)-5-(tert-butyl-dimethyl-silanyloxymethyl)-2,2-dimethyl-[1,3]dioxolan-4-yl methoxy]-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one. Subsequently, according to the same method as Compound T22-2, deprotection was carried out to obtain the title compound.

[Example 1202]

Compound GT25-1

6,6-Dimethyl-8-(4-methyl-piperazine-1-sulfonyl)-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2072]



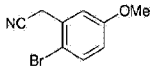
[2073] By using the method for preparing Compound B1, trifuloro-methanesulfonic acid 6,6-dimethyl-11-oxo-6,11-dihydro-benzo[b]naphtho[2,3-d]furan-8-yl ester was prepared from 8-hydroxy-6,6-dimethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one. This trifuloromethanesulfonic acid ester (205 mg), (2R)-1-[(1R)-1-[bis (1,1-dimethylethyl)phosphino] ethyl]-2-(dicyclohexylphosphino)ferrocene (13 mg), palladium acetate (6 mg), 2-trimethylsilanyl-ethanethiol (90 µL) and potassium carbonate (85 mg) were reacted in DME to obtain a product (120 mg). To the benzyl alcohol solution (90 µL) of the product (50 mg), DCM solution of N-chlorosuccinimide (90 mg) was added, and the mixture was stirred at room temperature. The reaction solution was partitioned between water and ethyl acetate, and the organic layer was concentrated under reduced pressure. To the DCM solution of thus-obtained white solid, N-methylpiperazine (10 µL) was added and the mixture was stirred. The residues obtained after removing the solvent by distillation were purified by TLC to obtain the title compound as a white solid (6 mg).

[Example 1203]

Compound GT26-1

(2-Bromo-5-methoxy-phenyl)-acetonitrile

[2074]



[2075] To the THF solution (1000 ml) of 2-bromo-5-methoxy-benzoic acid methyl ester (20 g, 81.6 mmol), the THF suspension (50 ml) of LAH (4.07 g, 102 mmol) was added under ice cooling. The mixture was stirred for 30 min under ice cooling. The reaction solution was partitioned between saturated aqueous solution of $Na2SO_4$ and ethyl acetate. The organic layer was washed with saturated brine and concentrated under reduced pressure. The resulting residues were dissolved in DCM (200 ml), and added with TEA (12.51 ml, 89.76 mmol) and MsCl (6.63 ml, 85.68 mmol) under ice cooling, followed by stirring overnight at room temperature. The reaction mixture was diluted with DCM, and washed in order with 10% aqueous solution of citric acid, saturated aqueous solution of $NaHCO_3$ and saturated brine. The residues obtained after concentration under reduced pressure were dissolved in DMF (100 ml), and added with the DMF (500 ml) solution of NaCN (40 g, 81.6 mmol) under ice cooling. After stirring for 2 hrs under ice cooling, the reaction mixture was extracted with ether, washed with saturated brine and dried over magnesium sulfate. The residues obtained after concentration under reduced pressure were purified by silica gel column (hexane : ethyl acetate = 10: 1) to obtain the title compound (12.1 g, 67%).

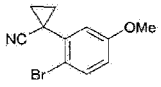
^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3 H), 6. 77(d, 1 H), 7. 07 (s, 1 H), 7. 47 (d, 1H)

[Example 1204]

1-(2-Bromo-5-methoxy-phenyl)-cyclopropane carbonitrile

Compound GT26-2

[2076]



[2077] 2-Bromo-5-methoxy-phenyl)-acetonitrile (12.2 g, 53.97 mmol) was dissolved in toluene (50 ml), and added with tetrabutylammonium bromide (3.55 g, 10.79 mmol), dibromoethane (7.05 ml, 80.95 mmol) and 50% aqueous solution of NaOH (50 ml) at room temperature. The mixture was stirred at room temperature for 4 hrs. The reaction mixture was added with water and extracted with ethyl acetate. The residues obtained after concentration under reduced pressure were purified by silica gel column (hexane : ethyl acetate) to obtain the title compound (11.18 g, 82%).

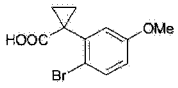
^{1}H-NMR (400 MHz, $CDCl_3$) δ 1. 33 (t, 1 H), 1. 76 (t, 1 H), 3. 79 (s, 3 H), 6. 75-6. 79(m, 1H), 6. 89 (d, 1H), 7. 47 (d, 1H)

[Example 1205]

1-(2-Bromo-5-methoxy-phenyl)-cyclopropane carboxylic acid

Compound GT26-3

[2078]



[2079] 1-(2-Bromo-5-methoxy-phenyl)-cyclopropane carbonitrile (3.0 g, 11.9 mmol) was dissolved in ethylene glycol (30 ml). After adding KOH (2.1 g, 33.3 mmol) thereto, the mixture was stirred and heated at 180°C for 7 hrs. After cooling, the reaction mixture was added with 1 N HCl (90 ml). The reaction mixture was extracted with ether, washed with water and saturated brine and dried over magnesium sulfate. After concentration under reduced pressure, the title compound was obtained (12.3 g, 72%).

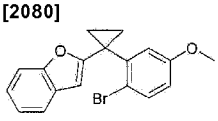
LCMS: m/z 272 $[M+H]^+$
HPLC retention time: 2.03 min (analysis condition Y)

[Example 1206]

Compound GT26-4

2-[1-(2-Bromo-5-methoxy-phenyl)-cyclopropyl]-benzofuran

[2080]



[2081] To the DCM solution (6 ml) of 1-(2-bromo-5-methoxy-phenyl)-cyclopropane carboxylic acid (0.3 g, 1.1 mmol), DMF (2 drops) and oxalyl chloride (0.23 ml, 2.5 mmol) were added at room temperature, and the mixture was stirred at room temperature for 2 hrs.

The residues obtained from the reaction solution after concentration under reduced pressure were dissolved in toluene (6 ml), added with (2-hydroxybenzyl)triphenylphosphonium bromide (0.605 g, 1.32 mmol) and TEA (0.46 ml, 3.3 mmol), and the resulting mixture was stirred and heated at 100°C overnight. The residues obtained after concentration under reduced pressure were purified by silica gel column (hexane : DCM) to obtain the title compound (0.309 g, 81%).

LCMS: m/z 343 $[M+H]^+$

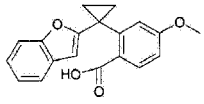
HPLC retention time: 3.55 min (analysis condition Y)

[Example 1207]

Compound GT26-5

2-(1-Benzofuran-2-yl-cyclopropyl)-4-methoxy-benzoic acid

[2082]



[2083] To the THF solution (3 ml) of 2-[1-(2-bromo-5-methoxy-phenyl)-cyclopropyl]-benzofuran (0.259 g, 0.75 mmol), n-BuLi was added at -78°C, and the mixture was stirred at -78°C for 20 min. Thereafter, the mixture was flushed with carbon dioxide gas. The reaction mixture was added with saturated solution of NH_4Cl and extracted with ethyl acetate. The residues obtained after concentration under reduced pressure were purified by silica gel column (DCM : MeOH) to obtain the title compound (0.163 g, 70%).

LCMS: m/z 309 $[M+H]^+$

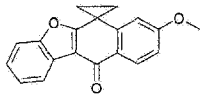
HPLC retention time: 2.67 min (analysis condition Y)

[Example 1208]

Compound GT26-6

8-Methoxy-11H-spiro[benzo[d]naphtho[2,3-b]furan-6,1'-cyclopropan]-11-one

[2084]



[2085] To the DCM solution (10 ml) of 2-(1-benzofuran-2-yl-cyclopropyl)-4-methoxybenzoic acid (1.0 g, 3.24 mmol), trifuloroacetic acid anhydride (0.45 ml, 3.24 mmol) was added at -78°C, and the mixture was stirred at -78°C for 10 min, at -50°C for 10 min, and at -30°C for 20 min. Thereafter, the mixture was added with water and extracted with DCM. The residues obtained after concentration under reduced pressure were washed with DCM and hexane to obtain the title compound (0.163 g, 70%).

LCMS: m/z 291 $[M+H]^+$

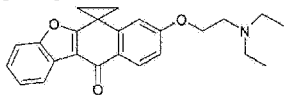
HPLC retention time: 2.90 min (analysis condition Y)

[Example 1209]

Compound GT26-7

8-(2-(Diethylamino)ethoxy)-11H-spiro[benzo[d]naphtho[2,3-b]furan-6,1'-cyclopropan]-11-one

[2086]



[2087] In the same manner as Compound A6 and Compound A7-17, the title compound was obtained from 8-methoxy-11H-spiro[benzo[d]naphtho[2,3-b]furan-6,1'-cyclopropan]-11-one.

LCMS: m/z 376 $[M+H]^+$

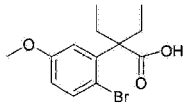
HPLC retention time: 1.65 min (analysis condition Y)

[Example 1210]

Compound GT27-1

2-(2-Bromo-5-methoxy-phenyl)-2-ethyl-butyric acid

[2088]



[2089] (2-Bromo-5-methoxy-phenyl)-acetic acid methyl ester (3.51 g, 13.5 mmol) was dissolved in DMF (4.5 ml), and added with NaH (2.1 g, 67.7 mmol). Subsequently, 15-crown-5 (1.38 ml, 6.8 mmol) and EtI (5.5 ml, 67.7 mmol) cooled to 0°C were added to the mixture. The mixture was diluted with ethyl acetate and washed with water and saturated brine. The residues obtained after concentration under reduced pressure were purified by silica gel column (hexane-ethyl acetate). Then, the resultant was dissolved in ethanol (80 ml) and water (80 ml), added with KOH (91 g), and stirred at 140°C. The reaction solution was extracted with ethyl acetate, and washed with water and saturated brine. After concentration under reduced pressure, the target compound was obtained (10.62 g, 78%).

