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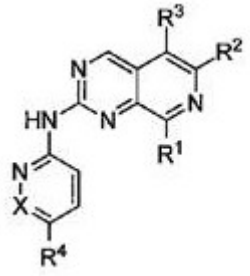
(54)发明名称

吡啶并[3,4-d]嘧啶衍生物及其药学上可接受的盐

(57)摘要

本发明的目的在于,提供具有优异的CDK4/6抑制活性的化合物。本发明是式(I)所表示的化合物或其药学上可接受的盐。



(I)

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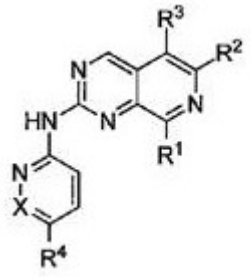
1.式(I)所表示的化合物或其药学上可接受的盐：

[化学式1]



(I)

式中，

R^1表示C_{3-12}环烷基、C_{4-12}环烯基、4~12元的杂环基、C_{6-10}芳基、或5~10元的杂芳基；R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1~4个的杂原子；

R^1可被选自下述的1~6个的取代基取代：卤素、＝O、-OH、-CN、-COOH、-$COOR^6$、-R^7、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{3-6}环烷基、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的3~10元的杂环基、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-8}酰基、和被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-8}烷氧基；

R^6和R^7各自独立地表示被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-6}烷基；

R^2表示C_{1-8}烷基、C_{3-8}环烷基、4~6元的杂环基、C_{1-8}酰基、-$COOR^8$、或-$CONR^9R^{10}$；

R^2的C_{1-8}烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、以及0~5个的氟原子；

R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、0~1个的羟甲基、以及0~5个的氟原子；

其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

R^8，R^9，和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

R^2的4~6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1~4个的取代基取代；

R^2的C_{1-8}酰基、-$COOR^8$、和-$CONR^9R^{10}$可被选自下述的1~4个的取代基取代：氟原子、-OH、和C_{1-4}烷氧基；

R^2的-$CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环；

关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1~2个的氧原子；

R^3表示氢原子、C_{1-8}烷基、或卤素原子；

X表示CR^{11}或氮原子；

R^{11}表示氢原子、C_{1-6}烷基、或C_{3-6}环烷基；

R^4由-A^1-A^2-A^3表示；

A^1表示单键、或C_{1-8}亚烷基；

处于A^1的任意位置的1~2个的sp^3碳原子可被选自[-O-、-NR^{14}-、-C(＝O)-、-C(＝O)-O-、-

O-C(=O)-、-O-C(=O)-O-、-C(=O)-NR^{15}-、-O-C(=O)-NR^{16}-、-NR^{17}-C(=O)-、-NR^{18}-C(=O)-O-、-NR^{19}-C(=O)-NR^{20}-、-S(=O)$_p$-、-S(=O)$_2$-NR^{21}-、-NR^{22}-S(=O)$_2$-、和-NR^{23}-S(=O)$_2$-NR^{24}-]的1~2个的结构置换，

其中，在2个的sp^3碳原子被置换的情况下，不形成-O-O-、-O-NR^{14}-、-NR^{14}-O-、-O-CH_2-O-、-O-CH_2-NR^{14}-、和-NR^{14}-CH_2-O-这样的结构；

A^2表示单键、C_{1-7}亚烷基、C_{3-12}亚环烷基、C_{3-12}环烷叉基、4~12元的亚杂环基、4~12元的杂环叉基、C_{6-10}亚芳基、或5~10元的亚杂芳基；

A^3表示卤素、-CN、-NO_2、-R^{25}、-OR^{26}、-$NR^{27}R^{28}$、-C(=O)R^{29}、-C(=O)-OR^{30}、-O-C(=O)R^{31}、-O-C(=O)-$NR^{32}R^{33}$、-C(=O)-$NR^{34}R^{35}$、-NR^{36}-C(=O)R^{37}、-NR^{38}-C(=O)-OR^{39}、-S(=O)$_2$-R^{40}、-S(=O)$_2$-$NR^{41}R^{42}$、或-NR^{43}-S(=O)$_2R^{44}$；

其中，在A^2侧的A^1末端为选自[-O-、-NR^{14}-、-C(=O)-、-C(=O)-O-、-O-C(=O)-、-O-C(=O)-O-、-C(=O)-NR^{15}-、-O-C(=O)-NR^{16}-、-NR^{17}-C(=O)-、-NR^{18}-C(=O)-O-、-NR^{19}-C(=O)-NR^{20}-、-S(=O)$_p$-、-S(=O)$_2$-NR^{21}-、-NR^{22}-S(=O)$_2$-、和-NR^{23}-S(=O)$_2$-NR^{24}-]的结构、并且A^2为单键的情况下，A^3表示-R^{25}；R^{14}、R^{32}、R^{34}、R^{36}、R^{38}、R^{41}、和R^{43}各自独立地表示氢原子、C_{1-8}烷基、C_{1-8}酰基、C_{1-8}烷基磺酰基、4~12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5~10元的杂芳基、(4~12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5~10元的杂芳基)C_{1-3}烷基；

R^{15}~R^{31}、R^{33}、R^{35}、R^{37}、R^{39}、R^{40}、R^{42}、和R^{44}各自独立地表示氢原子、C_{1-8}烷基、4~12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5~10元的杂芳基、(4~12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5~10元的杂芳基)C_{1-3}烷基；

A^1、A^2、A^3、以及A^1、A^2、和A^3中的R^{14}~R^{44}各自独立地可被选自下述的1~4个的取代基取代：-OH、=O、-COOH、-SO_3H、-PO_3H_2、-CN、-NO_2、卤素、被[0~2个的-OH、0~2个的-OR^{45}、和0~6个的氟原子]取代的C_{1-8}烷基、被[0~2个的-OH、0~2个的-OR^{46}、和0~6个的氟原子]取代的C_{3-12}环烷基、被[0~2个的-OH、0~2个的-OR^{47}、和0~6个的氟原子]取代的C_{1-8}烷氧基、和被[0~2个的-OH、0~2个的-OR^{49}、和0~6个的氟原子]取代的4~12元的杂环基；

R^{14}~R^{44}可在A^1内、A^2内、A^3内、[A^1与A^2之间]、[A^1与A^3之间]、或[A^2与A^3之间]经由[单键、-O-、-NR^{50}-、或-S(=O)$_p$-]键合而形成环；

R^{11}可与[A^1、A^2、或A^3]经由[单键、-O-、-NR^{51}-、或-S(=O)$_p$-]键合而形成环；

R^{45}~R^{51}表示氢原子、或被[0~1个的-OH、和0~6个的氟原子]取代的C_{1-4}烷基；

p表示0~2的整数；

A^1和A^3的杂环基、杂芳基、(杂环基)烷基、和(杂芳基)烷基、以及A^2的亚杂环基、杂环叉基、亚杂芳基中的杂原子为：在各自的基团中，独立地从氧原子、硫原子、和氮原子中选择1~4个的杂原子。

2.权利要求1所述的化合物或其药学上可接受的盐，其中，R^1表示C_{3-8}环烷基、C_{4-7}环烯基、4~8元的杂环基、苯基、或5~10元的杂芳基；

R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1~4个的杂原子；

R^1可被选自下述的1~6个的取代基取代：氟原子、=O、-OH、-COOH、和被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-6}烷基；

R^2表示C_{1-8}烷基、4~6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$；

R^2的C_{1-8}烷基被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、以及0~5个的氟原子；

其中，R^2不为无取代的C_{1-8}烷基、和三氟甲基；

R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

R^3表示氢原子、或C_{1-8}烷基；

X表示CR^{11}或氮原子；

R^{11}表示氢原子、或C_{1-6}烷基；

R^4由$-A^1-A^2-A^3$表示；

A^1表示单键、或C_{1-4}亚烷基；

处于A^1的任意位置的1个的sp^3碳原子可被选自[-O-、$-NR^{14}-$、$-NR^{17}-C(=O)-$、和$-NR^{22}-S(=O)_2-$]的1个的结构置换，

A^2表示单键、4~12元的亚杂环基、C_{6-10}亚芳基、或5~10元的亚杂芳基；

A^3表示卤素、-CN、$-R^{25}$、$-OR^{26}$、$-NR^{27}R^{28}$、$-C(=O)R^{29}$、$-C(=O)-OR^{30}$、$-O-C(=O)R^{31}$、$-O-C(=O)-NR^{32}R^{33}$、$-C(=O)-NR^{34}R^{35}$、$-NR^{36}-C(=O)R^{37}$、$-NR^{38}-C(=O)-OR^{39}$、$-S(=O)_2-R^{40}$、$-S(=O)_2-NR^{41}R^{42}$、或$-NR^{43}-S(=O)_2R^{44}$；

其中，在A^2侧的A^1末端为[-O-、$-NR^{14}-$、$-NR^{17}-C(=O)-$、或$-NR^{22}-S(=O)_2-$]、并且A^2为单键的情况下，A^3表示$-R^{25}$；

R^{14}、R^{32}、R^{34}、R^{36}、R^{38}、R^{41}、和R^{43}各自独立地表示氢原子、C_{1-8}烷基、C_{1-8}酰基、C_{1-8}烷基磺酰基、4~12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5~10元的杂芳基、(4~12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5~10元的杂芳基)C_{1-3}烷基；

R^{15}~R^{31}、R^{33}、R^{35}、R^{37}、R^{39}、R^{40}、R^{42}、和R^{44}各自独立地表示氢原子、C_{1-8}烷基、4~12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5~10元的杂芳基、(4~12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5~10元的杂芳基)C_{1-3}烷基；

A^1、A^2、A^3、以及A^1、A^2、和A^3中的R^{14}~R^{44}各自独立地可被选自下述的1~4个的取代基取代：-OH、=O、卤素、C_{1-6}烷基磺酰基、和被[0~1个的-OH、和0~6个的氟原子]取代的C_{1-8}烷基；

R^{11}和A^1可经由单键键合而形成环。

3.权利要求1所述的化合物或其药学上可接受的盐，其中，R^1表示C_{3-12}环烷基。

4.权利要求1所述的化合物或其药学上可接受的盐，其中，R^1表示4~12元的杂环基。

5.权利要求1所述的化合物或其药学上可接受的盐，其中，R^1表示C_{6-10}芳基、或5~10元的杂芳基。

6.权利要求1~5的任一项所述的化合物或其药学上可接受的盐，其中，R^2为被1~4个的氟原子取代的C_{1-8}烷基。

7.权利要求1~5的任一项所述的化合物或其药学上可接受的盐，其中，R^2为被下述的基团取代的C_{1-8}烷基：0~1个的-OH、和被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基。

8.权利要求1、3~5的任一项所述的化合物或其药学上可接受的盐，其中，R^2为可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1~4个的取代基取代的4~6元的杂环基。

9.权利要求1、3~5的任一项所述的化合物或其药学上可接受的盐，其中，R^2为可被选自

氟原子、-OH、和C_{1-8}烷氧基的1~4个的取代基取代的C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$。

10.权利要求1~9的任一项所述的化合物或其药学上可接受的盐，其中，X表示CR^{11}。

11.权利要求1~9的任一项所述的化合物或其药学上可接受的盐，其中，X表示氮原子。

12.权利要求1~11的任一项所述的化合物或其药学上可接受的盐，其中，A^1为单键。

13.权利要求1~11的任一项所述的化合物或其药学上可接受的盐，其中，A^1表示亚甲基，A^1的所有sp^3碳原子不被其他结构置换。

14.权利要求1~11的任一项所述的化合物或其药学上可接受的盐，其中，A^1为-O-。

15.权利要求1~9的任一项所述的化合物或其药学上可接受的盐，其中，X表示CR^{11}；

R^{11}表示C_{1-6}烷基；

A^1表示C_{1-8}亚烷基；

处于A^1的任意位置的1个的sp^3碳原子被选自[$-NR^{14}-$、$-NR^{17}-C(=O)-$、和$-NR^{22}-S(=O)_2-$]的1个的结构置换；

R^{11}和A^1经由单键键合而形成环。

16.权利要求1~15的任一项所述的化合物或其药学上可接受的盐，其中，A^2表示5~9元的亚杂环基；

A^2可被选自下述的1~4个的取代基取代：-OH、=O、-COOH、$-SO_3H$、$-PO_3H_2$、-CN、$-NO_2$、卤素、被[0~2个的-OH、0~2个的$-OR^{45}$、和0~6个的氟原子]取代的C_{1-8}烷基、被[0~2个的-OH、0~2个的$-OR^{46}$、和0-6个的氟原子]取代的C_{3-12}环烷基、被[0~2个的-OH、0~2个的$-OR^{47}$、和0~6个的氟原子]取代的C_{1-8}烷氧基、和被[0~2个的-OH、0~2个的$-OR^{49}$、和0~6个的氟原子]取代的4~12元的杂环基。

17.权利要求1~16的任一项所述的化合物或其药学上可接受的盐，其中，A^3为氢原子。

18.权利要求1~16的任一项所述的化合物或其药学上可接受的盐，其中，A^3为卤素、$-CN$、$-R^{25}$、$-OR^{26}$、$-NR^{27}R^{28}$、$-C(=O)R^{29}$、或$-C(=O)-OR^{30}$，R^{25}~R^{30}各自独立地表示氢原子、可被取代的C_{1-8}烷基、可被取代的4~12元的杂环基、可被取代的C_{3-12}环烷基、可被取代的(4~12元的杂环基)C_{1-3}烷基、或可被取代的(C_{3-12}环烷基)C_{1-3}烷基。

19.权利要求1~18的任一项所述的化合物或其药学上可接受的盐，其中，R^3为氢原子。

20.权利要求1、3~19的任一项所述的化合物或其药学上可接受的盐，其中，R^3表示C_{1-4}烷基、氟原子、或氯原子。

21.以下所述的化合物或其药学上可接受的盐：

[2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

1-[6-(羟甲基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-2-酮；

6-(二氟甲基)-N-[5-(4-甲基哌嗪-1-基)吡啶-2-基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-胺；

[8-环己基-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-苯基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

6-(二氟甲基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-苯基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

6-(二氟甲基)-N-(5-哌嗪-1-基吡啶-2-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

6-(二氟甲基)-8-苯基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

6-(二氟甲基)-N-[5-(4-甲基哌嗪-1-基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[8-(4-甲基苯基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(2-甲基苯基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-噻吩-3-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(呋喃-3-基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(4-甲基苯基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(2-甲基苯基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-噻吩-3-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(呋喃-3-基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[8-(环己烯-1-基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酸；