LCMS: m/z 301 $[M+H]^+$

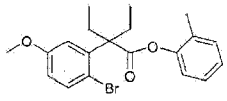
HPLC retention time: 3.07 min (analysis condition Y)

[Example 1211]

Compound GT27-2

2-(2-Bromo-5-methoxy-phenyl)-2-ethyl-butyric acid o-tolyl ester

[2090]



[2091] Compound GT27-1 (0.5 g, 1.66 mmol) was dissolved in DCM (10 ml), added with DMF (2 drops) and oxalyl chloride (0.28 ml, 3.32 mmol), and the mixture was stirred for 2 hrs. The reaction mixture obtained after concentration under reduced pressure was dissolved in toluene (5 ml), added with DMAP (406 mg, 3.32 mmol), and the mixture was heated under reflux. The reaction mixture was extracted with ethyl acetate, washed with 1 N HCl, and saturated brine. The residues obtained after concentration under reduced pressure were purified by silica gel column (hexane-ethyl acetate) to obtain the target compound (0.36 g, 86%).

LCMS: m/z 393 $[M+H]^+$

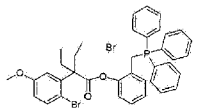
HPLC retention time: 3.03 min (analysis condition Y)

[Example 1212]

Compound GT27-3

2-(2-Bromo-5-methoxy-phenyl)-2-ethyl-butyric acid 2-[(triphenyl-phosphanyl)-methyl]-phenyl ester bromate salt

[2092]



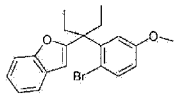
[2093] Compound GT27-2 (0.118 g, 0.302 mmol) was dissolved in carbon tetrachloride (3 ml), added with N-bromosuccinimide (54 mg, 0.302 mmol), and the mixture was heated under reflux. The reaction mixture was concentrated under reduced pressure and the resulting residues were purified by silica gel column (ethyl acetate-hexane). The product was dissolved in toluene (3 ml), added with PPh_3 (77 mg, 0.302 mmol), and the mixture was heated under reflux. The reaction mixture was concentrated under reduced pressure to obtain the target compound (130 mg, 57%).

[Example 1213]

Compound GT27-4

2-[1-(2-Bromo-5-methoxy-phenyl)-1-ethyl-propyl]-benzofuran

[2094]



[2095] To the toluene solution (3 ml) of Compound GT27-3 (0.14 g, 0.137 mmol), toluene solution (0.16 ml, 0.164 mmol) of 1 M LiHMDS was added. The mixture was heated and stirred for 4 hrs. The reaction mixture was concentrated under reduced pressure and the resulting residues were purified by silica gel column (ethyl acetate : hexane) to obtain the title compound (28 mg, 35%).

LCMS: m/z 373 $[M+H]^+$

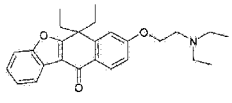
HPLC retention time: 2.73 min (analysis condition Y)

[Example 1214]

Compound GT27-5

8-(2-Diethylamino-ethoxy)-6,6-diethyl-6H-benzo[b]naphtho[2,3-d]furan-11-one

[2096]



[2097] In the same manner as Compound A7-17, the title compound was obtained from Compound GT27-4.

LCMS: m/z 407 $[M+H]^+$

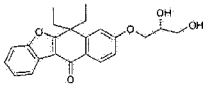
HPLC retention time: 1.92 min (analysis condition Y)

[Example 1215]

Compound GT27-6

8-((R)-2,3-Dihydroxy-propoxy)-6,6-diethyl-6H benzo[b]naphtho[2,3-d]furan-11-one

[2098]



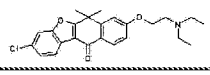
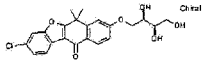
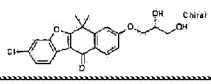
[2099] In the same manner as Compound A7-14-1 and Compound A7-14-2, the title compound was obtained from Compound GT27-4.

LCMS: m/z 381 $[M+H]^+$

HPLC retention time: 2.38 min (analysis condition Y)

[2100] The compounds described in the following Table 43 were synthesized according to the method shown below. According to the method used for the preparation of Compound Z10, Z11 and Z12, 3-chloro-8-methoxy-6H-benzo[b]naphtho[2,3-d]furan-11-one was prepared from Compound A2 and 2-bromo-5-chlorophenol. Subsequently, demethylation was carried out according to the method that is used for the preparation of Compound A6, and thus 3-chloro-8-hydroxy-6H-benzo[b]naphtho[2,3-d]furan-11-one was obtained. Thereafter, according to Mitsunobu reaction that is used for the preparation of Compound A7-1 or the alkylation method that is used for the preparation of A7-17, a corresponding side chain was introduced and, if necessary, functional group modification such as deprotection, etc. was carried out to prepare the compounds listed below.

[Table 43]

Example No.	Comp. No.	Structure	Compound Name	HPLC Condition	Retention Time	m/z
1216	GT28-1		3-Chloro-8-(2-diethylamino-ethoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	F	2.52	412.0
1217	GT28-2		3-Chloro-6,6-dimethyl-8-((2R,3R)-2,3,4-trihydroxy-butoxy)-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.39	417.0
1218	GT28-3		3-Chloro-8-((R)-2,3-di hydroxy-propoxy)-6,6-dimethyl-6*H*-benzo[*b*]naphtho[2,3-*d*]furan-11-one	H	5.77	387.0

Pharmacological testing method

1. Activity of inhibiting ALK enzyme

[2101] ALK-inhibiting activity was measured by following an activity of inhibiting phosphorylation by biotinylated peptide (EGPWLEEEEEAYGWMDF). For the detection of phosphorylation of the biotinylated peptide, time-resolved fluorescence measurement was performed using an anti-phosphorylated tyrosine antibody labeled with europium cryptate and streptavidin conjugated to XL665, i.e., an allophycocyanin derivative. From the inhibition ratio compared to the control group that does not comprise a test compound, 50% inhibitory concentration (i.e., IC_{50} value) was calculated.

2. Measurement of an activity of inhibiting Karpas-299 cell growth

[2102] The test compounds were serially diluted with dimethyl sulfoxide, further diluted with phosphate buffered saline which is free of any Ca^{2+}, Mg^{2+} (x 50 dilution), and 10 µL of the resulting solution was aliquoted in a 96-well plate. Human lymphoma cell line KARPAS-299 was prepared in RPMI-1640 medium to which 10% bovine fetal serum was added to give a cell suspension with the cell density of 10,000 cells/190 µL. The resulting cell suspension was aliquoted to the plate (190 µL per well) to which the test compound had been already added, and the plate was kept in a 5% carbon dioxide gas incubator at 37°C. Ninety-six hours later, 10 µL of WST-8 (manufactured by Dojindo Laboratories) was added to each well, and subsequently the absorbance was measured at 450 nm. From the ratio of inhibition on cell growth which had been obtained from the addition of a test compound compared to the control group with no addition, 50% growth inhibitory concentration (i.e., IC_{50} value) of the test compound was calculated. The results are summarized in Tables 44-49.

[Table 44]

Examples	ALK-inhibiting activity IC_{50}(µM)	Inhibitory activity on Karpas-299 cell growth IC_{50}(µM)
123 (Compound B2-27)	**0.00228**	**0.0138**
177 (Compound B4-7)	**0.00084**	**0.0105**
178 (Compound B4-8)	**0.00153**	**0.0214**
304(Compound F5-11)	**0.00081**	**0.0061**
338 (Compound F5-43)	**0.00032**	**0.0086**
341 (Compound F5-46)	**0.01056**	**0.0289**
364 (Compound F6-18)	**0.00177**	**0.0231**
366 (Compound F6-20)	**0.0053**	**0.0093**
372 (Compound G6)	**0.03074**	**0.1682**
380 (Compound H6-2)	**0.00053**	**0.0062**
429 (Compound J7-10-2)	**0.00083**	**0.0303**
543 (Compound O8-5)	**0.00032**	**0.03**
550 (Compound O9-7)	**0.00090**	**0.0044**
735 (Compound Z7)	**0.09385**	**1.1924**
516(Compound N6-2)	**0.003906748**	**0.0248**
725(Compound X5)	**0.687683357**	**2.8765**
882(Compound AZ7-10)	**0.000493765**	**0.005769**
916(Compound DZ7-1)	**0.001836659**	**0.357381**
937(Compound EZ9-3)	**0.006473484**	**0.056914**
939(Compound EZ9-5)	**0.399865279**	**13.421227**
1175(Compound GT18-4)	**0.093**	**2.012**

[Table 45]

Example No.	Compound	ALK-inhibiting activity IC_{50}(µM)
13	A7-1	0.052707597
14	A7-2	0.006159417
38	A7-20	0.026183852
39	A7-21	0.017713716
40	A7-22	0.030434111
41	A7-23	0.029469872
45	A8-2	0.008009528
47	A8-4	0.010253392
51	A8-6-3	0.097920152
52	A8-7	0.045959643
55	A8-10	0.00673264
57	A8-12	0.003594618
63	A8-18	0.016005139
65	A8-20	0.0029
67	A9-1	0.004943
70	A9-3-2	0.007649647
73	A9-6-2	0.001398207

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
74	A9-7	0.0034607
76	A9-9	0.017148495
78	A9-11	0.051123952
79	A9-12	0.017501168
83	A9-15-2	0.0035
84	A9-16	0.08468
90	B2-1	0.033572
100	B2-9	0.016225317
101	B2-10	0.039433518
102	B2-11	0.072607257
104	B2-13	0.001681324
109	B2-16-3	0.000980809
117	B2-23	0.005436966
118	B2-24	0.014834642
122	B2-26-2	0.007278245
124	B2-28	0.059632226
128	B3-2-2	0.003183521
130	B3-4	0.063798146
135	B3-9	0.01492317
137	B3-11	0.071084446
141	B3-14	0.011893599
142	B3-15	0.030133825
143	B3-16	0.027324427
146	B3-19	0.010369469
147	B3-20	0.026851192
149	B3-22	0.272356381
150	B3-23	0.023088404
151	B3-24	0.003610645
157	B3-27-2	0.002114607
158	B3-28	0.042375341
159	B3-29	0.006002322
165	B3-34	0.006783031
166	B3-35	0.003473067
168	B3-37	0.011859342
179	B4-9	0.002000975
187	CC4-2	0.096115639
189	C1-1	0.051102036
206	C4-9	0.005101172
210	C4-13	0.008752733
212	C4-15	0.009616778
226	D1	0.000991134
227	D2	0.003611773
228	D3-1	0.006279559
245	E4-5	0.009450575
256	E5-2	0.00133756
264	E6-2	0.006668071
265	E6-3	0.008113087
268	F1-3	0.005054399
277	F3-6-2	0.000167996

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
283	F4-1-1	0.001625048
286	F4-3	0.000951804
290	F4-7	0.001133931
293	F4-10	0.002098847
298	F5-5	0.002385717
300	F5-7	0.002575475
306	F5-13	0.002051837
314	F5-20	0.000996109
319	F5-25	0.000881378
322	F5-28	0.01227125
331	F5-36-2	0.001778367
334	F5-39	0.014824288

[Table 46]

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
340	F5-45	0.000579745
346	F5-51	0.002610782
350	F6-4	0.00715425
353	F6-7	0.020276801
355	F6-9	0.001092627
358	F6-12	0.015047658
359	F6-13	0.000399685
389	H9-3	0.002622129
403	16-4	0.000391036
407	17-1	0.001863642
421	J7-3	0.015290853
422	J7-4	0.004631153
423	J7-5	0.012009506
424	J7-6	0.001570404
426	J7-8	0.001170682
431	J7-11-2	0.01172814
435	J7-15	0.02319
437	J7-17	0.007091939
438	J8-1	0.012517614
443	J8-6	0.00396
455	JJ5	0.862941682
458	JJ7- 2	0.028993627
461	JJ9-1	0.004337558
465	JJ10-1	0.492725332
472	K6	0.029284532
486	K10-5	0.000589765
501	L10-2	0.00160
508	M6-2	0.006136762
517	N6-3	0.03272871
519	N6-5	0.026853329
531	O5-4	0.00431
546	O9-3	0.00086
571	Q8	0.005719259
579	R8-2	0.000769618
591	S4	1.664818863

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
599	S8-2	0.04064
601	S9-2	0.000456356
607	T2-1	0.432812267
618	T6-1	0.614075453
621	T6-4	0.341433432
628	T11	0.271479209
630	T12-2	0.15422
633	T13-3	0.16211
637	T13-7	0.16821
639	T13-9	0.16189
645	T14-5	0.41327
650	T14-10	0.18923
654	T16-1	0.01951
657	T16-4	0.07941
668	T21	0.8521
671	T22-1-1	0.151061541
678	T22-7	2.8135
679	T22-8	0.583
686	T26-2	0.08320
702	U8-6-2	0.00260
704	U8-7-2	0.00604
706	U8-8-2	0.35976
707	U8-8-3	0.84884
709	U10-1	0.55215
711	U11	0.00193
720	W4-2	0.13445
730	Y5-2	0.554738402
751	K10-10	0.0085
753	K10-12	0.0022
755	K10-14	0.0118
758	K10-17	0.1422
760	K10-19	0.0015
762	L10-3	0.0099
770	L10-11	0.0231
776	B3-42	0.0042
786	E9-4	0.0004
790	E9-8	0.0075
796	F4-11	0.0003
822	PR11-6	0.0003
823	PR11-7	0.0003
824	PR9-9	0.0142
829	PR9-13	0.0007
832	PR11-11	0.0006
846	PR9-25	0.021743738
847	PR11-14	0.001890642

[Table 47]

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
849	PR11-16	0.000813047
864	LB5-1	0.424843491

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
866	LB5-3	2.398295
875	AZ7-3	0.113911239
892	AZ7-20	0.009369855
893	AZ7-21	0.142933634
920	DZ7-5	0.326374265
938	EZ9-4	0.300760062
949	GT2-6	1.3255
956	GT2-13	0.1617
960	GT3-2	5.9473
962	GT3-4	1.0829
963	GT3-5	4.224
967	GT3-9	0.8981
970	GT3-12	1.6214
972	GT4-1	0.29
973	GT4-2	0.104
981	GT5-8	2.9743
982	GT5-9	21.3078
983	GT5-10	3.2
994	GT5-21	1.2466
995	GT6-1	12.9519
996	GT6-2	12.9704
997	GT6-3	0.575
998	GT6-4	4.3855
999	GT6-5	3.9
1000	GT6-6	5.4
1001	GT6-7	3.7
1004	GT6-10	0.9
1005	GT6-11	1.4385
1007	GT6-13	0.7526
1008	GT6-14	4.8429
1013	GT8-3	0.93
1017	GT9-3	0.3785
1019	GT9-5	0.77
1030	GT11-8	5.9346
1031	GT11-9	7.7947
1034	GT11-12	2.076
1035	GT11-13	1.6274
1039	GT11-17	0.7938
1042	GT11-20	0.5083
1043	GT11-21	2.2822
1047	GT11-25	1.9038
1048	GT11-26	5.3708
1050	GT11-28	3.2813
1051	GT11-29	1.811
1052	GT11-30	4.0931
1054	GT11-32	7.0451
1059	GT11-37	2.7739
1060	GT11-38	1.1587
1061	GT11-39	1.0914

Example No.	Compound	ALK-inhibiting activity IC_{50}(μM)
1065	GT11-43	3.7028
1066	GT11-44	3.1203
1072	GT11-50	3.3428
1073	GT11-51	2.547
1074	GT11-52	1.2588
1081	GT11-59	1.0586
1083	GT11-61	0.7928
1085	GT11-63	0.9013
1086	GT11-64	0.3127
1087	GT11-65	0.206
1090	GT12-3	0.8541
1096	GT12-9	5.7571
1102	GT13-3	0.4209
1105	GT13-6	0.3894
1113	GT13-14	0.1571
1114	GT13-15	0.7
1117	GT13-18	2.2
1118	GT13-19	0.5
1119	GT13-20	0.42
1125	GT13-26	0.028
1126	GT13-27	3.0645
1127	GT13-28	5.6311
1128	GT13-29	17.4641
1129	GT13-30	0.51
1130	GT13-31	0.54
1164	GT16-5	0.4149
1177	GT18-6	0.7527
1185	GT20-6	1.8

[Table 48]

Example No.	Compound	Inhibitory activity on Karpas-299 cell growth IC_{50}(μM)
15	A7-3	0.1138
17	A7-5	0.6268
19	A7-7	0.3293
21	A7-9	0.2037
22	A7-10	0.3031
25	A7-12	0.1119
46	A8-3	0.0866
56	A8-11	0.0677
58	A8-13	0.0226
60	A8-15	0.2322
61	A8-16	0.0345
62	A8-17	0.1269
64	A8-19	0.0726
66	A8-21	0.1050
68	A9-2	0.1372
72	A9-5	0.0523
93	B2-4	0.0365
138	B3-12	1.4358
154	B3-25-3	0.7298

Example No.	Compound	Inhibitory activity on Karpas-299 cell growth IC_{50}(μM)
155	B3-26	1.3613
160	B3-30	0.2282
163	B3-32	0.0652
167	B3-36	0.0390
174	B4-4	0.0812
229	D3-2	0.9700
230	D3-3	0.1320
244	E4-4	0.1090
257	E5-3	0.1895
260	E5-6	0.0527
273	F3-3	0.0162
287	F4-4	0.0071
289	F4-6	0.0291
291	F4-8	0.0221
292	F4-9	0.0650
294	F5-1	0.0091
297	F5-4	0.0018
301	F5-8	0.0297
302	F5-9	0.0043
303	F5-10	0.0135
309	F5-15-2	0.0098
310	F5-16	0.0042
315	F5-21	0.0663
316	F5-22	0.0066
323	F5-29	0.0076
325	F5-31	0.0727
326	F5-32	0.0240
335	F5-40	0.0256
336	F5-41	0.1491
339	F5-44	0.0060
348	F6-2	0.0295
351	F6-5	0.0274
352	F6-6	0.0364
357	F6-11	0.0776
359	F6-13	0.0079
420	J7-2-3	0.0295
434	J7-14	0.5567
446	J9-3	0.0532
467	JJ10-3	6.0632
488	K10-7	0.0518
518	N6-4	0.1224
562	P5	27.7670
605	T1-1	1.8669
636	T13-6	1.2901
640	T13-10	1.3775
642	T14-2	0.6324
646	T14-6	1.9418
649	T14-9	1.08
656	T16-3	2.25

Example No.	Compound	Inhibitory activity on Karpas-299 cell growth IC_{50}(μM)
672	T22-1-2	1.7820
680	T23-1	4.2526
681	T23-2	7.0799
688	T27-2	0.9970
689	U5	0.1217
695	U8-3-2	0.6773
698	U8-4-3	1.10
700	U8-5-2	0.3573
708	U9	0.4070
710	U10-2	0.94

[Table 49]

Example No.	Compound	Inhibitory activity on Karpas-299 cell growth IC_{50}(μM)
764	L10-5	0.019
766	L10-7	0.037
767	L10-8	0.024
769	L10-10	0.159
773	B3-40	0.022
787	E9-5	0.041
792	E9-9	0.004
793	PR11-20	0.020313
794	PR11-21	0.06439
827	PR9-11	0.036
839	PR9-20	0.018772
844	PR9-23	0.020492
845	PR9-24	0.067888
850	PR11-17	0.005766
852	PR11-19	0.034632
865	LB5-2	1.287666
878	AZ7-6	1.126471
896	AZ7-24	0.054
935	EZ9-1	16.635
941	W4-4	0.116
976	GT5-3	1.868
979	GT5-6	8.231
980	GT5-7	17.135
984	GT5-11	1.957
985	GT5-12	19.989
986	GT5-13	1.332
987	GT5-14	3.787
990	GT5-17	2.359
991	GT5-18	4.255
993	GT5-20	6.081
1020	GT9-6	2.655
1115	GT13-16	7.875
1123	GT13-24	3.951
1124	GT13-25	5.511
1131	GT13-32	2.501
1132	GT13-33	10.887