1-[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酸甲酯；

1-[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙酮；

N,N-二甲基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

N-甲基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

6-(二氟甲基)-8-(2-甲基苯基)-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

6-(二氟甲基)-8-(呋喃-3-基)-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

6-(甲氧基甲基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[5-甲基-8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

1-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

2,2,2-三氟-1-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

6-(1,1-二氟乙基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

2-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

2-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]吡咯烷-2-甲酸；

1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-3-甲酸；

1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-2-甲酸；

1-[6-[(1R)-1-羟乙基]-2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]吡咯烷-2-甲酸；

6-(1-甲氧基乙基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

8-(1,2,3,3a,4,5,7,7a-八氢吡咯并[2,3-c]吡啶-6-基)-6-(1-甲氧基乙基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

[1-[6-(1-甲氧基乙基)-2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-基]甲醇；

6-(1-甲氧基乙基)-8-[4-(甲氧基甲基)哌啶-1-基]-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

(1R)-1-[8-(氮杂环丁烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[8-(氮杂环丁烷-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

1-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(1R)-1-[2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(2-氮杂螺[3.3]庚烷-2-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(氮杂环庚烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-(4-氟哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4-氟哌啶-1-基)-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[8-(4,4-二氟哌啶-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

1-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌啶-4-醇；

1-[[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌啶-4-醇；

1-[[6-[[6-[(1R)-1-羟乙基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌啶-4-醇；

(1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]吡啶

并[3,4-d]嘧啶-8-基]哌啶-4-醇；

1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

1-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

1-[6-[[6-[(1R)-1-羟乙基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

(1R)-1-[8-(2,2-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-甲酸；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-(4-甲基哌嗪-1-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4-氟哌啶-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4,4-二氟哌啶-1-基)-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(2R)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[4-(三氟甲基)哌啶-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(1,1-二氧代-1,4-噻嗪-4-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[(6-甲基-5-哌嗪-1-基吡啶-2-基)氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[(6-甲基-5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[4-(2-羟乙基)哌嗪-1-基]-6-甲基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-5-酮；

1-[6-[[8-(4-氟哌啶-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(1R)-1-[2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

2-[2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[6-(2-羟乙基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

2-[2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

2-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

2-[4-[[6-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

1-[6-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(2S)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(3S)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(3R)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(2,5-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3,3-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3-氮杂双环[3.1.0]己烷-3-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(8-氮杂双环[3.2.1]辛烷-8-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

[2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

2-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶

并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4-氟哌啶-1-基)-2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3,4-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-[4-(2-甲基磺酰基乙基)哌嗪-1-基]哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4-氟哌啶-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3R)-3-氟吡咯烷-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3S)-3-氟吡咯烷-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

6-[(1R)-1-甲氧基乙基]-N-(6-哌嗪-1-基哒嗪-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

6-[(1R)-1-甲氧基乙基]-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

4-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1-甲基-1,4-二氮杂环庚烷-5-酮；

4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1-甲基-1,4-二氮杂环庚烷-5-酮；

(1R)-1-[2-[[5-[(4-乙基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(4-甲基哌嗪-1-基)哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(4-氟哌啶-1-基)-2-[[6-(4-甲基哌嗪-1-基)哒嗪-3-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

8-(4-氟哌啶-1-基)-6-[(1R)-1-甲氧基乙基]-N-[6-(4-甲基哌嗪-1-基)哒嗪-3-基]吡啶并[3,4-d]嘧啶-2-胺；

8-(4-氟哌啶-1-基)-6-[(1R)-1-甲氧基乙基]-N-(6-哌嗪-1-基哒嗪-3-基)吡啶并[3,4-d]嘧啶-2-胺；

1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮；

2-[4-[[6-[[6-(二氟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

1-[6-(二氟甲基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

3-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]丙烷-1-醇；

(1R)-1-[2-[[5-[(3S,4S)-3-氟-1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(3S,4R)-3-氟-1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3,3-二氟氮杂环丁烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[(1R)-1-羟乙基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

2-[2-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(2R)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(2S)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(3R)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(3S)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(2,5-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3,4-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3,3-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[4-(三氟甲基)哌啶-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-哌啶-4-基甲酮；

[1-(2-羟乙基)哌啶-4-基]-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基哌啶-4-基)甲酮；

(1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨

基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-(2-羟乙基)-4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-5-酮；

(1R)-1-[2-[[5-[[(2R)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-环丙基-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[8-环丙基-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(1R)-1-[2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(环己烯-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(3-氮杂双环[3.1.0]己烷-3-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(氮杂环庚烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

(1S)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

(1R)-1-[2-[[6-(氧杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(2-吗啉-4-基乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-哌啶-1-基-2-[(6-哌啶-4-基磺酰基-7,8-二氢-5H-1,6-萘啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-哌啶-1-基-2-[(5-哌啶-4-基氧基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(2S)-2-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

(2R)-2-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

(2R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

1-[6-[[6-[(2R)-2-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(2R)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

(2R)-2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

(1R)-1-[8-(氮杂环丁烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(2,2-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(8-氮杂双环[3.2.1]辛烷-8-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(氮杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-[1-(2-羟乙基)氮杂环丁烷-3-基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-(1,4-氧杂氮杂环庚烷-4-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-(1,4-氧杂氮杂环庚烷-4-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3S)-3-氟哌啶-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3S)-3-氟哌啶-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3S)-3-氟吡咯烷-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3R)-3-氟吡咯烷-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(2S)-1-[4-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]丙烷-2-醇；

(2R)-1-[4-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]丙烷-2-醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[(2S)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[(2S)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[(3S)-3,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[(3S)-3,4-二甲基哌嗪-1-基]

甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-苯基吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[6-[(1R)-1-羟乙基]-8-苯基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

1-[6-[[6-[(2S)-1-羟基丙烷-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(2S)-2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

1-[6-[[6-[(2R)-1-羟基丙烷-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(2S)-2-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

2-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]乙腈；

(1R)-1-[2-[[6-(氧杂环丁烷-3-基甲基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3R)-3-氟哌啶-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-[(3R)-3-氟哌啶-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(1-甲基氮杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-(2-羟乙基)-5,7-二氢吡咯并[3,4-b]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(2S)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

1-[6-[[6-[(2S)-2-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(2S)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环戊-3-基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

6-(氧杂环戊-3-基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环戊-3-基)-N-(6-哌嗪-1-基哒嗪-3-基)吡啶并[3,4-d]嘧啶-2-胺；

6-(氧杂环戊-3-基)-N-(6-哌嗪-1-基哒嗪-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-吡咯烷-2-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-吡咯烷-3-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-哌啶-2-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基吡咯烷-2-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基吡咯烷-2-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-哌啶-3-基]甲酮；

[(2R)-氮杂环丁烷-2-基]-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-吗啉-2-基甲酮；

(1R)-1-[2-[[6-(2-氨基乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-

基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-3-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-2-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基氮杂环丁烷-3-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[1-(2-羟乙基)氮杂环丁烷-3-基]甲酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-吡咯烷-1-基乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基吡咯烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟吡咯烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-哌啶-1-基乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-羟基哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-氟哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟哌啶-1-基)乙酮；

2-[4-[[6-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

2-[4-[[6-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-

5H-1,6-萘啶-6-基]-吗啉-3-基甲酮；

吗啉-2-基-[2-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

吗啉-3-基-[2-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基吡咯烷-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基哌啶-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基哌啶-3-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基氮杂环丁烷-2-基]甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-3-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-2-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基氮杂环丁烷-3-基)甲酮；

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)哌啶-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)哌啶-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)哌啶-3-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)哌啶-3-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-3-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-2-基]甲酮;

[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[1-(2-羟乙基)氮杂环丁烷-3-基]甲酮;

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧

啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-吡咯烷-1-基乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基吡咯烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟吡咯烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟氮杂环丁烷-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-哌啶-1-基乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-羟基哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-氟哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基哌啶-1-基)乙酮；

1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟哌啶-1-基)乙酮；

4-(2-羟乙基)-1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[4-(2-羟乙基)哌嗪-1-基]-6-甲基吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[2-[[6-[4-(2-羟乙基)哌嗪-1-基]哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

(1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[6-[4-(2-羟乙基)哌嗪-1-基]哒嗪-3-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

1-[6-[[6-[(1R)-1-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮；

4-(2-羟乙基)-1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮；

1-[6-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

1-[6-[[8-(8-氮杂双环[3.2.1]辛烷-8-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮。

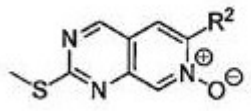
22.药物组合物，其包含权利要求1~21的任一项所述的化合物或其药学上可接受的盐、和药学上可接受的载体。

23.具有CDK4/6抑制活性的药物组合物，其含有权利要求1~21的任一项所述的化合物或其药学上可接受的盐作为有效成分。

24.类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、或癌症的预防药或治疗药，其含有权利要求1~21的任一项所述的化合物或其药学上可接受的盐作为有效成分。

25.式(II)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐：

[化学式2]



(II)

式(II)中，R^2表示C_{1-8}烷基、C_{3-8}环烷基、4~6元的杂环基、C_{1-8}酰基、-$COOR^8$、或-$CONR^9R^{10}$；

R^2的C_{1-8}烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、以及0~5个的氟原子；

R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、0~1个的羟甲基、以及0~5个的氟原子；

其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

R^2的4~6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1~4个的取代基取代；

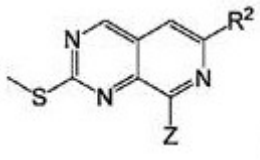
R^2的C_{1-8}酰基、-$COOR^8$、和-$CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1~4个的取代基取代；

R^2的-$CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环；

关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1~2个的氧原子，其中，R^2可被适宜的保护基保护。

26.式(III)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐：

[化学式3]



(III)

式(III)中，R^2表示C_{1-8}烷基、C_{3-8}环烷基、4~6元的杂环基、C_{1-8}酰基、-$COOR^8$、或-$CONR^9R^{10}$；

R^2的C_{1-8}烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、以及0~5个的氟原子；

R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代0~2个的C_{1-8}烷氧基、0~1个的羟甲基、以及0~5个的氟原子；

其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

R^2的4~6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1~4个的取代基取

代；

R^2的C_{1-8}酰基、-$COOR^8$、和-$CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1~4个的取代基取代；

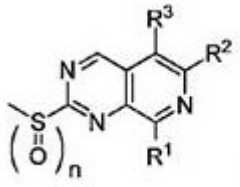
R^2的-$CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环；

关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1~2个的氧原子；

Z表示卤素原子，其中，R^2可被适宜的保护基保护。

27.式(IV)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐：

[化学式4]



(IV)

式(IV)中，R^1表示C_{3-12}环烷基、C_{4-12}环烯基、4~12元的杂环基、C_{6-10}芳基、或5~10元的杂芳基；R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1~4个的杂原子；

R^1可被选自下述的1~6个的取代基取代：卤素、=O、-OH、-CN、-COOH、-$COOR^6$、-R^7、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{3-6}环烷基、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的3~10元的杂环基、被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-8}酰基、和被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-8}烷氧基；

R^6和R^7各自独立地表示被[0~2个的-OH、0~2个的C_{1-8}烷氧基、和0~6个的氟原子]取代的C_{1-6}烷基；

R^2表示C_{1-8}烷基、C_{3-8}环烷基、4~6元的杂环基、C_{1-8}酰基、-$COOR^8$、或-$CONR^9R^{10}$；

R^2的C_{1-8}烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、以及0~5个的氟原子；

R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0~1个的-OH、被[0~1个的-OH、0~1个的C_{1-4}烷氧基、和0~3个的氟原子]取代的0~2个的C_{1-8}烷氧基、0~1个的羟甲基、以及0~5个的氟原子；

其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

R^2的4~6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1~4个的取代基取代；

R^2的C_{1-8}酰基、-$COOR^8$、和-$CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1~4个的取代基取代；

R^2的-$CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环；

关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1~2个的氧原子；

n表示0、1、或2，其中，R^1、和R^2可被适宜的保护基保护。

吡啶并[3,4-d]嘧啶衍生物及其药学上可接受的盐

技术领域

[0001] 本发明涉及吡啶并[3,4-d]嘧啶衍生物及其药学上可接受的盐,特别是涉及具有细胞周期蛋白依赖性激酶4和/或细胞周期蛋白依赖性激酶6(以下,也称为“CDK4/6”)的抑制活性、对于类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、或癌症的预防或治疗有效的化合物。

背景技术

[0002] 细胞增殖响应于各种刺激而发生,是细胞增加和分裂的过程。

[0003] 以癌症为代表的由细胞的过度增殖而引起的疾病的特征在于,例如由于直接或间接地调节细胞周期的进展的基因或蛋白质产生异常,结果陷入细胞不可控制,并且细胞周期过度地进展。因此,通过控制细胞周期,调节细胞过度增殖的物质可以用于治疗以不可控制或不希望的细胞增殖为特征的各种疾病。

[0004] 细胞周期的进展是一个复杂的过程,每个周期的阶段转换被高度地控制,且提供了多个检查点。

[0005] 细胞周期蛋白依赖性激酶和关联的丝氨酸/苏氨酸蛋白激酶是在细胞的分裂和增殖的调节中发挥必需功能的重要的细胞内酶。已知:细胞周期蛋白依赖性激酶的催化单元通过作为细胞周期蛋白所已知的调节亚单元而活化,哺乳类中也鉴定了多个细胞周期蛋白(非专利文献1)。

[0006] 视网膜母细胞瘤蛋白(Rb)是细胞周期中的从G1期转变为S期的检查点蛋白。Rb与E2F转录因子的家族相关联,在没有适当的生长刺激的存在下,妨碍它们的活性(非专利文献2和3)。受到有丝分裂促进物质刺激,细胞通过新合成作为CDK4/6的活化因子的细胞周期蛋白D而开始进入S期。一旦细胞周期蛋白D结合的CDK4/6,通过磷酸化而使Rb蛋白失活。Rb的磷酸化释放E2F以指示S期所需的基因转录。Rb的完全失活需要细胞周期蛋白D-CDK4/6和细胞周期蛋白E-CDK2这两者的磷酸化。已经显示出:在Rb的特定位点的基于CDK4/6的磷酸化是细胞周期蛋白E-CDK2磷酸化的必需条件(非专利文献4)。因此,细胞周期蛋白D-CDK4/6是控制从G1期至S期的重要的酶复合物。