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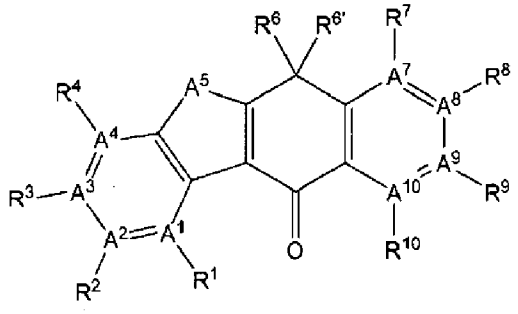
Patentkrav

1. Forbindelse eller salt eller solvat deraf, der er repræsenteret ved formel (I):



(I)

[hvor,

A^1, A^2, A^3, A^4, A^7, A^8, A^9 og A^{10} alle repræsenterer C, eller en af A^2, A^3, A^4, A^7, A^8 og A^9 repræsenterer N (forudsat at, når det repræsenterer N, eksisterer der ingen substituentgruppe derfor) og resten repræsenterer C;

A^5 er valgt blandt NR^5, O og S;

R^1 og R^{10} hver især uafhængigt repræsenterer [1] et hydrogenatom, [2] en cyanogruppe, [3] et halogenatom eller [4] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med en eller flere 4- til 10-leddede heterocycloalkylgruppe(r);

R^2 er valgt fra gruppen bestående af:

(1) et hydrogenatom,

(2) en C_{1-8}-alkylgruppe,

(3) en C_{2-8}-alkenylgruppe,

(4) en C_{2-8}-alkynylgruppe,

(5) en cyanogruppe,

(6) et halogenatom,

(7) en $(C_{1-8}\text{-alkyl})_{m2}$-aminogruppe, der kan være substitueret med C_{1-8}-alkylsulfonylgruppe(r),

m2: 0~2 og

(8) en nitrogruppe;

R^3 er valgt fra gruppen bestående af:

(1) et hydrogenatom,

(2) en C_{1-8}-alkylgruppe, der kan være substitueret med [1] halogenatom(er), [2] hydroxygruppe(r) eller [3] C_{1-8}-alkoxygruppe(r),

(3) en C_{6-10}-arylgruppe,

(4) en cyanogruppe,

(5) en C_{1-8}-alkanoylgruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
(6) en $(C_{1-8}\text{-alkyl})_{m3a}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{3A},
R^{3A}: [1] en C_{6-10}-arylgruppe, [2] en C_{1-8}-alkoxygruppe, [3] en 5- til 14-leddet heteroarylgruppe eller [4] en C_{6-10}-arylsulfonylgruppe,
m3a: 0~2,
(7) en hydroxycarbonylgruppe,
(8) en C_{1-8}-alkoxycarbonylgruppe, der kan være substitueret med [1] hydroxygruppe(r) eller [2] C_{1-8}-alkoxygruppe(r),
(9) et halogenatom,
(10) en $(C_{1-8}\text{-alkyl})_{m3b}$-aminogruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
m3b: 0~2,
(11) en C_{1-8}-alkylcarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med [1] C_{6-10}-arylgruppe(r) eller [2] C_{6-10}-aryloxygruppe(r),
(12) en C_{6-10}-arylcarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med halogenatom(er),
(13) en $(C_{1-8}\text{-alkyl})_{m3c}$-aminocarbonyl ($C_{0-8}$ alkyl)-aminogruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
m3c: 0~2,
(14) en nitrogruppe,
(15) en hydroxygruppe,
(16) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{3B},
R^{3B}: [1] en hydroxygruppe, [2] en C_{1-8}-alkoxygruppe, [3] en C_{6-10}-aryl (C_{0-8}-alkyl)-aminocarbonylgruppe, [4] en $(C_{1-8}\text{-alkyl})_{m3d}$-aminogruppe eller [5] et halogenatom,
m3d: 0~2,
(17) en 4- til 10-leddet heterocycloalkyloxygruppe,
(18) en 5- til 14-leddet heteroaryloxygruppe,
(19) en $(C_{1-8}\text{-alkyl})_{m3e}$-aminocarbonyloxygruppe, der kan være substitueret med C_{6-10}-arylgruppe(r)
m3e: 0~2,
(20) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe,
(21) en C_{1-8}-alkylsulfonyloxygruppe, der kan være substitueret med halogenatom(er),

(22) en C_{1-8}-alkylthiogruppe,
(23) en C_{1-8}-alkylsulfonylgruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
(24) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med C_{1-8}-alkoxygruppe(r),
(25) en C_{1-8}-alkoxycarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r),
(26) en C_{6-10}-aryloxycarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med halogenatom(er),
(27) en C_{6-10}-aryl (C_{0-8}-alkyl)-aminocarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med et eller flere R^{3C},
R^{3C}: [1] en C_{1-8}-alkylgruppe, der kan være substitueret med halogenatom(er) eller [2] en C_{1-8}-alkoxygruppe,
(28) en C_{3-8}-cycloalkyl (C_{0-8}-alkyl)-aminocarbonyloxygruppe og
(29) en C_{6-10}-aryl (C_{0-8}-alkyl)-aminocarbonyloxygruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkylgruppe og [2] en C_{1-8}-alkoxygruppe;

R^4 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med halogenatom(er),
(3) en C_{2-8}-alkenylgruppe,
(4) en C_{2-8}-alkynylgruppe,
(5) en C_{3-8}-cycloalkylgruppe,
(6) en cyanogruppe,
(7) en aminocarbonylgruppe,
(8) en $(C_{1-8}\text{-alkyl})_{m4a}$-aminocarbonylgruppe,
m4a: 1~2,
(9) en hydroxycarbonylgruppe,
(10) en C_{1-8}-alkoxycarbonylgruppe,
(11) et halogenatom,
(12) en $(C_{1-8}\text{-alkyl})_{m4b}$-aminogruppe,
m4b: 0~2,
(13) en hydroxygruppe og
(14) en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r);

R^5 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{5A},
R^{5A}: [1] en hydroxycarbonylgruppe, [2] en C_{1-8}-alkoxycarbonylgruppe, [3] en hydroxygruppe, [4] en C_{1-8}-alkoxygruppe, [5] en $(C_{1-8}$-alkyl$)_{m5}$-aminogruppe, [6] en C_{6-10}-arylgruppe eller [7] en C_{1-8}-alkylthiogruppe,
m5: 0~2,
(3) en C_{2-8}-alkenylgruppe,
(4) en C_{2-8}-alkynylgruppe,
(5) en C_{3-8}-cycloalkylgruppe og
(6) en C_{1-8}-alkylsulfonylgruppe;

R^6 og $R^{6'}$ hver især uafhængigt er valgt fra gruppen bestående af:

(1) en C_{1-8}-alkylgruppe, der kan være substitueret med halogenatom(er),
(2) en C_{2-8}-alkenylgruppe og
(3) en C_{2-8}-alkynylgruppe; eller

R^6 og $R^{6'}$ tages sammen med de carbonatomer, hvortil de er bundet, til dannelse af:
(4) en C_{3-8}-cycloalkylgruppe eller
(5) en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med C_{1-8}-alkyl C_{6-10}-arylsulfonylgruppe(r), der kan være substitueret med C_{1-8}-alkylgruppe(r);

R^7 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) et halogenatom,
(3) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{7A},
R^{7A}: [1] en $(C_{1-8}$-alkyl)m7a-aminogruppe, [2] en hydroxy, [3] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
m7a: 0~2,
(4) en C_{1-8}-alkylsulfonylgruppe,
(5) en nitrogruppe og
(6) en hydroxylgruppe;

R^8 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8A},
R^{8A}: [1] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8A1}, [2] en $(C_{1-8}$-alkyl$)_{m8a}$-aminogruppe, der kan være sub-

stitueret med et halogenatom, eller [3] en hydroxygruppe,
m8a:0~2,
R^{8A1}: [1] en C_{1-8}-alkylgruppe, [2] en C_{1-8}-alkylsulfonylgruppe, [3] en $(C_{1-8}$-alkyl$)_{m8b}$-aminosulfonylgruppe, [4] en oxogruppe, [5] en C_{1-8}-alkoxycarbonyl eller [6] en C_{1-8}-alkoxycarbonyl (C_{0-8}-alkyl)-aminosulfonyl,
m8b: 0~2,
(3) en C_{2-8}-alkenylgruppe,
(4) en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8B},
R^{8B}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8B1},
<2> en C_{2-8}-alkeynylgruppe,
<3> en C_{2-8}-alkynylgruppe,
<4> en C_{3-8}-cycloalkylgruppe, der kan være substitueret med [1] cyanogruppe(r) eller [2] C_{1-8}-alkylgruppe(r),
<5> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8B2},
<6> en C_{1-8}-alkoxygruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkoxygruppe og [2] en C_{3-8}-cycloalkylgruppe,
<7> en C_{1-8}-alkoxycarbonylgruppe,
<8> en C_{1-8}-alkylsulfonylgruppe,
<9> en 5- til 14-leddet heteroarylsulfonylgruppe,
<10> en oxogruppe,
<11> en cyanogruppe,
<12> en C_{1-8}-alkanoylgruppe, der kan være substitueret med et eller flere R^{8B3},
<13> en C_{3-8}-cycloalkylcarbonylgruppe,
<14> en $(C_{1-8}$-alkyl$)_{m8c}$-aminosulfonylgruppe,
<15> en C_{1-8}-alkylsulfonyl (C_{0-8}-alkyl)-aminogruppe,
<16> en $(C_{1-8}$-alkyl$)_{m8d}$-aminogruppe, der kan være substitueret med et eller flere R^{8B4},
<17> en hydroxygruppe,
<18> en $(C_{1-8}$-alkyl$)_{m8e}$-aminocarbonylgruppe eller
<19> en C_{1-8}-alkoxycarbonyl (C_{0-8}-alkyl)-aminogruppe
m8c: 0~2

m8d: 0~2

m8e: 0~2

R^{8B1}: [1] en C_{3-8}-cycloalkylgruppe, [2] en hydroxygruppe eller [3] en C_{1-8}-alkoxygruppe(r),