[0007] 已知CDK2除了细胞周期蛋白E之外还与细胞周期蛋白A形成复合物,而且还在S期以后的过程中发挥功能,并且还参与DNA的复制。还存在下述的报道:在抑制CDK2的情况下,可能导致基因毒性的表达(非专利文献5)。

[0008] 已知:细胞周期蛋白D是正控制CDK4/6的活性的分子机制,与此相对比,由INK4a基因编码的p16选择性地负控制CDK4/6的活性(非专利文献6)。

[0009] CDK抑制剂可以用于治疗由异常细胞增殖引起的各种疾病,包括癌症、心血管疾病、肾脏疾病、特定的感染症和自己免疫疾病。不限于这些,例如还期待对于类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、癌症的治疗也有效。这样的病例中,根据以下的技术发现可期待经由CDK抑制的细胞周期、细胞增殖抑制是有效的。

[0010] 已有报道:在类风湿性关节炎中,由滑膜细胞的过度增殖所致的血管翳(pannus)

形成是已知的，该过度增殖可通过在模型动物的患部导入p16、或对动物给予CDK4/6抑制剂，而得到改善(非专利文献7～9)。另外，还有报道：在来源于类风湿性关节炎患者的滑膜细胞中，CDK4-细胞周期蛋白D复合物也控制MMP3的产生，通过负控制CDK4/6的活性，不仅抑制MMP3的增殖而且抑制MMP3的产生(非专利文献10)。

[0011] 根据以上的观点，还可以期待CDK4/6抑制剂对于类风湿性关节炎具有滑膜细胞增殖抑制效果以及软骨保护效果。

[0012] 包含参与细胞周期G1和S期检查点的基因的细胞增殖调节途径，与血管形成后的斑块进展、狭窄和再狭窄相关。已经显示出：CDK抑制蛋白质p21的过度表达会抑制血管形成后的血管平滑肌增殖和内膜增生(非专利文献11～12)。

[0013] 细胞周期的控制异常也与以在肾小管中充满液体的囊肿的生长为特征的多发性肾囊肿相关，使用CDK的小分子抑制剂的治疗是有效果的(非专利文献13)。

[0014] 据报道，在小鼠的肺纤维化模型中，通过腺病毒载体诱导细胞周期抑制蛋白质p21的表达是有效的(非专利文献14)。

[0015] 在大鼠的脑梗塞模型中，已知细胞周期蛋白D1/CDK4水平随着由局部缺血所致的神经细胞死亡而提高，据报道，通过给予非选择性CDK抑制剂即夫拉平度(flavopyridol)，可抑制神经细胞死亡(非专利文献15)。

[0016] 细胞周期蛋白D-CDK4/6-INK4a-Rb途径在人类癌症中经常检测到有利于癌细胞增殖的任何因子的异常，例如功能性p16INK4a的缺失或细胞周期蛋白D1高表达、CDK4高表达、功能性Rb的缺失等(非专利文献16～18)。它们都是促进从G1期到S期的进展方向的异常，并且明确了该途径在癌化或癌细胞的异常增殖中起重要的作用。

[0017] CDK4/6抑制剂特别是对于具有活化CDK4/6激酶活性的基因异常的肿瘤有效，例如具有细胞周期蛋白D的易位的癌症、具有细胞周期蛋白D的扩增的癌症、具有CDK4或CDK6的扩增或过度表达的癌症、具有p16失活的癌症。另外，该缺陷可用于在导致细胞周期蛋白D的存在量增加的细胞周期蛋白D的上流调节因子具有基因异常的癌症的治疗，并且还可以期待治疗效果。

[0018] 事实上，已经尝试合成抑制CDK4/6活性的化合物，本领域中公开了许多化合物，并且在包括乳癌在内的多种癌症中实施了临床试验(非专利文献19)。

[0019] 已知神经胶质瘤(Glioma)中恶性度高的胶质母细胞瘤(Glioblastoma)是期待CDK4/6抑制剂的治疗效果的肿瘤之一。在来源于胶质母细胞瘤的培养细胞中显示出CDK4/6抑制剂的增殖抑制作用。为了期待在脑内病灶中的作用，需要从血液经过血脑屏障的脑移行或不通过血液的给予法，例如脑内给药、脑内留置制剂或经鼻给药。在血脑屏障中，通过外排转运蛋白、例如P糖蛋白或BCRP限制化合物的透过性。实际上，对于移植到小鼠皮下或头盖内的胶质母细胞瘤，由于帕博西尼(Palbociclib)(CDK4/6抑制剂)在皮下显示出增殖抑制作用而在头盖内未确认到作用，所以报道了帕博西尼的血脑屏障低透过性限制了作用的表达(非专利文献28)。

[0020] 大部分的急性和严重的放疗或化疗的毒性是通过对干细胞和前体细胞的效果。通过CDK4/6抑制剂而成为休止状态的造血干细胞和前体细胞，受到保护以免受放疗或化疗的细胞毒性。停止抑制剂处理之后，造血干细胞和前体细胞(HSPC)，从暂时的休止期间恢复，然后正常地发挥功能，因此可期待使用CDK4/6抑制剂的化疗抗性提供显著的保护骨髓的作

用(非专利文献20)。

[0021] 根据以上所述,CDK4/6抑制剂对于类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、癌症的治疗、保护骨髓有效,特别是可期待对于类风湿性关节炎、癌症的治疗、保护骨髓有效。

[0022] 专利文献1和非专利文献21公开了CDK4抑制剂,专利文献2、3和非专利文献22～24公开了包含CDK4/6的CDK抑制剂,非专利文献25公开了CDK4/FLT3抑制剂。

[0023] 另外,已知吡啶并[3,4-d]嘧啶衍生物具有Mps1(也作为TTK已知的激酶)的抑制作用(专利文献4),与本发明的CDK4/6抑制是完全不同的作用。

[0024] 另外,非专利文献26和非专利文献27中还对吡啶并[3,4-d]嘧啶衍生物进行了描述,但报道的是在多个化合物中可见CDK2抑制活性,这与本发明的优异的CDK4/6抑制是完全不同的方向性的化合物组。

[0025] 另外,已知专利文献5中记载的吡啶并[3,4-d]嘧啶衍生物具有EGFR的抑制作用,但这与本发明的CDK4/6抑制是完全不同的作用。

[0026] 现有技术文献

[0027] 专利文献

[0028] 专利文献1:国际公开第2003/062236号

[0029] 专利文献2:国际公开第2010/020675号

[0030] 专利文献3:国际公开第2010/075074号

[0031] 专利文献4:国际公开第2014/037750号

[0032] 专利文献5:国际公开第2015/027222号

[0033] 非专利文献

[0034] 非专利文献1:Johnson D.G.and Walker C.L.,Annual Review of Pharmacology and Toxicology 1999年,39:295-312页

[0035] 非专利文献2:Ortega等人,Biochimica et Biophysica Acta-Reviews on Cancer,2002年,1602(1):73-87页

[0036] 非专利文献3:Shapiro,Journal of Clinical Oncology,2006年;24(11):1770-1783页

[0037] 非专利文献4:Lundberg等人,Molecular and Cellular Biology,1998年,18(2):753-761页

[0038] 非专利文献5:Andrew J.Olaharski,PLoS Computational Biology,2009年,5(7):e1000446

[0039] 非专利文献6:Kamb等人,Science,1994年,264(5157):436-440页

[0040] 非专利文献7:Taniguchi,K等,Nature Medicine,1999年,5,760-767页

[0041] 非专利文献8:Sekine,C等,Journal of immunology,2008年,180:1954-1961页

[0042] 非专利文献9:Hosoya,T等,Annnl Rheumatic Diseases,2014年8月27日,Epub ahead ofprint

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发明内容

[0062] 发明所要解决的课题

[0063] 本发明的目的在于提供具有优异的CDK4/6抑制活性的化合物。

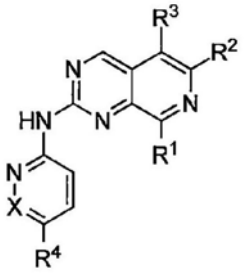
[0064] 用于解决课题的手段

[0065] 本发明人为了解决上述课题进行了深入的研究,结果发现:具有CDK4/6抑制活性的式(I)所表示的新型的吡啶并[3,4-d]嘧啶衍生物,从而完成了本发明。

[0066] 本发明如下所述。

[0067] (1)式(I)所表示的化合物或其药学上可接受的盐:

[0068] [化学式1]

[0069] 

(I)

[0070] 式中,

[0071] R^1表示C_{3-12}环烷基、C_{4-12}环烯基、4～12元的杂环基、C_{6-10}芳基、或5～10元的杂芳基；R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1～4个的杂原子；

[0072] R^1可被选自下述的1～6个的取代基取代：卤素、=O、-OH、-CN、-COOH、$-COOR^6$、$-R^7$、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{3-6}环烷基、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的3～10元的杂环基、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-8}酰基、和被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-8}烷氧基；

[0073] R^6和R^7各自独立地表示被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-6}烷基；

[0074] R^2表示C_{1-8}烷基、C_{3-8}环烷基、4～6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$；

[0075] R^2的C_{1-8}烷基各自独立地被下述的基团取代：0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、以及0～5个的氟原子；

[0076] R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、0～1个的羟甲基、以及0～5个的氟原子；

[0077] 其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

[0078] R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

[0079] R^2的4～6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1～4个的取代基取代；

[0080] R^2的C_{1-8}酰基、$-COOR^8$、和$-CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1～4个的取代基取代；

[0081] R^2的$-CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子环；

[0082] 关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1～2个的氧原子；

[0083] R^3表示氢原子、C_{1-8}烷基、或卤素原子；

[0084] X表示CR^{11}或氮原子；

[0085] R^{11}表示氢原子、C_{1-6}烷基、或C_{3-6}环烷基；

[0086] R^4由$-A^1-A^2-A^3$表示；

[0087] A^1表示单键、或C_{1-8}亚烷基；

[0088] 处于A^1的任意位置的1～2个的sp^3碳原子可被选自[-O-、$-NR^{14}-$、-C(=O)-、-C(=O)-O-、-O-C(=O)-、-O-C(=O)-O-、-C(=O)$-NR^{15}-$、-O-C(=O)$-NR^{16}-$、$-NR^{17}$-C(=O)-、$-NR^{18}$-C(=O)-O-、$-NR^{19}$-C(=O)$-NR^{20}-$、$-S(=O)_p-$、$-S(=O)_2-NR^{21}-$、$-NR^{22}-S(=O)_2-$、和$-NR^{23}-S(=O)_2-NR^{24}-$]的1～2个的结构置换，

[0089] 其中，在2个的sp^3碳原子被置换的情况下，不形成-O-O-、$-O-NR^{14}-$、$-NR^{14}-O-$、$-O-CH_2-O-$、$-O-CH_2-NR^{14}-$、和$-NR^{14}-CH_2-O-$这样的结构；

[0090] A^2表示单键、C_{1-7}亚烷基、C_{3-12}亚环烷基、C_{3-12}环烷叉基、4～12元的亚杂环基、4～12元的杂环叉基、C_{6-10}亚芳基、或5～10元的亚杂芳基；

[0091] A^3表示卤素、-CN、$-NO_2$、$-R^{25}$、$-OR^{26}$、$-NR^{27}R^{28}$、-C(=O)R^{29}、-C(=O)$-OR^{30}$、-O-C(=O)R^{31}、-O-C(=O)$-NR^{32}R^{33}$、-C(=O)$-NR^{34}R^{35}$、$-NR^{36}$-C(=O)R^{37}、$-NR^{38}$-C(=O)$-OR^{39}$、$-S(=O)_2-R^{40}$、$-S(=O)_2-NR^{41}R^{42}$、或$-NR^{43}-S(=O)_2R^{44}$；

[0092] 其中，在A^2侧的A^1末端为选自[-O-、$-NR^{14}$-、-C(=O)-、-C(=O)-O-、-O-C(=O)-、-O-C(=O)-O-、-C(=O)$-NR^{15}$-、-O-C(=O)$-NR^{16}$-、$-NR^{17}$-C(=O)-、$-NR^{18}$-C(=O)-O-、$-NR^{19}$-C(=O)$-NR^{20}$-、$-S(=O)_p$-、$-S(=O)_2-NR^{21}$-、$-NR^{22}-S(=O)_2$-、和$-NR^{23}-S(=O)_2-NR^{24}$-]的结构、并且A^2为单键的情况下，A^3表示$-R^{25}$；R^{14}、R^{32}、R^{34}、R^{36}、R^{38}、R^{41}、和R^{43}各自独立地表示氢原子、C_{1-8}烷基、C_{1-8}酰基、C_{1-8}烷基磺酰基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基；

[0093] R^{15}～R^{31}、R^{33}、R^{35}、R^{37}、R^{39}、R^{40}、R^{42}、和R^{44}各自独立地表示氢原子、C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基；

[0094] A^1、A^2、A^3、以及A^1、A^2、和A^3中的R^{14}～R^{44}各自独立地可被选自下述的1～4个的取代基取代：-OH、=O、-COOH、$-SO_3H$、$-PO_3H_2$、-CN、$-NO_2$、卤素、被[0～2个的-OH、0～2个的$-OR^{45}$、和0～6个的氟原子]取代的C_{1-8}烷基、被[0～2个的-OH、0～2个的$-OR^{46}$、和0～6个的氟原子]取代的C_{3-12}环烷基、被[0～2个的-OH、0～2个的$-OR^{47}$、和0～6个的氟原子]取代的C_{1-8}烷氧基、和被[0～2个的-OH、0～2个的$-OR^{49}$、和0～6个的氟原子]取代的4～12元的杂环基；

[0095] R^{14}～R^{44}可在A^1内、A^2内、A^3内、[A^1与A^2之间]，[A^1与A^3之间]、或[A^2与A^3之间]经由[单键、-O-、$-NR^{50}$-、或$-S(=O)_p$-]键合而形成环；

[0096] R^{11}可与[A^1、A^2、或A^3]经由[单键、-O-、$-NR^{51}$-、或$-S(=O)_p$-]键合而形成环；

[0097] R^{45}～R^{51}表示氢原子、或被[0～1个的-OH、和0～6个的氟原子]取代的C_{1-4}烷基；

[0098] p表示0～2的整数；

[0099] A^1、A^2、和A^3中的杂原子为：在各自的基团中，独立地从氧原子、硫原子、和氮原子中选择1～4个的杂原子。

[0100] (2)(1)所述的化合物或其药学上可接受的盐，其中，R^1表示C_{3-8}环烷基、C_{4-7}环烯基、4～8元的杂环基、苯基、或5～10元的杂芳基；

[0101] R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1～4个的杂原子；

[0102] R^1可被选自下述的1～6个取代基取代：氟原子、=O、-OH、-COOH、和被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-6}烷基；

[0103] R^2表示C_{1-8}烷基、4～6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$；

[0104] R^2的C_{1-8}烷基被下述的基团取代：0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、以及0～5个的氟原子；

[0105] 其中，R^2不为无取代的C_{1-8}烷基、和三氟甲基；

[0106] R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

[0107] R^3表示氢原子、或C_{1-8}烷基；

[0108] X表示CR^{11}或氮原子；

[0109] R^{11}表示氢原子、或C_{1-6}烷基；

[0110] R^4由-A^1-A^2-A^3表示；

[0111] A^1表示单键、或C_{1-4}亚烷基；

[0112] 处于A^1的任意位置的1个的sp^3碳原子可被选自[-O-，-NR^{14}-，-NR^{17}-C(=O)-，和-NR^{22}-S(=O)$_2$-]的1个结构置换，

[0113] A^2表示单键、4～12元的亚杂环基、C_{6-10}亚芳基、或5～10元的亚杂芳基；

[0114] A^3表示卤素、-CN、-R^{25}、-OR^{26}、-$NR^{27}R^{28}$、-C(=O)R^{29}、-C(=O)-OR^{30}、-O-C(=O)R^{31}、-O-C(=O)-$NR^{32}R^{33}$、-C(=O)-$NR^{34}R^{35}$、-NR^{36}-C(=O)R^{37}、-NR^{38}-C(=O)-OR^{39}、-S(=O)$_2$-R^{40}、-S(=O)$_2$-$NR^{41}R^{42}$、或-NR^{43}-S(=O)$_2R^{44}$；

[0115] 其中，在A^2侧的A^1末端为[-O-、-NR^{14}-、-NR^{17}-C(=O)-、或-NR^{22}-S(=O)$_2$-]、并且A^2为单键的情况下，A^3表示-R^{25}；

[0116] R^{14}、R^{32}、R^{34}、R^{36}、R^{38}、R^{41}、和R^{43}各自独立地表示氢原子、C_{1-8}烷基、C_{1-8}酰基、C_{1-8}烷基磺酰基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基；

[0117] R^{15}～R^{31}、R^{33}、R^{35}、R^{37}、R^{39}、R^{40}、R^{42}、和R^{44}各自独立地表示氢原子、C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基；

[0118] A^1、A^2、A^3、以及A^1、A^2、和A^3中的R^{14}～R^{44}各自独立地可被选自下述的1～4个取代基取代：-OH、=O、卤素、C_{1-6}烷基磺酰基、和被[0～1个的-OH、和0～6个的氟原子]取代的C_{1-8}烷基；

[0119] R^{11}和A^1可经由单键键合而形成环；

[0120] A^1、A^2、和A^3中的杂原子为：在各自的基团中，独立地从氧原子、硫原子、和氮原子中选择1～4个的杂原子。

[0121] (3)(1)所述的化合物或其药学上可接受的盐，其中，R^1表示C_{3-12}环烷基。

[0122] (4)(1)所述的化合物或其药学上可接受的盐，其中，R^1表示4～12元的杂环基。

[0123] (5)(1)所述的化合物或其药学上可接受的盐，其中，R^1表示C_{6-10}芳基、或5～10元的杂芳基。

[0124] (6)(1)～(5)的任一项所述的化合物或其药学上可接受的盐，其中，R^2为被1～4个的氟原子取代的C_{1-8}烷基。

[0125] (7)(1)～(5)的任一项所述的化合物或其药学上可接受的盐，其中，R^2为被下述的基团取代的C_{1-8}烷基：0～1个的-OH、和被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基。

[0126] (8)(1)、(3)～(5)的任一项所述的化合物或其药学上可接受的盐，其中，R^2为可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1～4个的取代基取代的4～6元的杂环基。

[0127] (9)(1)、(3)～(5)的任一项所述的化合物或其药学上可接受的盐，其中，R^2为可被选自氟原子、-OH、和C_{1-8}烷氧基的1～4个的取代基取代的C_{1-8}酰基、-$COOR^8$、或-$CONR^9R^{10}$。

[0128] (10)(1)～(9)的任一项所述的化合物或其药学上可接受的盐，其中，X表示CR^{11}。

[0129] (11)(1)～(9)的任一项所述的化合物或其药学上可接受的盐，其中，X表示氮原子。

[0130] (12)(1)～(11)的任一项所述的化合物或其药学上可接受的盐，其中，A^1为单键。

[0131] (13)(1)～(11)的任一项所述的化合物或其药学上可接受的盐，其中，A^1表示亚甲基，A^1的所有sp^3碳原子不被其他结构置换。

[0132] (14)(1)～(11)的任一项所述的化合物或其药学上可接受的盐，其中，A^1为-O-。

[0133] (15)(1)～(9)的任一项所述的化合物或其药学上可接受的盐，其中，X表示CR^{11}；

[0134] R^{11}表示C_{1-6}烷基；

[0135] A^1表示C_{1-8}亚烷基；

[0136] 处于A^1的任意位置的1个的sp^3碳原子被选自[$-NR^{14}-$、$-NR^{17}-C(=O)-$、和$-NR^{22}-S(=O)_2-$]的1个的结构置换；

[0137] R^{11}和A^1经由单键键合而形成环。

[0138] (16)(1)～(15)的任一项所述的化合物或其药学上可接受的盐，其中，A^2表示5～9元的亚杂环基；

[0139] A^2可被选自下述的1～4个的取代基取代：-OH、=O、-COOH、$-SO_3H$、$-PO_3H_2$、-CN、$-NO_2$、卤素、被[0～2个的-OH、0～2个的$-OR^{45}$、和0～6个的氟原子]取代的C_{1-8}烷基、被[0～2个的-OH、0～2个的$-OR^{46}$、和0-6个的氟原子]取代的C_{3-12}环烷基、被[0～2个的-OH、0～2个的$-OR^{47}$、和0～6个的氟原子]取代的C_{1-8}烷氧基、和被[0～2个的-OH、0～2个的$-OR^{49}$、和0～6个的氟原子]取代的4～12元的杂环基。

[0140] (17)(1)～(16)的任一项所述的化合物或其药学上可接受的盐，其中，A^3为氢原子。

[0141] (18)(1)～(16)的任一项所述的化合物或其药学上可接受的盐，其中，A^3为卤素、-CN、$-R^{25}$、$-OR^{26}$、$-NR^{27}R^{28}$、$-C(=O)R^{29}$、或$-C(=O)-OR^{30}$，R^{25}～R^{30}各自独立地表示氢原子、可被取代的C_{1-8}烷基、可被取代的4～12元的杂环基、可被取代的C_{3-12}环烷基、可被取代的(4～12元的杂环基)C_{1-3}烷基、或可被取代的(C_{3-12}环烷基)C_{1-3}烷基。

[0142] (19)(1)～(18)的任一项所述的化合物或其药学上可接受的盐，其中，R^3为氢原子。

[0143] (20)(1)、(3)～(19)的任一项所述的化合物或其药学上可接受的盐，其中，R^3表示C_{1-4}烷基、氟原子、或氯原子。

[0144] (21)以下所述的化合物或其药学上可接受的盐：

[0145] [2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0146] [2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0147] 1-[6-(羟甲基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-2-酮；

[0148] 6-(二氟甲基)-N-[5-(4-甲基哌嗪-1-基)吡啶-2-基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-胺；

[0149] [8-环己基-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0150] [2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-苯基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0151] [8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0152] 6-(二氟甲基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0153] [2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0154] [8-苯基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0155] 6-(二氟甲基)-N-(5-哌嗪-1-基吡啶-2-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0156] 6-(二氟甲基)-8-苯基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0157] 6-(二氟甲基)-N-[5-(4-甲基哌嗪-1-基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0158] [8-(4-甲基苯基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0159] [8-(2-甲基苯基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0160] [2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-噻吩-3-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0161] [8-(呋喃-3-基)-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0162] [8-(4-甲基苯基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0163] [8-(2-甲基苯基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0164] [2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-噻吩-3-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0165] [8-(呋喃-3-基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0166] [8-(环己烯-1-基)-2-[[5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0167] 2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酸；

[0168] 1-[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0169] 2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酸甲酯；

[0170] 1-[2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙酮；

[0171] N,N-二甲基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

[0172] 2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

[0173] N-甲基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-甲酰胺；

[0174] 6-(二氟甲基)-8-(2-甲基苯基)-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0175] 6-(二氟甲基)-8-(呋喃-3-基)-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0176] 6-(甲氧基甲基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0177] [5-甲基-8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0178] 1-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0179] 2,2,2-三氟-1-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0180] 6-(1,1-二氟乙基)-8-吗啉-4-基-N-(5-哌嗪-1-基吡啶-2-基)吡啶并[3,4-d]嘧啶-2-胺；

[0181] 2-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

[0182] 2-[8-吗啉-4-基-2-[(5-哌嗪-1-基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0183] 1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]吡咯烷-2-甲酸；

[0184] 1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-3-甲酸；

[0185] 1-[6-[(1R)-1-羟乙基]-2-[(6-哌嗪-1-基哒嗪-3-基)氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-2-甲酸；

[0186] 1-[6-[(1R)-1-羟乙基]-2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]吡咯烷-2-甲酸；

[0187] 6-(1-甲氧基乙基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0188] 8-(1,2,3,3a,4,5,7,7a-八氢吡咯并[2,3-c]吡啶-6-基)-6-(1-甲氧基乙基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

[0189] [1-[6-(1-甲氧基乙基)-2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-基]甲醇；

[0190] 6-(1-甲氧基乙基)-8-[4-(甲氧基甲基)哌啶-1-基]-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

[0191] (1R)-1-[8-(氮杂环丁烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0192] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0193] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0194] 1-[6-[[8-(氮杂环丁烷-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0195] 1-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0196] 1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0197] (1R)-1-[2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0198] (1R)-1-[2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0199] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0200] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0201] (1R)-1-[8-(2-氮杂螺[3.3]庚烷-2-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0202] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0203] (1R)-1-[8-(氮杂环庚烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0204] (1R)-1-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0205] (1R)-1-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-(4-氟哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0206] (1R)-1-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0207] (1R)-1-[8-(4-氟哌啶-1-基)-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0208] 1-[6-[[8-(4,4-二氟哌啶-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0209] 1-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌啶-4-醇；

[0210] 1-[[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌啶-4-醇；

[0211] 1-[[6-[[6-[(1R)-1-羟乙基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡

啶-3-基]甲基]哌啶-4-醇；

[0212] (1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0213] (1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0214] (1R)-1-[2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0215] 1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(羟甲基)哌啶-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

[0216] 1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

[0217] 1-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

[0218] 1-[6-[[6-[(1R)-1-羟乙基]-8-吗啉-4-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮；

[0219] (1R)-1-[8-(2,2-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0220] 1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-甲酸；

[0221] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-(4-甲基哌嗪-1-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0222] (1R)-1-[8-(4-氟哌啶-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0223] (1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0224] (1R)-1-[8-(4,4-二氟哌啶-1-基)-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0225] (1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0226] (1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0227] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(2R)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0228] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[4-(三氟甲基)哌啶-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0229] (1R)-1-[8-(1,1-二氧代-1,4-噻嗪-4-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0230] (1R)-1-[2-[(6-甲基-5-哌嗪-1-基吡啶-2-基)氨基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0231] (1R)-1-[2-[(6-甲基-5-哌嗪-1-基吡啶-2-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0232] (1R)-1-[2-[[5-[4-(2-羟乙基)哌嗪-1-基]-6-甲基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0233] 4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-5-酮；

[0234] 1-[6-[[8-(4-氟哌啶-1-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0235] (1R)-1-[2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0236] 2-[2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0237] 1-[6-[[6-(2-羟乙基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0238] 2-[2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0239] 2-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0240] 2-[4-[[6-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

[0241] 1-[6-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0242] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(2S)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0243] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(3S)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0244] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-[(3R)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0245] (1R)-1-[8-(2,5-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0246] (1R)-1-[8-(3,3-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0247] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0248] (1R)-1-[8-(3-氮杂双环[3.1.0]己烷-3-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0249] (1R)-1-[8-(8-氮杂双环[3.2.1]辛烷-8-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0250] 1-[6-[(1R)-1-羟乙基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨

基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

[0251] [2-[(6-哌嗪-1-基哒嗪-3-基)氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0252] [2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]甲醇；

[0253] 2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0254] 2-[2-[[6-[2-(二甲氨基)乙基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0255] (1R)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0256] (1R)-1-[8-(4-氟哌啶-1-基)-2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0257] (1R)-1-[8-(3,4-二甲基吡咯烷-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0258] (1R)-1-[2-[[6-[4-(2-甲基磺酰基乙基)哌嗪-1-基]哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0259] (1R)-1-[8-(4-氟哌啶-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0260] (1R)-1-[8-[(3R)-3-氟吡咯烷-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0261] (1R)-1-[8-[(3S)-3-氟吡咯烷-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0262] 6-[(1R)-1-甲氧基乙基]-N-(6-哌嗪-1-基哒嗪-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0263] 6-[(1R)-1-甲氧基乙基]-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0264] 4-[6-[[6-[(1R)-1-羟乙基]-8-吡咯烷-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1-甲基-1,4-二氮杂环庚烷-5-酮；

[0265] 4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1-甲基-1,4-二氮杂环庚烷-5-酮；

[0266] (1R)-1-[2-[[5-[(4-乙基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0267] (1R)-1-[2-[[6-(4-甲基哌嗪-1-基)哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0268] (1R)-1-[8-(4-氟哌啶-1-基)-2-[[6-(4-甲基哌嗪-1-基)哒嗪-3-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0269] 8-(4-氟哌啶-1-基)-6-[(1R)-1-甲氧基乙基]-N-[6-(4-甲基哌嗪-1-基)哒嗪-3-基]吡啶并[3,4-d]嘧啶-2-胺；