R^{8B2}: [1] et halogenatom, [2] en C_{1-8}-alkylgruppe, [3] en oxogruppe, [4] en hydroxygruppe eller [5] et deuteriumatom,

R^{8B3}: en $(C_{1-8}\text{-alkyl})_{m8f}$-aminogruppe,

m8f: 0~2,

R^{8B4}: [1] en C_{3-8}-cycloalkylgruppe eller [2] en hydroxygruppe,

(5) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med en C_{1-8}-alkylgruppe,

(6) en $(C_{1-8}\text{-alkyl})_{m8g}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{8C},

m8g: 0~2,

R^{8C}:[1] en hydroxygruppe, [2] en $(C_{1-8}\text{-alkyl})_{m8h}$-aminogruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af <1> en $(C_{1-8}\text{-alkyl})_{m8i}$-aminosulfonylgruppe, <2> en C_{1-8}-alkylsulfonylgruppe, <3> en C_{1-8}-alkoxycarbonylgruppe og <4> en C_{1-8}-alkoxycarbonyl(C_{0-8}-alkyl)-aminosulfonylgruppe, [3] en C_{1-8}-alkylsulfonylgruppe eller [4] en C_{1-8}-alkoxygruppe, der kan være substitueret med en hydroxygruppe,

m8h: 0~2,

m8i: 0~2,

(7) en 4- til 10-leddet heterocycloalkyl (C_{0-8}-alkyl)-aminocarbonylgruppe, der kan være substitueret med oxogruppe(r),

(8) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med et eller flere R^{8D},

R^{8D}: [1] en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8D1}, [2] en hydroxygruppe, [3] en C_{1-8}-alkylsulfonylgruppe eller [4] en C_{1-8}-alkoxycarbonylgruppe,

R^{8D1}: [1] en hydroxygruppe eller [2] en C_{1-8}-alkoxygruppe,

(9) en hydroxycarbonylgruppe,

(10) en C_{0-8}-alkoxy (C_{0-8}-alkyl)-aminocarbonylgruppe, der kan være substitueret med hydroxygruppe(r),

(11) et halogenatom,

(12) en $(C_{1-8}\text{-alkyl})_{m8j}$-aminogruppe, der kan være substitueret med et eller flere R^{8H}, m8j: 0~2,

R^{8H}:[1] en hydroxygruppe eller [2] en 4- til 10-leddet heterocycloalkylgruppe,
(13) en hydroxylgruppe,
(14) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{8E},
R^{8E}:
<1> en hydroxygruppe,
<2> halogenatom,
<3> en hydroxycarbonylgruppe,
<4> en C_{1-8}-alkoxycarbonylgruppe,
<5> en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med et eller flere R^{8E1},
<6> en $(C_{1-8}\text{-alkyl})_{m8k1}$-aminogruppe, der kan være substitueret med et eller flere R^{8E2},
m8k1: 0~2,
<7> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8E3},
<8> en 5- til 14-leddet heteroarylgruppe,
<9> en $(C_{1-8}\text{-alkyl})_{m8k2}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{8E6},
m8k2: 0~2,
<10> en C_{1-8}-alkoxygruppe, der kan substitueret med et eller flere R^{8E7},
<11> en C_{1-8}-alkylthiogruppe,
<12> en C_{1-8}-alkylsulfinylgruppe,
<13> en C_{1-8}-alkylsulfonylgruppe,
R^{8E1}:
<1> en C_{1-8}-alkoxycarbonylgruppe,
<2> en C_{1-8}-alkanoylgruppe,
<3> en C_{1-8}-alkylsulfonylgruppe,
<4> en $(C_{1-8}\text{-alkyl})_{m8k3}$-aminosulfonylgruppe,
m8k3: 0~2 eller
<5> en 4- til 10-leddet heterocycloalkylgruppe,
R^{8E2}:
<1> en hydroxygruppe,
<2> en C_{1-8}-alkoxycarbonylgruppe, der kan være substitueret med halogenatom(er),
<3> en C_{3-8}-cycloalkylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med hydroxygruppe(r),

<4> en C_{1-8}-alkanoylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en $(C_{1-8}\text{-alkyl})_{m8k4}$-aminogruppe og [2] et halogenatom(er),
m8k4: 0~2,
<5> en $(C_{1-8}\text{-alkyl})_{m8k5}$-aminocarbonylgruppe,
m8k5: 0~2,
<6> en C_{1-8}-alkylsulfonylgruppe,
<7> en 4- til 10-leddet nitrogen-holdig heterocycloalkylsulfonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
<8> en $(C_{1-8}\text{-alkyl})_{m8k6}$-aminosulfonylgruppe, der kan være substitueret med C_{1-8}-alkoxycarbonylgruppe(r),
m8k6: 0~2, eller
R^{8E3}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en hydroxygruppe og [2] en C_{1-8}-alkylcarbonyloxygruppe,
<2> en C_{1-8}-alkylcarbonyloxygruppe,
<3> en hydroxygruppe,
<4> en C_{3-8}-cycloalkylgruppe,
<5> en C_{1-8}-alkoxygruppe,
<6> en C_{1-8}-alkoxycarbonylgruppe,
<7> en C_{1-8}-alkylsulfonylgruppe,
<8> en $(C_{1-8}\text{-alkyl})_{m8k8}$-aminocarbonylgruppe
m8k8: 0~2,
<9> en C_{1-8}-alkanoylgruppe, der kan være substitueret med hydroxygruppe(r),
<10> en oxogruppe eller
<11> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkanoylgruppe, [2] en C_{1-8}-alkoxycarbonylgruppe, og [3] en C_{1-8}-alkylsulfonylgruppe,
R^{8E6}:
<1> en C_{2-8}-alkenylcarbonyloxygruppe,
<2> en hydroxygruppe,
<3> en cyanogruppe,

<4> en (C_{1-8}-alkyl)$_{m8k9}$-aminogruppe, der kan være substitueret med hydroxygruppe(r) m8k9: 0~2,
<5> en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r),
<6> en C_{1-8}-alkylcarbonyloxygruppe,
<7> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), eller
<8> en 5- til 14-leddet heteroarylgruppe,
R^{8E7}:
<1> en hydroxygruppe, eller
<2> en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r),
(15) en 4- til 10-leddet heterocycloalkyloxygruppe, der kan være substitueret med et eller flere R^{8F},
R^{8F}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8F1},
<2> en C_{3-8}-cycloalkylgruppe,
<3> en C_{1-8}-alkanoylgruppe, der kan være substitueret med halogenatom(er),
<4> en C_{1-8}-alkylcarbonyloxygruppe,
<5> en C_{1-8}-alkoxycarbonylgruppe,
<6> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8F2},
<7> en C_{1-8}-alkylsulfonylgruppe,
<8> en hydroxygruppe eller
[9] en C_{6-10}-arylgruppe,
R^{8F1}: [1] en hydroxygruppe, [2] en C_{1-8}-alkoxygruppe eller [3] et halogenatom,
R^{8F2}: [1] en 4- til 10-leddet heterocycloalkylgruppe, [2] en C_{1-8}-alkoxycarbonylgruppe eller [3] en C_{1-8}-alkylsulfonylgruppe,
(16) en 5- til 14-leddet heteroaryloxygruppe,
(17) en 4- til 10-leddet heterocycloalkylcarbonyloxygruppe,
(18) en (C_{1-8}-alkyl)$_{m8l1}$-aminosulfonyloxygruppe,
m8l1: 0~2,
(19) en C_{1-8}-alkylthiogruppe, der kan være substitueret med [1] (C_{1-8}-alkyl)$_{m8l2}$-aminogruppe(r), [2] hydroxygruppe(r) eller [3] hydroxycarbonylgruppe(r),
m8l2: 0~2,
(20) en C_{1-8}-alkylsulfonylgruppe, der kan være substitueret med et eller flere R^{8G},

R^{8G}: [1] en hydroxycarbonylgruppe, [2] en hydroxygruppe eller [3] en $(C_{1-8}$-alkyl$)_{m8l3}$-aminogruppe,
m8l3: 0~2,
(21) en 4- til 10-leddet nitrogen-holdig heterocycloalkylsulfonyloxygruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
(22) en C_{2-8}-alkenyloxygruppe, og
(23) en C_{1-8}-alkylsulfonyloxygruppe, der kan være substitueret med halogenatom(er);