[0270] 8-(4-氟哌啶-1-基)-6-[(1R)-1-甲氧基乙基]-N-(6-哌嗪-1-基哒嗪-3-基)吡啶并[3,4-d]嘧啶-2-胺；

[0271] 1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮；

[0272] 2-[4-[[6-[[6-(二氟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

[0273] 1-[6-(二氟甲基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

[0274] 3-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]丙烷-1-醇；

[0275] (1R)-1-[2-[[5-[(3S,4S)-3-氟-1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0276] (1R)-1-[2-[[5-[(3S,4R)-3-氟-1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0277] (1R)-1-[8-(3,3-二氟氮杂环丁烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0278] 1-[6-[(1R)-1-羟乙基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-8-基]哌啶-4-醇；

[0279] 2-[2-[[6-(羟甲基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]乙醇；

[0280] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(2R)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0281] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(2S)-2-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0282] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(3R)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0283] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[(3S)-3-甲基吡咯烷-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0284] (1R)-1-[8-(2,5-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0285] (1R)-1-[8-(3,4-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0286] (1R)-1-[8-(3,3-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0287] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0288] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-[4-(三氟甲基)哌啶-1-基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0289] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-吗啉-4-基吡啶

并[3,4-d]嘧啶-6-基]乙醇；

[0290] 1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0291] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-哌啶-4-基甲酮；

[0292] [1-(2-羟乙基)哌啶-4-基]-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[0293] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基哌啶-4-基)甲酮；

[0294] (1R)-1-[8-(4,4-二氟哌啶-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0295] 1-(2-羟乙基)-4-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-5-酮；

[0296] (1R)-1-[2-[[5-[[(2R)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0297] (1R)-1-[8-环丙基-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0298] 1-[6-[[8-环丙基-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0299] (1R)-1-[2-[[5-(哌嗪-1-基甲基)吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0300] (1R)-1-[8-(环己烯-1-基)-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0301] (1R)-1-[8-(3-氮杂双环[3.1.0]己烷-3-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0302] (1R)-1-[8-(氮杂环庚烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0303] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0304] (1S)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0305] (1R)-1-[2-[[6-(氧杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0306] (1R)-1-[2-[[6-(2-吗啉-4-基乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0307] (1R)-1-[8-哌啶-1-基-2-[(6-哌啶-4-基磺酰基-7,8-二氢-5H-1,6-萘啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0308] (1R)-1-[8-哌啶-1-基-2-[(5-哌啶-4-基氧基吡啶-2-基)氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0309] (1R)-1-[2-[[5-[1-(2-羟乙基)哌啶-4-基]氧基吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0310] (2S)-2-[8-哌啶-1-基-2-(5,6,7,8-四氢-1,6-萘啶-2-基氨基)吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0311] (2R)-2-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0312] (2R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

[0313] 1-[6-[[6-[(2R)-2-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0314] (2R)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

[0315] (2R)-2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0316] (1R)-1-[8-(氮杂环丁烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0317] (1R)-1-[8-(2,2-二甲基吡咯烷-1-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0318] (1R)-1-[8-(8-氮杂双环[3.2.1]辛烷-8-基)-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0319] (1R)-1-[2-[[6-(氮杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0320] (1R)-1-[2-[[6-[1-(2-羟乙基)氮杂环丁烷-3-基]-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0321] (1R)-1-[2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]-8-(1,4-氧杂氮杂环庚烷-4-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0322] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-(1,4-氧杂氮杂环庚烷-4-基)吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0323] (1R)-1-[8-[(3S)-3-氟哌啶-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0324] (1R)-1-[8-[(3S)-3-氟哌啶-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0325] (1R)-1-[8-[(3S)-3-氟吡咯烷-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0326] (1R)-1-[8-[(3R)-3-氟吡咯烷-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0327] (2S)-1-[4-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]丙烷-2-醇；

[0328] (2R)-1-[4-[[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]

氨基]吡啶-3-基]甲基]哌嗪-1-基]丙烷-2-醇；

[0329] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[6-甲基-5-(4-甲基哌嗪-1-基)吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0330] (1R)-1-[2-[[5-[[(2S)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0331] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[(2S)-2,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0332] (1R)-1-[2-[[5-[[(3S)-3,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0333] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[[(3S)-3,4-二甲基哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0334] (1R)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-苯基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0335] 1-[6-[[6-[(1R)-1-羟乙基]-8-苯基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0336] 1-[6-[[6-[(2S)-1-羟基丙烷-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0337] (2S)-2-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0338] 1-[6-[[6-[(2R)-1-羟基丙烷-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0339] (2S)-2-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-1-醇；

[0340] 2-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]乙腈；

[0341] (1R)-1-[2-[[6-(氧杂环丁烷-3-基甲基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0342] (1R)-1-[8-[(3R)-3-氟哌啶-1-基]-2-[[5-[(4-甲基哌嗪-1-基)甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0343] (1R)-1-[8-[(3R)-3-氟哌啶-1-基]-2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0344] (1R)-1-[2-[[6-(1-甲基氮杂环丁烷-3-基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0345] (1R)-1-[2-[[6-(2-羟乙基)-5,7-二氢吡咯并[3,4-b]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0346] (2S)-1-[2-[[5-[[4-(2-羟乙基)哌嗪-1-基]甲基]吡啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

[0347] 1-[6-[[6-[(2S)-2-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮；

[0348] (2S)-1-[2-[[6-(2-羟乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]丙烷-2-醇；

[0349] 8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环戊-3-基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]吡啶并[3,4-d]嘧啶-2-胺；

[0350] 6-(氧杂环戊-3-基)-N-[5-(哌嗪-1-基甲基)吡啶-2-基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0351] 8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环戊-3-基)-N-(6-哌嗪-1-基哒嗪-3-基)吡啶并[3,4-d]嘧啶-2-胺；

[0352] 6-(氧杂环戊-3-基)-N-(6-哌嗪-1-基哒嗪-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-胺；

[0353] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-吡咯烷-2-基]甲酮；

[0354] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-吡咯烷-3-基]甲酮；

[0355] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-哌啶-2-基]甲酮；

[0356] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基吡咯烷-2-基]甲酮；

[0357] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基吡咯烷-2-基]甲酮；

[0358] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-哌啶-3-基]甲酮；

[0359] [(2R)-氮杂环丁烷-2-基]-[2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[0360] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-吗啉-2-基甲酮；

[0361] (1R)-1-[2-[[6-(2-氨基乙基)-7,8-二氢-5H-1,6-萘啶-2-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇；

[0362] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基吡咯烷-2-基]甲酮；

[0363] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基吡咯烷-2-基]甲酮；

[0364] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基吡咯烷-3-基]甲酮；

[0365] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基吡咯烷-3-基]甲酮；

[0366] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基哌啶-2-基]甲酮；

[0367] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧

啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基哌啶-2-基]甲酮;

[0368] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0369] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0370] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0371] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0372] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基哌啶-3-基]甲酮;

[0373] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基哌啶-3-基]甲酮;

[0374] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基氮杂环丁烷-2-基]甲酮;

[0375] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基氮杂环丁烷-2-基]甲酮;

[0376] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-3-基)甲酮;

[0377] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-2-基)甲酮;

[0378] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基氮杂环丁烷-3-基)甲酮;

[0379] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0380] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0381] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[0382] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[0383] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)哌啶-2-基]甲酮;

[0384] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)哌啶-2-基]甲酮;

[0385] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0386] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0387] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0388] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0389] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)哌啶-3-基]甲酮;

[0390] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)哌啶-3-基]甲酮;

[0391] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[0392] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[0393] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-3-基]甲酮;

[0394] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-2-基]甲酮;

[0395] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[1-(2-羟乙基)氮杂环丁烷-3-基]甲酮;

[0396] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-吡咯烷-1-基乙酮;

[0397] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基吡咯烷-1-基)乙酮;

[0398] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟吡咯烷-1-基)乙酮;

[0399] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(氮杂环丁烷-1-基)乙酮;

[0400] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基氮杂环丁烷-1-基)乙酮;

[0401] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]

嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟氮杂环丁烷-1-基)乙酮；

[0402] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-哌啶-1-基乙酮；

[0403] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-羟基哌啶-1-基)乙酮；

[0404] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-氟哌啶-1-基)乙酮；

[0405] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基哌啶-1-基)乙酮；

[0406] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟哌啶-1-基)乙酮；

[0407] 2-[4-[[6-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

[0408] 2-[4-[[6-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]甲基]哌嗪-1-基]乙醇；

[0409] [2-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-吗啉-3-基甲酮；

[0410] 吗啉-2-基-[2-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[0411] 吗啉-3-基-[2-[[6-(氧杂环丁烷-3-基)-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]甲酮；

[0412] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基吡咯烷-2-基]甲酮；

[0413] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基吡咯烷-2-基]甲酮；

[0414] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基吡咯烷-3-基]甲酮；

[0415] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基吡咯烷-3-基]甲酮；

[0416] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基哌啶-2-基]甲酮；

[0417] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基哌啶-2-基]甲酮；

[0418] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[0419] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮；

[0420] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0421] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-甲基吡咯烷-2-基]甲酮;

[0422] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-甲基哌啶-3-基]甲酮;

[0423] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-甲基哌啶-3-基]甲酮;

[0424] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-甲基氮杂环丁烷-2-基]甲酮;

[0425] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-甲基氮杂环丁烷-2-基]甲酮;

[0426] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-3-基)甲酮;

[0427] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(4-甲基吗啉-2-基)甲酮;

[0428] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-(1-甲基氮杂环丁烷-3-基)甲酮;

[0429] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0430] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0431] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[0432] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)吡咯烷-3-基]甲酮;

[0433] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)哌啶-2-基]甲酮;

[0434] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)哌啶-2-基]甲酮;

[0435] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0436] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0437] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R,4R)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0438] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S,4S)-4-羟基-1-(2-羟乙基)吡咯烷-2-基]甲酮;

[0439] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3R)-1-(2-羟乙基)哌啶-3-基]甲酮;

[0440] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(3S)-1-(2-羟乙基)哌啶-3-基]甲酮;

[0441] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2R)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[0442] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[(2S)-1-(2-羟乙基)氮杂环丁烷-2-基]甲酮;

[0443] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-3-基]甲酮;

[0444] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[4-(2-羟乙基)吗啉-2-基]甲酮;

[0445] [2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-[1-(2-羟乙基)氮杂环丁烷-3-基]甲酮;

[0446] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-吡咯烷-1-基乙酮;

[0447] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基吡咯烷-1-基)乙酮;

[0448] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟吡咯烷-1-基)乙酮;

[0449] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(氮杂环丁烷-1-基)乙酮;

[0450] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基氮杂环丁烷-1-基)乙酮;

[0451] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟氮杂环丁烷-1-基)乙酮;

[0452] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-哌啶-1-基乙酮;

[0453] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-羟基哌啶-1-基)乙酮;

[0454] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(4-氟哌啶-1-基)乙酮;

[0455] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-羟基哌啶-1-基)乙酮;

[0456] 1-[2-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-(氧杂环丁烷-3-基)吡啶并[3,4-d]嘧啶-2-基]氨基]-7,8-二氢-5H-1,6-萘啶-6-基]-2-(3-氟哌啶-1-基)乙酮;

[0457] 4-(2-羟乙基)-1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]哌嗪-2-酮;

[0458] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[5-[4-(2-羟乙基)哌嗪-1-基]-6-甲基吡啶-2-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇;

[0459] (1R)-1-[2-[[6-[4-(2-羟乙基)哌嗪-1-基]哒嗪-3-基]氨基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-6-基]乙醇;

[0460] (1R)-1-[8-(7-氮杂双环[2.2.1]庚烷-7-基)-2-[[6-[4-(2-羟乙基)哌嗪-1-基]哒嗪-3-基]氨基]吡啶并[3,4-d]嘧啶-6-基]乙醇;

[0461] 1-[6-[[6-[(1R)-1-羟丙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮;

[0462] 4-(2-羟乙基)-1-[6-[[6-[(1R)-1-羟乙基]-8-哌啶-1-基吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-1,4-二氮杂环庚烷-2-酮;

[0463] 1-[6-[[8-(7-氮杂双环[2.2.1]庚烷-7-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮;

[0464] 1-[6-[[8-(8-氮杂双环[3.2.1]辛烷-8-基)-6-[(1R)-1-羟乙基]吡啶并[3,4-d]嘧啶-2-基]氨基]吡啶-3-基]-4-甲基哌嗪-2-酮。

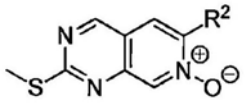
[0465] (22)药物组合物,其包含(1)～(21)的任一项所述的化合物或其药学上可接受的盐、和药学上可接受的载体。

[0466] (23)具有CDK4/6抑制活性的药物组合物,其含有(1)～(21)的任一项所述的化合物或其药学上可接受的盐作为有效成分。

[0467] (24)类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、或癌症的预防药或治疗药,其含有(1)～(21)的任一项所述的化合物或其药学上可接受的盐作为有效成分。

[0468] (25)式(II)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐:

[0469] [化学式2]

[0470]  (II)

[0471] 式(II)中,R^2表示C_{1-8}烷基、C_{3-8}环烷基、4～6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$;

[0472] R^2的C_{1-8}烷基各自独立地被下述的基团取代:0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、以及0～5个的氟原子;

[0473] R^2的C_{3-8}环烷基各自独立地被下述的基团取代:0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、0～1个的羟甲基、以及0～5个的氟原子;

[0474] 其中,R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基;

[0475] R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基;

[0476] R^2的4～6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1～4个的取代基取代;

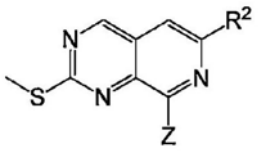
[0477] R^2的C_{1-8}酰基、$-COOR^8$、和$-CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1～4个的取代基取代;

[0478] R^2的$-CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环;

[0479] 关于R^2的杂环基中的杂原子,4-5元环时为1个的氧原子,6元环时为1～2个的氧原子,其中,R^2可被适宜的保护基保护。

[0480] (26)式(III)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐:

[0481] [化学式3]

[0482] 

(III)

[0483] 式(III)中,R^2表示C_{1-8}烷基、C_{3-8}环烷基、4～6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$;

[0484] R^2的C_{1-8}烷基各自独立地被下述的基团取代:0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、以及0～5个的氟原子;

[0485] R^2的C_{3-8}环烷基各自独立地被下述的基团取代:0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、0～1个的羟甲基、以及0～5个的氟原子;

[0486] 其中,R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基;

[0487] R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基;

[0488] R^2的4～6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1～4个的取代基取代;

[0489] R^2的C_{1-8}酰基、$-COOR^8$、和$-CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1～4个的取代基取代;

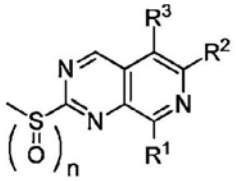
[0490] R^2的$-CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环;

[0491] 关于R^2的杂环基中的杂原子,4-5元环时为1个的氧原子,6元环时为1～2个的氧原子;

[0492] Z表示卤素原子,其中,R^2可被适宜的保护基保护。

[0493] (27)式(IV)所表示的吡啶并[3,4-d]嘧啶衍生物或其盐:

[0494] [化学式4]

[0495] 

（IV）

[0496] 式(IV)中，R^1表示C_{3-12}环烷基、C_{4-12}环烯基、4～12元的杂环基、C_{6-10}芳基、或5～10元的杂芳基；R^1中的杂原子为：在各自的基团中，从氧原子、硫原子、和氮原子中独立地选择1～4个的杂原子；

[0497] R^1可被选自下述的1～6个的取代基取代：卤素、＝O、-OH、-CN、-COOH、$-COOR^6$、$-R^7$、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{3-6}环烷基、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的3～10元的杂环基、被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-8}酰基、和被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-8}烷氧基；

[0498] R^6和R^7各自独立地表示被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{1-6}烷基；

[0499] R^2表示C_{1-8}烷基、C_{3-8}环烷基、4～6元的杂环基、C_{1-8}酰基、$-COOR^8$、或$-CONR^9R^{10}$；

[0500] R^2的C_{1-8}烷基各自独立地被下述的基团取代：0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、以及0～5个的氟原子；

[0501] R^2的C_{3-8}环烷基各自独立地被下述的基团取代：0～1个的-OH、被[0～1个的-OH、0～1个的C_{1-4}烷氧基、和0～3个的氟原子]取代的0～2个的C_{1-8}烷氧基、0～1个的羟甲基、以及0～5个的氟原子；

[0502] 其中，R^2不为无取代的C_{1-8}烷基、无取代的C_{3-8}环烷基、和三氟甲基；

[0503] R^8、R^9、和R^{10}各自独立地表示氢原子或C_{1-8}烷基；

[0504] R^2的4～6元的杂环基可被选自氟原子、-OH、C_{1-4}烷基、和C_{1-4}烷氧基的1～4个的取代基取代；

[0505] R^2的C_{1-8}酰基、$-COOR^8$、和$-CONR^9R^{10}$可被选自氟原子、-OH、和C_{1-4}烷氧基的1～4个的取代基取代；

[0506] R^2的$-CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环；

[0507] 关于R^2的杂环基中的杂原子，4-5元环时为1个的氧原子，6元环时为1～2个的氧原子；

[0508] n表示0、1、或2，其中，R^1、和R^2可被适宜的保护基保护。

[0509] 发明效果

[0510] 本发明的化合物具有优异的CDK4/6抑制活性，作为类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、或癌症的预防药或治疗药有效。

具体实施方式

[0511] 关于本发明的通式(I)所示的化合物的各结构(基团)，描述(表記)如下。关于“基团”的描述，关于使用括号的标记，例如(环烷基)烷基是指，环烷基与烷基键合而得的基团，且烷基侧成为与其他结构键合的一侧。同样地(杂环基)烷基是指，杂环基与烷基键合而得

的基团，且烷基侧成为与其他结构键合的一侧。

[0512] 在本说明书和所附的权利要求书中，在存在单数形式“一”、“一个”、和“该”的表述的情况下，除非上下文另有明确说明，否则也包含其复数形式的概念。

[0513] 另外，本发明中，例如被“[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的C_{3-6}环烷基”是指，被0～2个的-OH、0～2个的C1-8烷氧基、和0～6个的氟原子的取代基取代。例如是指，被2个的-OH、1个的C1-8烷氧基、和3个的氟原子取代的C3-6环烷基，被2个的C_{1-8}烷氧基和4个的氟原子取代的C_{3-6}环烷基，和被1个的-OH取代的C_{3-6}环烷基等，在全部为零的数值的情况下，是指完全不被取代的C_{3-6}环烷基。另外，取代基的数目是指化学上可能的数目。例如，被“0～6个的氟原子取代的C_1烷基”是指，“被0～3个为止的氟原子取代的C_1烷基”。

[0514] “C_{1-8}”是指碳数为1～8个，如果为“C_{1-6}”，则在“C_{1-8}”的说明中，是指碳数为1～6个。同样地，“5～10元”是指由碳5～10个构成的结构，其中“5～6元”在“5～10元”的说明中，是指“5～6元”。

[0515] 下面，对本说明书中的各基团的含义进行说明，但不限于作为各例示所举出的基团。

[0516] 本发明中的烷基是指，从烷烃的任意碳原子上除去1个氢原子而得的1价基团。

[0517] 本发明中的亚烷基是指，从烷烃的任意碳原子上除去2个氢原子而得的2价基团。

[0518] 本发明中的烷烃是指，饱和脂肪族烃。

[0519] 本发明中的“C_{1-8}烷基”是指，具有碳数1～8个的直链或支链状的碳链，例如可举出：甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、新戊基、异戊基、1,2-二甲基丙基、正己基、异己基、1,1-二甲基丁基、2,2-二甲基丁基、1-乙基丁基、2-乙基丁基、异庚基、正辛基、和异辛基等。

[0520] 本发明中的“C_{1-8}亚烷基”的烷烃是指，具有碳数1～8个的直链或支链状的碳链，例如可举出：甲烷、乙烷、丙烷、正丁烷、2-甲基丙烷、正戊烷、2,2-二甲基丙烷、正己烷、2-甲基戊烷、3-甲基戊烷、2,2-二甲基丁烷、2,3-二甲基丁烷、正庚烷、2,2-二甲基己烷、2,3-二甲基己烷、正辛烷、和2-甲基庚烷等。

[0521] 本发明中的环烷基是指，从环烷烃的任意碳原子上除去1个氢原子而得的1价基团。

[0522] 本发明中的环烯基是指，从环烯烃的任意碳原子上除去1个氢原子而得的1价基团。

[0523] 本发明中的亚环烷基是指，从环烷烃的任意两个不同的碳原子上除去2个氢原子而得的2价基团。

[0524] 本发明中的环烷叉基是指，从环烷烃的一个碳原子上除去2个氢原子而得的2价基团。

[0525] 本发明中的环烷烃是指，脂环式烃。

[0526] 本发明中的“C_{3-12}环烷基”、本发明中的“C_{3-12}亚环烷基”、和本发明中的“C_{3-12}环烷叉基”的环烷烃是指，单环式或多环式的3～12元的脂肪族烃环，具体而言，可举出：环丙烷、环丁烷、环戊烷、环己烷、环庚烷、环辛烷、螺[3.3]庚烷、双环[1.1.1]戊烷、双环[2.2.2]辛烷、和金刚烷等。

[0527] 本发明中的“C_{4-12}环烯基”的环烯烃是指，单环式或多环式的4～12元的脂肪族烃环，具体而言，可举出，环丁烯、环戊烯、环己烯、环庚烯、环辛烯、螺[3.3]庚烯、和双环[2.2.2]辛烯等。

[0528] 本发明中的杂环基是指，从杂环的任意的碳原子或氮原子上除去1个氢原子而得的1价基团。

[0529] 本发明中的亚杂环基是指，从杂环的任意的两个不同的碳原子或氮原子上除去2个氢原子的2价基团。

[0530] 本发明中的杂环叉基是指，从杂环的一个碳原子上除去2个氢原子而得的2价基团。

[0531] 本发明中的杂环是指，含有选自硫原子、氮原子、和氧原子的杂原子的环，环的一部分或全部为脂肪族的环。

[0532] 本发明中的“4～12元的杂环基”、本发明中的“4～12元的亚杂环基”、和本发明中的“4～12元的杂环叉基”的杂环是指，“4～12元的杂环烷烃”、在“4～12元的杂环烷烃”上具有不饱和键者、杂芳烃或芳烃与杂环烷烃的一部分键合而作为整体为4～12元的环者、杂芳烃与环烷烃的一部分键合而作为整体为4～12元的环者、4～12元的包含杂原子且具有螺结构的环者、和4～12元的包含杂原子且具有交联结构的环者。“4～12元的杂环烷烃”是指，为单环式或多环式的脂肪族烃环，且包含1～4个选自硫原子、氮原子、和氧原子的杂原子的4～12元的环状杂烷烃。关于“4～12元的杂环烷烃”，具体而言，可举出：氮杂环丙烷、硫杂环丙烷、氮杂环丁烷、氧杂环丁烷、硫杂环丁烷、四氢呋喃、四氢吡喃、1,4-二噁烷、哌啶、哌嗪、吡咯烷、咪唑烷、吡唑烷、吗啉、硫代吗啉、四氢噻喃、四氢噻吩、1,4-二氮杂环庚烷、氧杂环庚烷等。“螺结构”是指，两个的环结构(环烷烃或杂环烷烃)共有1个碳原子的化合物，可举出：2-氮杂螺[3.3]庚烷、1,6-二氮杂螺[3.3]庚烷、2,6-二氮杂螺[3.3]庚烷、2,6-二氮杂螺[3.4]辛烷、2,7-二氮杂螺[3.5]壬烷、1,7-二氮杂螺[4.5]癸烷、2,8-二氮杂螺[4.5]癸烷、4,7-二氮杂螺[2.5]辛烷等。“交联结构”是指，两个的环结构(环烷烃或杂环烷烃)共有2个或其以上的碳原子、氮原子、或氧原子的化合物，可举出：2,5-二氮杂双环[2.2.2]辛烷、3,8-二氮杂双环[3.2.1]辛烷、1,4-二氮杂双环[3.2.2]壬烷、八氢吡咯并[3,4-b]吡咯等。

[0533] 本发明中的芳基是指，从芳烃的任意的碳原子上除去1个氢原子而得的1价基团。

[0534] 本发明中的亚芳基是指，从芳烃的任意的碳原子上除去2个氢原子而得的2价基团。

[0535] 本发明中的芳烃是指，芳香族烃。

[0536] 本发明中的“C_{6-10}芳基”、和本发明中的“C_{6-10}亚芳基”的芳烃是指，碳数6～10个的芳香族烃环，具体而言，可举出：苯、萘等。

[0537] 本发明中的杂芳基是指，从杂芳烃的任意的碳原子或氮原子上除去1个氢原子而得的1价基团。

[0538] 本发明中的亚杂芳基是指，从杂芳烃的任意的碳原子或氮原子上除去2个氢原子而得的2价基团。

[0539] 本发明中的杂芳烃是指，含有选自硫原子、氮原子、和氧原子的杂原子的芳香族杂环。

[0540] 本发明中的“5～10元的杂芳基”、和本发明中的“5～10元的亚杂芳基”的杂芳烃是

指，含有1～4个选自硫原子、氮原子、和氧原子的杂原子的5～10元的芳香族杂环，具体而言，可举出：呋喃、噻吩、吡咯、咪唑、吡唑、三唑、四唑、噻唑、噁唑、异噁唑、噁二唑、噻二唑、异噻唑、吡啶、哒嗪、吡嗪、嘧啶、喹啉、异喹啉、苯并呋喃、苯并噻吩、吲哚，吲唑，和苯并咪唑等。

[0541] 本发明中的“(4～12元的杂环基)C_{1-6}烷基”是指，4～12元的杂环基与C_{1-6}烷基键合、C_{1-6}烷基与其他结构键合而得者。具体而言，可举出：上述的4～12元的杂环基的具体例与C_{1-6}烷基的具体例键合而得者。

[0542] 本发明中的“(C_{6-10}芳基)C_{1-6}烷基”是指，C_{6-10}芳基与C_{1-6}烷基键合、C_{1-6}烷基与其他结构键合而得者，具体而言，可举出：上述的C_{6-10}芳基的具体例与C_{1-6}烷基的具体例键合而得者。

[0543] 本发明中的“(5～10元的杂芳基)C_{1-6}烷基”是指，5～10元的杂芳基与C_{1-6}烷基键合、C_{1-6}烷基与其他结构键合而得者。具体而言，可举出：上述的5～10元的杂芳基的具体例与C_{1-6}烷基的具体例键合而得者。

[0544] 本发明中的“C_{1-8}烷基磺酰基”是指，C_{1-8}烷基与磺酰基(-S(=O)$_2$-)键合、磺酰基与其他结构键合而得者。

[0545] 本发明中的“C_{1-8}酰基”是指，C_{1-7}烷基与羰基(-CO-)键合、羰基与其他结构键合而得者。

[0546] 本发明中的“卤素”是指，氟原子、氯原子、溴原子、或碘原子。

[0547] 本发明中的“C_{1-8}烷氧基”是指，具有碳数1～8个的直链、支链状、或环状的烷氧基，具体而言，可举出：甲氧基、乙氧基、正丙氧基、异丙氧基、正丁氧基、异丁氧基、仲丁氧基、叔丁氧基、正戊氧基、新戊氧基、叔戊氧基、2-甲基丁氧基、正己氧基、异己氧基、环丙氧基、环丁氧基、环戊氧基、环己氧基、环庚氧基、环辛氧基、螺[3.3]庚氧基、和双环[2.2.2]辛氧基等。

[0548] R^1中的“C_{3-12}环烷基”，优选环丙基、环丁基、环戊基、环己基、螺[3.3]庚基、双环[1.1.1]戊烷、双环[2.2.2]辛基、或金刚烷基。

[0549] R^1中的“C_{4-12}环烯基”，优选环戊烯基、环己烯基、或环庚烯基。

[0550] R^1中的“4～12元的杂环基”中的杂环，优选氮杂环丁烷、氧杂环丁烷、硫杂环丁烷、四氢呋喃、1,4-二噁烷、吗啉、硫代吗啉、四氢吡喃、四氢噻吩、或氧杂环庚烷。