R^9 er fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{9A},
R^{9A}: [1] en C_{3-8}-cycloalkylgruppe, [2] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9A1}, [3] en hydroxygruppe, [4] en C_{1-8}-alkoxygruppe eller [5] en hydroxycarbonylgruppe,
R^{9A1}: [1] en C_{1-8}-alkylgruppe, [2] en C_{3-8}-cycloalkylgruppe eller [3] en 4- til 10-leddet heterocycloalkylgruppe,
(3) en C_{2-8}-alkenylgruppe, der kan være substitueret med et eller flere R^{9B},
R^{9B}: [1] en $(C_{1-8}$-alkyl$)_{m9a}$-aminogruppe, [2] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med en eller flere gruppe R^{9B1},
R^{9B1}: [1] en C_{3-8}-cycloalkylgruppe eller [2] en 4- til 10-leddet heterocycloalkylgruppe,
m9a: 0~2,
(4) en C_{2-8}-alkynylgruppe, der kan være substitueret med et eller flere R^{9C},
R^{9C}: [1] en C_{1-8}-alkoxygruppe, [2] en $(C_{1-8}$-alkyl$)_{m9b}$-aminogruppe, der kan være substitueret med C_{6-10}-arylgruppe(r), [3] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9C1}, [4] en C_{3-8}-cycloalkylgruppe, [5] en hydroxygruppe, [6] en hydroxycarbonylgruppe eller [7] en C_{1-8}-alkyloxycarbonylgruppe,
m9b: 0~2,
R^{9C1}: [1] en C_{3-8}-cycloalkylgruppe, [2] en 4- til 10-leddet heterocycloalkylgruppe eller [3] en oxogruppe,
(5) en C_{3-8}-cycloalkylgruppe,
(6) en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9D},
R^{9D}: [1] en C_{1-8}-alkylgruppe, der kan være substitueret med 4- til 10-leddet heterocycloalkylgruppe(r), [2] en C_{3-8}-cycloalkylgruppe, [3] en 4- til 10-leddet

heterocycloalkylgruppe eller [4] en C_{1-6}-alkylsulfonylgruppe eller [5] en C_{1-8}-alkoxycarbonylgruppe,

(7) en C_{6-10}-arylgruppe, der kan være substitueret med et eller flere R^{9E},

R^{9E}: [1] et halogenatom, [2] en hydroxygruppe, [3] en hydroxycarbonylgruppe eller [4] en C_{1-8}-alkylgruppe, der kan være substitueret med hydroxygruppe(r), eller [5] en C_{1-8}-alkoxygruppe,

(8) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),

(9) en cyanogruppe,

(10) en C_{1-8}-alkanoylgruppe,

(11) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),

(12) et halogenatom,

(13) en $(C_{1-8}$-alkyl$)_{m9c}$-aminogruppe, der kan være substitueret med et eller flere R^{9F},

m9c: 0~2,

(14) en C_{1-8}-alkylcarbonyl(C_{0-8}-alkyl)aminogruppe, der kan være substitueret med $(C_{1-8}$-alkyl$)_{m9d}$-aminogruppe(r),

m9d: 0~2,

(15) en C_{1-8}-alkylsulfonyl(C_{0-8}-alkyl)aminogruppe,

(16) en $(C_{1-8}$-alkyl$)_{m9e}$-aminosulfonyl(C_{0-8}-alkyl)aminogruppe,

m9e: 0~2,

(17) en nitrogruppe,

(18) en hydroxygruppe,

(19) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{9G},

R^{9F}: [1] C_{1-3}-alkylsulfonylgruppe, [2] $(C_{1-3}$-alkyl$)_{m9f1}$-aminosulfonylgruppe (m9fl: 0~2), eller

[3] C_{1-3}-alkanoylgruppe, der kan være substitueret med $(C_{1-3}$-alkyl$)_{m9f2}$-aminogruppe(r) (m9f2: 0~2)

R^{9G}: [1] en hydroxygruppe, [2] en hydroxycarbonylgruppe, [3] en C_{6-10}-arylgruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r), [4] en $(C_{1-8}$-alkyl$)_{m9g1}$-aminogruppe, [5] a C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{9G1}, [6] en 5- til 14-leddet heteroarylgruppe eller [7] en 4- til 10-leddet heterocycloalkyloxygruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),

m9g1: 0~2,

R^{9G1}: [1] en C_{1-8}-alkoxygruppe, eller [2] en hydroxycarbonylgruppe,
(20) en 4- til 10-leddet heterocycloalkyloxygruppe, der kan være substitueret med [1] 4- til 10-leddet heterocycloalkylgruppe(r), eller [2] C_{1-8}-alkoxycarbonylgruppe(r),
(21) en C_{1-8}-alkylsulfonyloxygruppe, der kan være substitueret med halogenatom(er),
(22) en C_{1-8}-alkylthiogruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m9f}$-aminogruppe(r),
m9f: 0~2,
(23) en C_{1-8}-alkylsulfonylgruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m9g}$-aminogruppe(r),
m9g: 0~2,
(24) en $(C_{1-8}\text{-alkyl})_{m9h}$-aminosulfonylgruppe,
m9h: 0~2,
(25) en 4- til 10-leddet nitrogen-holdig heterocycloalkylsulfonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), og
(26) en hydroxycarbonylgruppe].

2. Forbindelse ifølge krav 1 eller et salt eller solvat deraf, hvor R^3 er en cyanogruppe eller et halogenatom.

3. Forbindelse ifølge krav 1 eller et salt eller solvat deraf, hvor A^5 er NR^5, og R^5 er et hydrogenatom.

4. Forbindelse ifølge krav 1 eller et salt eller solvat deraf, hvor alle af A^1, A^2, A^3, A^4, A^7, A^8, A^9 og A^{10} er et carbonatom.

5. Forbindelse ifølge krav 1 eller et salt eller solvat deraf, hvor: A^1, A^2, A^3, A^4, A^7, A^8, A^9 og A^{10} alle repræsenterer C, eller et af A^2, A^3, A^4, A^7, A^8 og A^9 repræsenterer N (forudsat at, når det repræsenterer N, eksisterer der ingen substituentgruppe derfor) og resten repræsenterer C;
A^5 er valgt blandt NR^5, O og S;
R^1 repræsenterer [1] et hydrogenatom, [2] en cyanogruppe eller [3] et halogenatom; **R^2 er valgt fra gruppen bestående af:**
(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe,

(3) en cyanogruppe,
(4) et halogenatom og
(5) en (C_{1-8}-alkyl)$_{m2}$-aminogruppe, der kan være substitueret med C_{1-8}-alkylsulfonylgruppe(r),
m2: 0~2;
R^3 er valgt fra gruppen bestående af:
(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med halogenatom(er),
(3) en cyanogruppe,
(4) en (C_{1-8}-alkyl)$_{m3a}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{3A},
R^{3A}: [1] en C_{6-10}-arylgruppe, [2] en C_{1-8}-alkoxygruppe, [3] en 5- til 14-leddet heteroarylgruppe eller [4] en C_{6-10}-arylsulfonylgruppe,
m3a: 0~2,
(5) en hydroxycarbonylgruppe,
(6) en C_{1-8}-alkoxycarbonylgruppe, der kan være substitueret med hydroxygruppe(r),
(7) et halogenatom,
(8) en (C_{1-8}-alkyl)$_{m3b}$-aminogruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
m3b: 0~2,
(9) en C_{1-8}-alkylcarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med [1] C_{6-10}-arylgruppe(r) eller [2] C_{6-10}-aryloxygruppe(r),
(10) en C_{6-10}-arylcarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med halogenatom(r),
(11) en nitrogruppe,
(12) en hydroxygruppe,
(13) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{3B},
R^{3B}: [1] en hydroxygruppe, [2] en C_{1-8}-alkoxygruppe, [3] en C_{6-10}-aryl (C_{0-8}-alkyl)-aminocarbonylgruppe, [4] en (C_{1-8}-alkyl)$_{m3d}$-aminogruppe eller [5] et halogenatom,
m3d: 0~2,
(14) en 4- til 10-leddet heterocycloalkyloxygruppe,
(15) en 5- til 14-leddet heteroaryloxygruppe,

(16) en $(C_{1-8}\text{-alkyl})_{m3e}$-aminocarbonyloxygruppe, der kan være substitueret med C_{6-10}-arylgruppe(r),
m3e: 0~2,
(17) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe,
(18) en C_{1-8}-alkylthiogruppe,
(19) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med C_{1-8}-alkoxygruppe(r),
(20) en C_{1-8}-alkoxycarbonyl (C_{0-8}alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r),
(21) en C_{6-10}-aryloxycarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med halogenatom(er),
(22) en C_{6-10}-aryl (C_{0-8}-alkyl)-aminocarbonyl (C_{0-8}-alkyl)-aminogruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r),
(23) en C_{3-8}-cycloalkyl (C_{0-8}-alkyl)-aminocarbonyloxygruppe, og
(24) en C_{6-10}-aryl (C_{0-8} alkyl)-aminocarbonyloxygruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkylgruppe og [2] en C_{1-8}-alkoxygruppe;

R^4 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med halogenatom(er),
(3) en C_{3-8}-cycloalkylgruppe,
(4) en cyanogruppe,
(5) en aminocarbonylgruppe,
(6) en hydroxycarbonylgruppe,
(7) et halogenatom,
(8) en $(C_{1-8}\text{-alkyl})_{m4b}$-aminogruppe,
m4b: 0~2,
(9) en hydroxygruppe, og
(10) en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r);

R^5 er valgt fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{5A},
R^{5A}: [1] en hydroxycarbonylgruppe, [2] en C_{1-8}-alkoxycarbonylgruppe, [3] en hydroxygruppe, [4] en C_{1-8}-alkoxygruppe, [5] en $(C_{1-8}\text{-alkyl})_{m5}$-aminogruppe

eller [6] en C_{1-8}-alkylthiogruppe,
m5: 0~2, og
(3) en C_{1-8}-alkylsulfonylgruppe;
R^6 og $R^{6'}$ hver især uafhængigt:
(1) en C_{1-8}-alkylgruppe, eller
R^6 og $R^{6'}$ tages sammen med de carbonatomer, hvortil de er bundet, til dannelse af,
(2) en C_{3-8}-cycloalkylgruppe, eller
(3) en 4- til 10-leddet heterocycloalkylgruppe;
R^7 er valgt fra gruppen bestående af:
(1) et hydrogenatom,
(2) et halogenatom, og
(3) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{7A},
R^{7A}: [1] en $(C_{1-8}\text{-alkyl})_{m7a}$-aminogruppe eller [2] en hydroxygruppe, m7a:0~2;
R^8 er valgt fra gruppen bestående af:
(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8A},
R^{8A}: [1] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8A1}, [2] en $(C_{1-8}\text{-alkyl})_{m8a}$-aminogruppe, der kan være substitueret med et halogenatom, eller [3] en hydroxygruppe,
m8a:0~2,
R^{8A1}: [1] en C_{1-8}-alkylgruppe, [2] en C_{1-8}-alkylsulfonylgruppe, [3] en $(C_{1-8}\text{-alkyl})_{m8b}$-aminosulfonylgruppe eller [4] en oxogruppe,
m8b: 0~2,
(3) en C_{2-8}-alkenylgruppe,
(4) en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8B},
R^{8B}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8B1},
<2> en C_{2-8}-alkynylgruppe,
<3> en C_{3-8}-cycloalkylgruppe, der kan være substitueret med [1] cyanogruppe(r) eller [2] C_{1-8}-alkylgruppe(r),
<4> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8B2},

<5> en C_{1-8}-alkoxygruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkoxygruppe og [2] en C_{3-8}-cycloalkylgruppe,
<6> en C_{1-8}-alkylsulfonylgruppe,
<7> en oxogruppe,
<8> en cyanogruppe,
<9> en C_{1-8}-alkanoylgruppe, der kan være substitueret med et eller flere R^{8B3},
<10> en C_{3-8}-cycloalkylcarbonylgruppe,
<11> en $(C_{1-8}\text{-alkyl})_{m8c}$-aminosulfonylgruppe,
<12> en C_{1-8}-alkylsulfonyl (C_{0-8} alkyl)-aminogruppe,
<13> en $(C_{1-8}\text{-alkyl})_{m8d}$-aminogruppe, der kan være substitueret med et eller flere R^{8B4},
<14> en hydroxygruppe, eller
<15> en $(C_{1-8}\text{-alkyl})_{m8e}$-aminocarbonylgruppe,
m8c: 0~2,
m8d: 0~2,
m8e: 0~2,
R^{8B1}: [1] en C_{3-8}-cycloalkylgruppe, [2] en hydroxygruppe eller [3] C_{1-8}-alkoxygruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r),
R^{8B2}: [1] et halogenatom, [2] en C_{1-8}-alkylgruppe, [3] en oxogruppe eller [4] en hydroxygruppe,
R^{8B3}: en $(C_{1-8}\text{-alkyl})_{m8f}$-aminogruppe,
m8f: 0~2,
R^{8B4}: [1] en C_{3-8}-cycloalkylgruppe eller [2] en hydroxygruppe,
(5) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med en C_{1-8}-alkylgruppe,
(6) en $(C_{1-8}\text{-alkyl})_{m8g}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{8C},
m8g: 0~2,
R^{8C}:[1] en hydroxygruppe, [2] en $(C_{1-8}\text{-alkyl})_{m8h}$-aminogruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af <1> en $(C_{1-8}\text{-alkyl})_{m8i}$-aminosulfonylgruppe, og <2> en C_{1-8}-alkylsulfonylgruppe eller [3] en C_{1-8}-alkylsulfonylgruppe,
m8h: 0~2,
m8i: 0~2,

(7) en 4- til 10-leddet heterocycloalkyl (C_{0-8}-alkyl)-aminocarbonylgruppe, der kan være substitueret med oxogruppe(r),
(8) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med et eller flere R^{8D},
R^{8D}: [1] en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8D1}, [2] en hydroxygruppe eller [3] en C_{1-8}-alkylsulfonylgruppe,
R^{8D1}: [1] en hydroxygruppe eller [2] en C_{1-8}-alkoxygruppe,
(9) en hydroxycarbonylgruppe,
(10) en C_{0-8}-alkoxy (C_{0-8}-alkyl)-aminocarbonylgruppe, der kan være substitueret med hydroxygruppe(r),
(11) et halogenatom,
(12) en $(C_{1-8}\text{-alkyl})_{m8j}$-aminogruppe, der kan være substitueret med 4- til 10-leddet heterocycloalkylgruppe(r),
m8j: 0~2,
(13) en hydroxylgruppe,
(14) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{8E},
R^{8E}:
<1> en hydroxygruppe,
<2> en C_{1-8}-alkoxycarbonylgruppe,
<3> en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med et eller flere R^{8E1},
<4> en $(C_{1-8}\text{-alkyl})_{m8k1}$-aminogruppe, der kan være substitueret med et eller flere R^{8E2}, m8k1: 0~2,
<5> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8E3},
<6> en 5- til 14-leddet heteroarylgruppe,
<7> en $(C_{1-8}\text{-alkyl})_{m8k2}$-aminocarbonylgruppe, der kan være substitueret med et eller flere R^{8E6}
m8k2: 0~2,
<8> en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{8E7},
<9> en C_{1-8}-alkylthiogruppe,
<10> en C_{1-8}-alkylsulfinylgruppe, eller
<11> en C_{1-8}-alkylsulfonylgruppe,
R^{8E1}:
<1> en C_{1-8}-alkoxycarbonylgruppe,
<2> en C_{1-8}-alkanoylgruppe,

<3> en C_{1-8}-alkylsulfonylgruppe,
<4> en $(C_{1-8}$-alkyl$)_{m8k3}$-aminosulfonylgruppe
m8k3: 0~2, eller
<5> en 4- til 10-leddet heterocycloalkylgruppe,
R^{8E2}:
<1> en hydroxygruppe,
<2> en C_{1-8}-alkoxycarbonylgruppe,
<3> en C_{3-8}-cycloalkylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), der kan være substitueret med hydroxygruppe(r),
<4> en C_{1-8}-alkanoylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en $(C_{1-8}$-alkyl$)_{m8k4}$-aminogruppe og [2] et halogenatom,
m8k4: 0~2,
<5> en $(C_{1-8}$-alkyl$)_{m8k5}$-aminocarbonylgruppe,
m8k5: 0~2,
<6> en C_{1-8}-alkylsulfonylgruppe,
<7> en 4- til 10-leddet nitrogen-holdig heterocycloalkylsulfonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
<8> en $(C_{1-8}$-alkyl$)_{m8k6}$-aminosulfonylgruppe,
m8k6: 0~2, eller
R^{8E3}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en hydroxygruppe og [2] en C_{1-8}-alkylcarbonyloxygruppe,
<2> en hydroxygruppe,
<3> en C_{3-8}-cycloalkylgruppe,
<4> en C_{1-8}-alkylsulfonylgruppe,
<5> en $(C_{1-8}$-alkyl$)_{m8k8}$-aminocarbonylgruppe,
m8k8: 0~2,
<6> en C_{1-8}-alkanoylgruppe, der kan være substitueret med hydroxygruppe(r),
<7> en oxogruppe eller
<8> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med substituent(er), der er valgt fra gruppen bestående af [1] en C_{1-8}-alkanoylgruppe og [2] en C_{1-8}-alkylsulfonylgruppe,
R^{8E6}:

<1> en C_{2-8}-alkenylcarbonyloxygruppe,
<2> en hydroxygruppe,
<3> en cyanogruppe,
<4> en $(C_{1-8}\text{-alkyl})_{m8k9}$-aminogruppe, der kan være substitueret med hydroxygruppe(r), m8k9: 0~2,
<5> en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r),
<6> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r), eller
<7> en 5- til 14-leddet heteroarylgruppe,
R^{8E7}:
<1> en hydroxygruppe, eller
<2> en C_{1-8}-alkoxygruppe, der kan være substitueret med hydroxygruppe(r),
(15) en 4- til 10-leddet heterocycloalkyloxygruppe, der kan være substitueret med et eller flere R^{8F}:
R^{8F}:
<1> en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{8F1},
<4> en C_{3-8}-cycloalkylgruppe,
<3> en C_{1-8}-alkanoylgruppe, der kan være substitueret med halogenatom(er),
<4> en C_{1-8}-alkoxycarbonylgruppe,
<5> en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{8F2},
<6> en C_{1-8}-alkylsulfonylgruppe, eller
<7> en hydroxygruppe,
R^{8F1}: [1] en hydroxygruppe, [2] en C_{1-8}-alkoxygruppe eller [3] et halogenatom,
R^{8F2}: [1] en 4- til 10-leddet heterocycloalkylgruppe, [2] en C_{1-8}-alkoxycarbonylgruppe eller [3] en C_{1-8}-alkylsulfonylgruppe,
(16) en 5- til 14-leddet heteroaryloxygruppe,
(17) en $(C_{1-8}\text{-alkyl})_{m8l1}$-aminosulfonyloxygruppe,
m8l1: 0~2,
(18) en C_{1-8}-alkylthiogruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m8l2}$-aminogruppe(r),
m8l2: 0~2,
(19) en C_{1-8}-alkylsulfonylgruppe, der kan være substitueret med et eller flere R^{8G},

R^{8G}: [1] en hydroxycarbonylgruppe, [2] en hydroxygruppe eller [3] en $(C_{1-8}$-alkyl$)_{m8l3}$-aminogruppe,
m8l3: 0~2,
(20) en C_{2-8}-alkenyloxygruppe, og
(21) en C_{1-8}-alkylsulfonyloxygruppe, der kan være substitueret med halogenatom(er);

R^9 er fra gruppen bestående af:

(1) et hydrogenatom,
(2) en C_{1-8}-alkylgruppe, der kan være substitueret med et eller flere R^{9A},
R^{9A}: [1] en C_{3-8}-cycloalkylgruppe, [2] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9A1}, [3] en hydroxygruppe eller [4] en C_{1-8}-alkoxygruppe,
R^{9A1}: [1] en C_{1-8}-alkylgruppe, [2] en C_{3-8}-cycloalkylgruppe eller [3] en 4- til 10-leddet heterocycloalkylgruppe,
(3) en C_{2-8}-alkenylgruppe,
(4) en C_{2-8}-alkynylgruppe, der kan være substitueret med et eller flere R^{9C},
R^{9C}: [1] en C_{1-8}-alkoxygruppe, [2] en $(C_{1-8}$-alkyl$)_{m9b}$-aminogruppe, der kan være substitueret med C_{6-10}-arylgruppe(r), [3] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9C1}, [4] en C_{3-8}-cycloalkylgruppe, [5] en hydroxygruppe eller [6] en hydroxycarbonylgruppe,
m9b: 0~2,
R^{9C1}: [1] en C_{3-8}-cycloalkylgruppe, [2] en 4- til 10-leddet heterocycloalkylgruppe eller [3] en oxogruppe,
(5) en C_{3-8}-cycloalkylgruppe,
(6) en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med et eller flere R^{9D},
R^{9D}: [1] en C_{1-8}-alkylgruppe, der kan være substitueret med 4- til 10-leddet heterocycloalkylgruppe(r), [2] en C_{3-8}-cycloalkylgruppe, [3] en 4- til 10-leddet heterocycloalkylgruppe eller [4] en C_{1-6}-alkylsulfonylgruppe,
(7) en C_{6-10}-arylgruppe, der kan være substitueret med et eller flere R^{9E},
R^{9E}: [1] et halogenatom, [2] en hydroxygruppe, [3] en hydroxycarbonylgruppe eller [4] en C_{1-8}-alkylgruppe, der kan være substitueret med hydroxygruppe(r),
(8) en 5- til 14-leddet heteroarylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
(9) en cyanogruppe,

(10) en C_{1-8}-alkanoylgruppe,
(11) en 4- til 10-leddet nitrogen-holdig heterocycloalkylcarbonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r),
(12) et halogenatom,
(13) en $(C_{1-8}\text{-alkyl})_{m9c}$-aminogruppe,
m9c: 0~2,
(14) en C_{1-8}-alkylcarbonyl(C_{0-8}-alkyl)aminogruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m9d}$-aminogruppe(r),
m9d: 0~2,
(15) en C_{1-8}-alkylsulfonyl(C_{0-8}-alkyl)aminogruppe,
(16) en $(C_{1-8}\text{-alkyl})_{m9e}$-aminosulfonyl($C_{0-8}$-alkyl)aminogruppe,
m9e: 0~2,
(17) en nitrogruppe,
(18) en hydroxygruppe,
(19) en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{9G},
R^{9G}: [1] en hydroxygruppe, [2] en hydroxycarbonylgruppe, [3] en C_{6-10}-arylgruppe, der kan være substitueret med C_{1-8}-alkoxygruppe(r), [4] en $(C_{1-8}\text{-alkyl})_{m9g1}$-aminogruppe, [5] en C_{1-8}-alkoxygruppe, der kan være substitueret med et eller flere R^{9G1}, eller [6] en 5- til 14-leddet heteroarylgruppe,
m9g1: 0~2,
R^{9G1}: [1] en C_{1-8}-alkoxygruppe, eller [2] en hydroxycarbonylgruppe,
(20) en 4- til 10-leddet heterocycloalkyloxygruppe, der kan være substitueret med 4- til 10-leddet heterocycloalkylgruppe(r),
(21) en C_{1-8}-alkylthiogruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m9f}$-aminogruppe(r),
m9f: 0~2,
(22) en C_{1-8}-alkylsulfonylgruppe, der kan være substitueret med $(C_{1-8}\text{-alkyl})_{m9g}$-aminogruppe(r),
m9g: 0~2,
(23) en $(C_{1-8}\text{-alkyl})_{m9h}$-aminosulfonylgruppe,
m9h: 0~2 og
(24) en 4- til 10-leddet nitrogen-holdig heterocycloalkylsulfonylgruppe, der kan være substitueret med C_{1-8}-alkylgruppe(r);
R^{10} repræsenterer [1] et hydrogenatom eller [2] en 4- til 10-leddet heterocycloalkylgruppe, der kan være substitueret med 4- til 10-leddet heterocycloalkylgruppe(r)].

6. Forbindelse ifølge krav 1 eller salt eller solvat deraf, hvor forbindelsen er valgt fra gruppen bestående af:
9-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-cyclopropylethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
6,6-dimethyl-8-(1-oxetan-3-yl-piperidin-4-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-brom-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-brom-8-(4-cyclopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-chlor-6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-prop-1-ynyl-6,11-dihydro-5H-benzo[b]carbazol-3 -carbonitril;
6,6,9-trimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-ethyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-ethynyl-6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-cyclobutyl-piperazin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-ethynyl-6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
6,6-dimethyl-11-oxo-8-(4-pyrrolidin-1-yl-piperidin-1-yl)-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-cyclobutyl-piperazin-1-yl)-9-ethynyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;

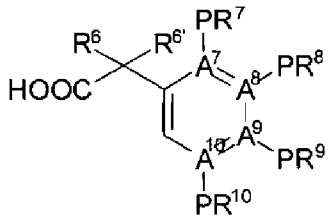
8-(1-isopropyl-piperidin-4-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-isopropyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(4-cyclobutyl-piperazin-1-yl)-9-cyclopropyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
8-(2-tert-butylamino-ethoxy)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-ethynyl-8-(4-methanesulfonyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
9-brom-8-(4-cyclobutyl-piperazin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril;
6,6-dimethyl-8-(4-oxetan-3-yl-piperazin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril; og
9-ethynyl-6,6-dimethyl-8-morpholin-4-yl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril.

7. Farmaceutisk sammensætning omfattende forbindelsen ifølge et af kravene 1 til 5 eller et salt eller solvat deraf og og en farmaceutisk acceptabel bærer(e).

8. Forbindelse ifølge et af kravene 1 til 5 eller et salt eller solvat deraf til anvendelse som en ALK-inhibitor.

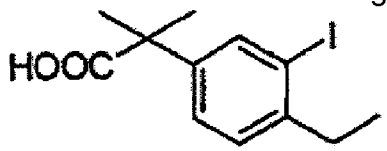
9. Forbindelse ifølge et af kravene 1 til 5 eller et salt eller solvat deraf til anvendelse ved forebyggelse eller behandling af cancer, cancermetastase, depression eller forstyrrelse af den kognitive funktion.

10. Forbindelse med formlen IIe:

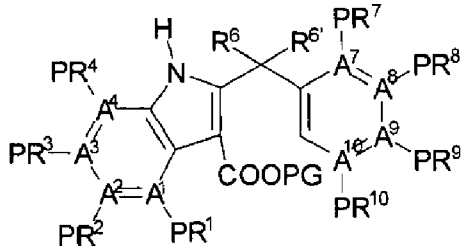


hvor, A^7 til A^{10}, R^6 og $R^{6'}$ er som defineret i krav 1; PR^7 til PR^{10} er de samme som R^7 til R^{10}, der er defineret i krav 1 eller repræsenterer en gruppe, der kan omdannes til R^7 til R^{10},

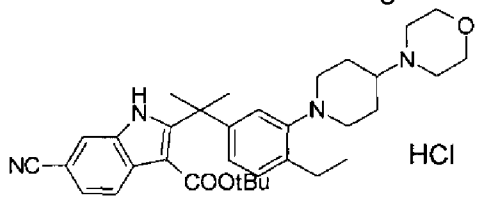
hvor formlen IIe er den følgende forbindelse:



11. Forbindelse med formlen IIIb eller et salt deraf:



hvor, A^1 til A^4, A^7 til A^{10}, R^6 og $R^{6'}$ er som defineret i krav 1; PR^1 til PR^4 og PR^7 til PR^{10} er de samme som R^1 til R^4 og R^7 til R^{10}, der er defineret i krav 1 eller repræsenterer en gruppe, der kan omdannes til R^1 til R^4 og R^7 til R^{10}; PG repræsenterer en beskyttelsesgruppe,
hvor formlen IIIb er den følgende forbindelse:



12. Forbindelse eller et salt eller et solvat deraf, hvor forbindelsen er valgt fra gruppen bestående af 6,6-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-9-propyl-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 9-methoxy-6,6-dimethyl-8-(4-morpholin-1-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 9-ethyl-8-(4-morpholinopiperidin-1-yl)-11-oxo-2',3',5,5',6',11-hexahydrospiro[benzo[b]carbazol-6,4'-pyran]-3-carbonitril, 8-[4-((2R,6S)-2,6-dimethyl-morpholin-4-yl)-piperidin-1-yl]-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazol-3-carbonitril, 9-ethyl-6,6-dimethyl-8-(3-morpholin-4-yl-azetidin-1-yl)-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazol-3-carbonitril, 9-ethyl-8-[4-(2-hydroxy-ethylamino)-piperidin-1-yl]-6,6-dimethyl-11-oxo-6,11-dihydro-5*H*-benzo[b]carbazol-3-carbonitril, 9-ethyl-8-(4-ethyl-4-morpholin-4-yl-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]

carbazol-3-carbonitril, 9-ethyl-8-(4-isopropyl-4-morpholin-4-yl-piperidin-1-yl)-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 8-(4-amino-piperidin-1-yl)-9-ethyl-6,6-dimethyl-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 9-ethyl-6,6-dimethyl-8-(4-2,2,3,3,5,5,6,6-d8-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 9-ethyl-6,6-dimethyl-11-oxo-8-[4-(4-oxy-morpholin-4-yl)-piperidin-1-yl]-6,11-dihydro-5H-benzo[b]carbazol-3-carbonitril, 5,5-dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5H-pyrido[4,3-b]carbazol-8-carbonitril, 4-fluor-5,5-dimethyl-3-(4-morpholin-4-yl-piperidin-1-yl)-11-oxo-6,11-dihydro-5*H*-pyrido[4,3-b]carbazol-8-carbonitril og 7-ethyl-10,10-dimethyl-8-(4-morpholin-4-yl-piperidin-1-yl)-5-oxo-10,11-dihydro-5H-1,11-diazo-benzo[b]fluoren-2-carbonitril.