[0551] R^1中的“C_{6-10}芳基”，优选苯基。

[0552] R^1中的“5～10元的杂芳基”，优选呋喃基、吡唑基、或噻吩基。

[0553] R^1的取代基中的“卤素”，优选氟原子或氯原子。

[0554] R^1的取代基中的“$-COOR^6$”，优选-COOH、或$-COOCH_3$。

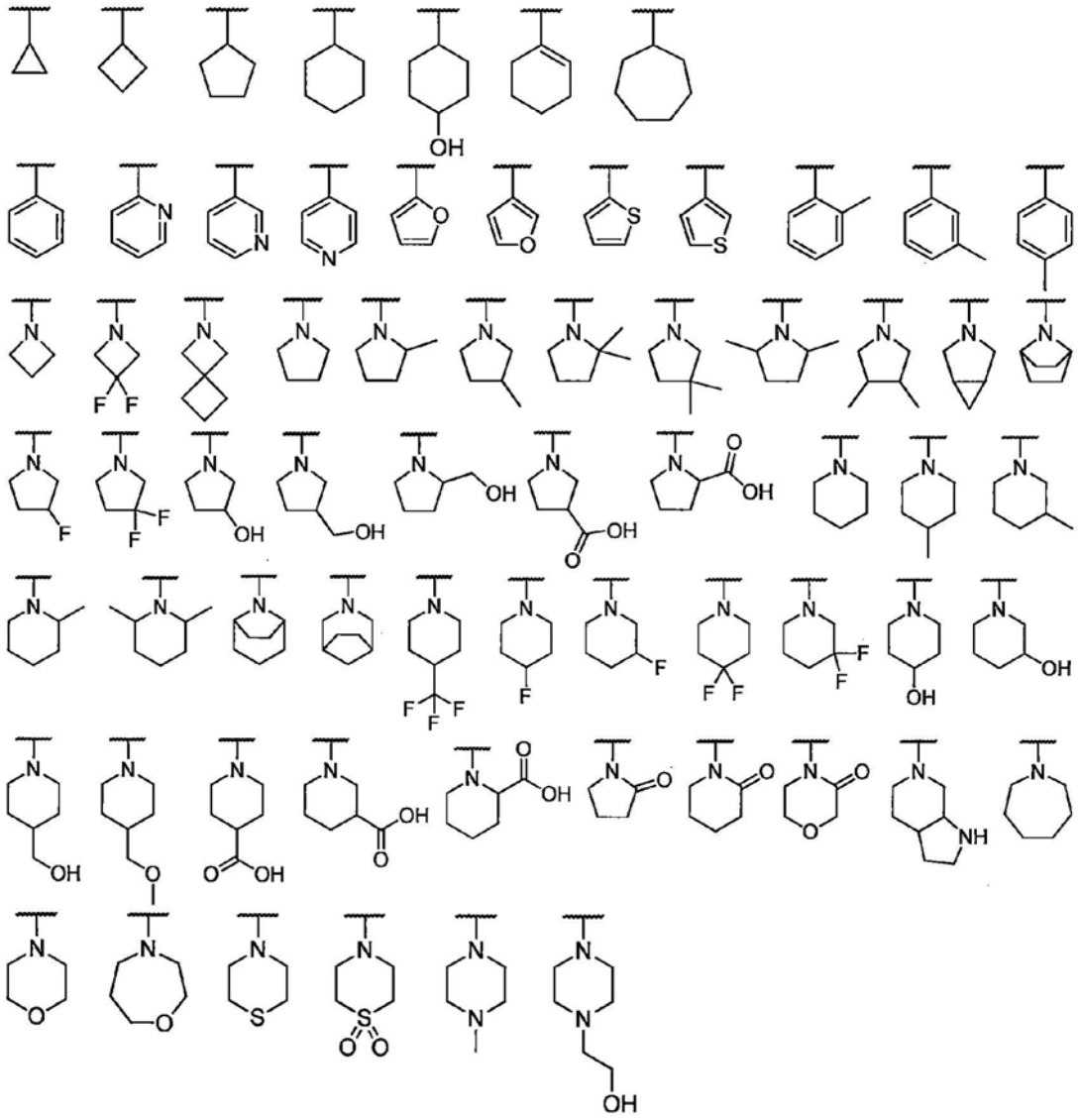
[0555] R^1的取代基中的“R^7”，优选甲基、乙基、正丙基、异丙基、正丁基、异丁基、仲丁基、叔丁基、正戊基、新戊基、异戊基、1,1-二甲基-2-甲氧基乙基、1-甲基-2-甲氧基乙基、1-甲基-2-羟乙基、2,2,2-三氟乙基、羟甲基、或1-甲基-2,2,2-三氟乙基。

[0556] R^1的取代基中的被“[0～2个的-OH，0～2个的C_{1-8}烷氧基，和0～6个的氟原子]取代的C_{3-6}环烷基”，优选环戊基、环己基、4-甲氧基环己基、或4-异丙氧基环己基。

[0557] R^1的取代基中的被[0～2个的-OH、0～2个的C_{1-8}烷氧基、和0～6个的氟原子]取代的3～10元的杂环基，优选四氢呋喃基，四氢吡喃基，或2,2-二甲基四氢吡喃基。

[0558] 作为R^1整体，优选以下的结构。

[0559] [化学式5]

[0560] 

[0561] R^2中的“C_{1-8}烷基”优选甲基、乙基、或正丙基，取代基优选羟基、甲氧基、乙氧基、或氟原子。

[0562] R^2中的“C_{3-8}环烷基”优选环丙基，取代基优选羟基、羟甲基、或氟原子。

[0563] R^2中的“4～6元的杂环基”，优选氧杂环丁基、或四氢呋喃基。

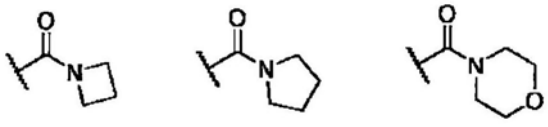
[0564] R^2中的“C_{1-8}酰基”，优选乙酰基。

[0565] R^2中的“$-COOR^8$”，优选-COOH、或$-COOCH_3$。

[0566] R^2中的“$-CONR^9R^{10}$”，优选$-CON(CH_3)_2$。

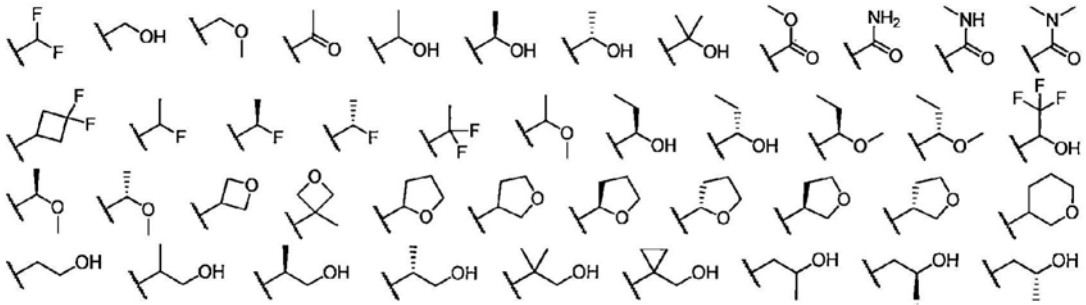
[0567] 关于R^2的$-CONR^9R^{10}$中的R^9和R^{10}可经由单键或-O-键合而形成包含与它们键合的氮原子的环，例如可举出以下的结构。

[0568] [化学式6]

[0569] 

[0570] 作为R^2整体，优选以下的结构。

[0571] [化学式7]

[0572] 

[0573] R^3中的“C_{1-8}烷基”，优选甲基。

[0574] R^3中的“卤素”，优选氟原子、或氯原子。

[0575] 作为R^3整体，优选氢原子、氟原子、氯原子、或甲基。

[0576] R^{11}优选氢原子、甲基、乙基、或环丙基。

[0577] A^1中的“C_{1-8}亚烷基”，优选亚甲基、亚乙基、或正亚丙基。

[0578] 作为置换处于A^1的任意位置的1～2个的sp^3碳原子的结构，优选-O-、-OCH_2-、-OCH_2CH_2-、-$OCH_2CH_2CH_2$-、-CH_2O-、-CH_2OCH_2-、-$CH_2OCH_2CH_2$-、-CH_2CO-、-$COCH_2$-、-CH_2CH_2CO-、-$COCH_2CH_2$-、-CH_2COCH_2-、-$CH_2COCH_2CH_2$-、-NR^{14}-、-$NR^{14}CH_2$-、-CH_2NR^{14}-、-$NR^{14}CH_2CH_2$-、-$CH_2NR^{14}CH_2$-、-$CH_2CH_2NR^{14}$-。

[0579] 在R^{11}与A^1经由单键键合而形成环的情况下，优选用选自[-NR^{14}-、或-C(=O)-NR^{15}-]的1个结构置换处于A^1的任意位置的1个的sp^3碳原子而得的结构，A^1优选-CH_2NR^{14}-、-C(=O)NR^{15}-、-CH_2-NR^{17}-C(=O)-、或-CH_2-NR^{22}-S(=O)$_2$-。

[0580] A^2中的“C_{1-7}亚烷基”，优选亚甲基、亚乙基、或正亚丙基。

[0581] A^2中的“C_{3-12}亚环烷基”优选亚环丙基、亚环丁基、亚环戊基、或亚环己基。

[0582] A^2中的“C_{3-12}环烷叉基”，优选环丙叉基、环丁叉基、环戊叉基、或环己叉基。

[0583] A^2中的“4～12元的亚杂环基”中的杂环，优选哌啶、哌嗪、吡咯烷、吗啉、四氢呋喃、四氢吡喃、1,4-二氮杂环庚烷、氧杂环庚烷、2-氮杂螺[3.3]庚烷、1,6-二氮杂螺[3.3]庚烷、2,6-二氮杂螺[3.3]庚烷、2,6-二氮杂螺[3.4]辛烷、2,5-二氮杂双环[2.2.2]辛烷、3,8-二氮杂双环[3.2.1]辛烷、2,7-二氮杂螺[3.5]壬烷、1,7-二氮杂螺[4.5]癸烷、2,8-二氮杂螺[4.5]癸烷、4,7-二氮杂螺[2.5]辛烷、1,4-二氮杂双环[3.2.2]壬烷、或八氢吡咯并[3,4-b]吡咯。

[0584] A^2中的“4～12元的杂环叉基”中的杂环，优选氧杂环丁烷、四氢呋喃、四氢吡喃、吡咯烷、哌啶、哌嗪、吗啉、或氧杂环庚烷。

[0585] A^2中的“C_{6-10}亚芳基”，优选亚苯基。

[0586] A^2中的“5～10元的亚杂芳基”中的杂芳烃，优选呋喃、噻吩、吡咯、咪唑、吡唑、三唑、四唑、噻唑、噁唑、异噁唑、噁二唑、噻二唑、异噻唑、吡啶、哒嗪、吡嗪、嘧啶、喹啉、异喹啉、苯并呋喃、苯并噻吩、吲哚、吲唑、或苯并咪唑。

[0587] A^3中的“卤素”，优选氟原子、或氯原子。

[0588] A^3中的“-R^{25}”，优选氢原子、甲基、乙基、正丙基、异丙基、正丁基、异丁基、叔丁基。在-R^{25}被取代基取代的情况下，优选羟甲基、1-羟乙基、2-羟乙基、2-羟基-2-丙基、2-羟基-

1-丙基、1-羟基-2-丙基、1-羟基-2-甲基-2-丙基、2-羟基-2-甲基-1-丙基、三氟甲基、2,2,2-三氟乙基、羧甲基、1-羧乙基、2-羧乙基、2-羧基-2-丙基、或氰甲基。

[0589] A^3中的"$-OR^{26}$"，优选-OH、甲氧基、乙氧基、或异丙氧基。

[0590] A^3中的"$-NR^{27}R^{28}$"，优选氨基、二甲氨基、甲氨基、吡咯烷-1-基、哌啶-1-基、哌嗪-1-基、或吗啉-1-基。

[0591] A^3中的"$-C(=O)R^{29}$"，优选乙酰基、四氢呋喃-2-羰基、四氢呋喃-3-羰基、吡咯烷-2-羰基、吡咯烷-3-羰基、哌啶-2-羰基、哌啶-3-羰基、哌啶-4-羰基、吡啶甲酰基、烟酰基、或异烟酰基。在$-C(=O)R^{29}$被取代基取代的情况下，优选羟基乙酰基。

[0592] A^3中的"$-C(=O)-OR^{30}$"，优选-COOH、甲氧羰基、乙氧羰基、或异丙氧羰基。

[0593] A^3中的"$-O-C(=O)R^{31}$"，优选乙酰氧基。

[0594] A^3中的"$-O-C(=O)-NR^{32}R^{33}$"，优选((二甲氨基)羰基)氧基、((吡咯烷-1-基)羰基)氧基、((哌啶-1-基)羰基)氧基、((吗啉-1-基)羰基)氧基、或((哌嗪-1-基)羰基)氧基。

[0595] A^3中的"$-C(=O)-NR^{34}R^{35}$"，优选氨基羰基(别名:氨基甲酰基)、(甲氨基)羰基、(二甲氨基)羰基、(吡咯烷-1-基)羰基、(哌啶-1-基)羰基、(吗啉-1-基)羰基、或(哌嗪-1-基)羰基。

[0596] A^3中的"$-NR^{36}-C(=O)R^{37}$"，优选(乙酰基)氨基、(羟基乙酰基)氨基、(四氢呋喃-2-羰基)氨基、(四氢呋喃-3-羰基)氨基、2-氧代吡咯烷-1-基、或3-氧代吗啉代。

[0597] A^3中的"$-NR^{38}-C(=O)-OR^{39}$"，优选(甲氧羰基)氨基、(甲氧羰基)(甲基)氨基、或(2-氧代)噁唑烷-3-基。

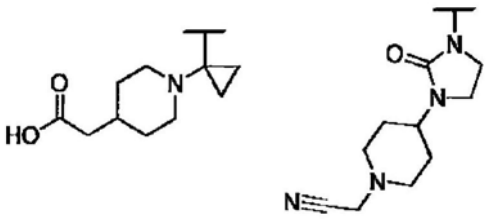
[0598] A^3中的"$-S(=O)_2-R^{40}$"，优选甲磺酰基、乙磺酰基、(吡咯烷-3-基)磺酰基、(哌啶-3-基)磺酰基、或(哌啶-4-基)磺酰基。

[0599] A^3中的"$-S(=O)_2-NR^{41}R^{42}$"，优选(二甲氨基)磺酰基、(吡咯烷-1-基)磺酰基、(哌啶-1-基)磺酰基、(吗啉-1-基)磺酰基、或(哌嗪-1-基)磺酰基。

[0600] A^3中的"$-NR^{43}-S(=O)_2R^{44}$"，优选甲磺酰基氨基、(甲磺酰基)(甲基)氨基、1,1-二氧代异噻唑烷-2-基、1,1-二氧代-1,2,5-噻二嗪-2-基、或3,3-二氧代-1,3,4-氧杂噻嗪-4-基。

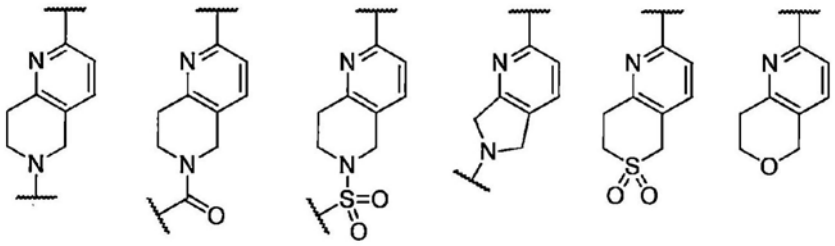
[0601] 关于A^1、A^2、A^3中的R^{14}～R^{44}可在A^1内、A^2内、A^3内、[A^1与A^2之间]、[A^1与A^3之间]、或[A^2与A^3之间]经由[单键、-O-、$-NR^{50}-$、或$-S(=O)_p-$]键合而形成环，例如可举出以下的结构。

[0602] [化学式8]

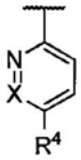
[0603] 

[0604] 关于R^{11}与[A^1,A^2,或A^3]可经由[单键、-O-、$-NR^{51}-$、或$-S(=O)_p-$]键合而形成环，例如可举出以下的结构。

[0605] [化学式9]

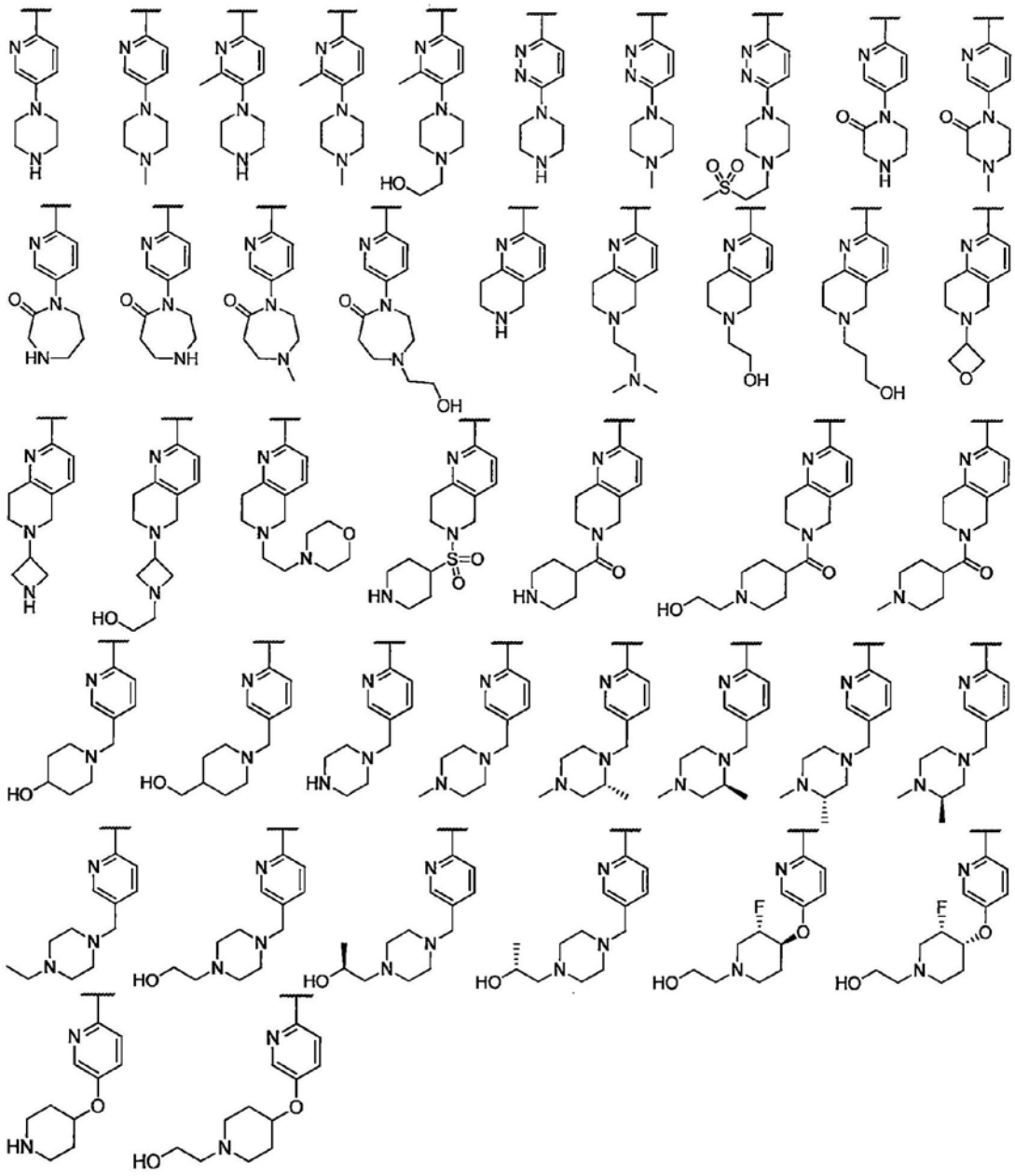
[0606] 

[0607] [化学式10]

[0608] 

[0609] 作为上述的结构的整体,优选以下的结构。

[0610] [化学式11]

[0611] 

[0612] 在式(I)所表示的化合物中，具有上述选择项的各基团的定义和优选的基团、或优选的基团彼此相互组合也是优选的化合物。

[0613] 作为本发明中的R^1、R^2、和R^4中的-OH的适当的保护基，可举出：乙酰基、苯甲酰基、叔丁基二甲基甲硅烷基、叔丁基二苯基甲硅烷基、苄基、4-甲氧基苄基、2,4-二甲氧基苄基、(甲氧基)甲基、或2-(三甲基甲硅烷基)乙氧基甲基等。

[0614] 作为本发明中的R^1、和R^4中的氨基、烷基氨基、和含氮杂芳基的NH的适当的保护基，可举出：叔丁氧基羰基、苄氧基羰基、苄基、4-甲氧基苄基、2,4-二甲氧基苄基、三氟乙酰基、或2-(三甲基甲硅烷基)乙氧基甲基等。

[0615] 本发明的式(I)所表示的化合物根据需要可以转换成医学上可接受的盐。作为所涉及的盐，例如可举出：与盐酸、氢溴酸、氢碘酸、硫酸、硝酸、磷酸、碳酸等的无机酸的盐；与甲酸、乙酸、丙酸、三氟乙酸、邻苯二甲酸、草酸、丙二酸、琥珀酸、富马酸、马来酸、乳酸、苹果酸、酒石酸、柠檬酸、苯甲酸、甲磺酸、乙磺酸、苯磺酸、对甲苯磺酸等的有机酸的盐；与赖氨酸、精氨酸、鸟氨酸、谷氨酸、天冬氨酸等的氨基酸的盐；与钠、钾、锂等的碱金属的盐；与钙、镁等的碱土金属的盐；与铝、锌、铁等的金属的盐；与甲胺、乙胺、叔辛胺、二乙胺、三甲胺、三乙胺、乙二胺、哌啶、哌嗪、吡啶、甲基吡啶、乙醇胺、二乙醇胺、三乙醇胺、环己胺、二环己胺、N-甲基葡糖胺、三(羟甲基)氨基甲烷、N,N'-二苄基乙二胺等的有机碱的盐；铵盐等。

[0616] 本发明中还包括式(I)所表示的化合物的一个或多个原子被稳定同位素、和放射性同位素取代的化合物。

[0617] 本发明中还包括式(I)所表示的化合物的立体异构体、外消旋体、和所有可能的光学活性体。另外，发明的化合物具有通过各取代基的组合产生互变异构体的情况，这样的互变异构体也包括在本发明的化合物中。

[0618] 以下，对通式(I)所表示的本发明化合物的代表性的合成法进行说明。

[0619] 本发明的化合物可以通过下述的方法进行合成。需说明的是，各式中，R^1、R^2、R^3、R^4如同式(I)的定义。另外，作为化学式中所记载的条件的试剂或溶剂等，仅仅是如本文中所记载的例示。根据需要，各取代基可被适当的保护基保护，并且可在适当的阶段中进行脱保护(参考文献：PROTECTIVE GROUPS in ORGANIC SYNTHESIS,4TH EDITION,John Wiley& Sons,Inc.)。本文中或表中的取代基、试剂和溶剂的缩写分别表示如下。

[0620] Me：甲基

[0621] Et：乙基

[0622] Ph：苯基

[0623] Boc：叔丁氧基羰基

[0624] Cbz：苄氧基羰基

[0625] THF：四氢呋喃

[0626] DMF：N,N-二甲基甲酰胺

[0627] NMP：N-甲基吡咯烷酮

[0628] TFA：三氟乙酸

[0629] TBS：叔丁基二甲基甲硅烷基

[0630] BINAP：2,2'-双(二苯基膦基)-1,1'-联萘

[0631] TBDPS：叔丁基二苯基甲硅烷基

[0632] DIPEA:N,N-二异丙基乙胺

[0633] LAH:氢化铝锂

[0634] DMAP:4-二甲氨基吡啶

[0635] Ac:乙酰基

[0636] Ms:甲磺酰基

[0637] WSC:水溶性碳二亚胺(1-乙基-3-(3-二甲氨基丙基)碳二亚胺)

[0638] m-CPBA:间氯过苯甲酸

[0639] DAST:三氟化二乙氨基硫

[0640] dba:二亚苄基丙酮

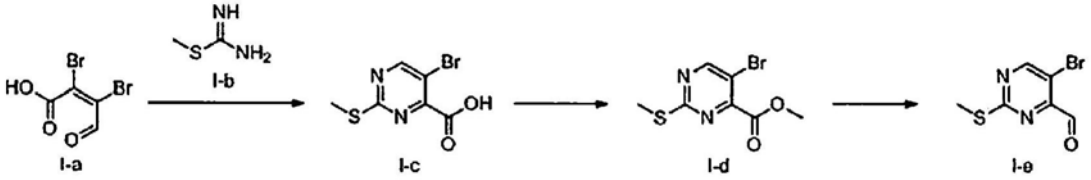
[0641] DIBAL-H:二异丁基氢化铝

[0642] dppf:1,1'-双(二苯基膦基)二茂铁

[0643] HATU:O-(7-氮杂苯并三唑-1-基)-N,N,N',N'-四甲基脲六氟磷酸盐

[0644] 1)化合物I-e的合成

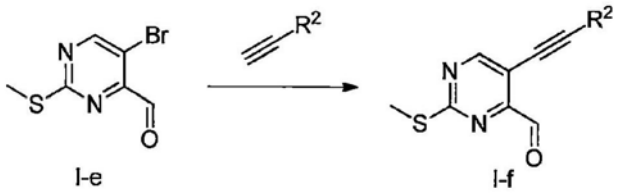
[0645] [化学式12]

[0646] 

[0647] 由于化合物I-e所表示的化合物为已知化合物,因此可以通过本领域技术人员所已知的方法合成。例如,可以通过上述的步骤合成。

[0648] 2)由化合物I-e合成化合物I-f

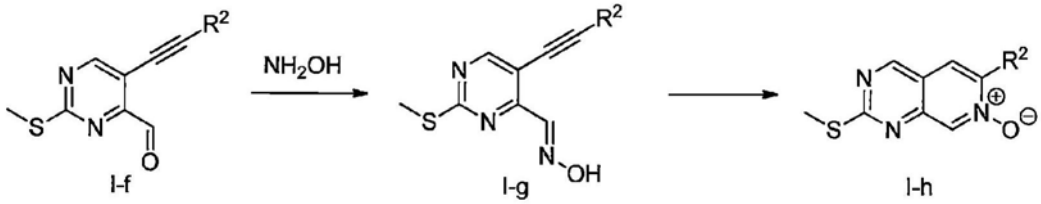
[0649] [化学式13]

[0650] 

[0651] 在适当的钯催化剂(例如,四(三苯基膦)钯)的存在下、适当的铜催化剂(例如,碘化铜(I))的存在下、适当的碱(例如,三乙胺)的存在下,在适当的有机溶剂(例如,THF、DMF)中,在0℃至溶剂加热回流的温度范围内,使化合物I-e与R^2-C≡CH所表示的末端炔烃衍生物反应,由此得到化合物I-f。

[0652] 3)由化合物I-f合成化合物I-h

[0653] [化学式14]

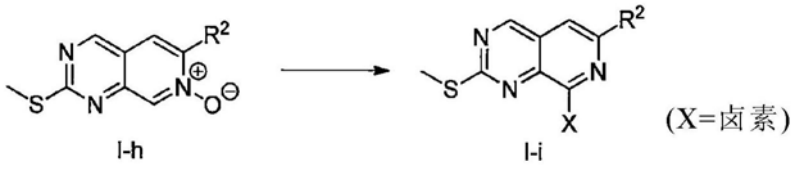
[0654] 

[0655] 在适当的碱(例如,乙酸钠)的存在下或非存在下,在适当的有机溶剂(例如,乙醇)中,在0℃至溶剂加热回流的条件下,使化合物I-f与羟基胺或其盐反应进行羟基亚胺化后,

与适当的酸或碱(例如,三氟甲磺酸银、碳酸钾)反应,由此得到化合物I-h。

[0656] 4)由化合物I-h合成化合物I-i

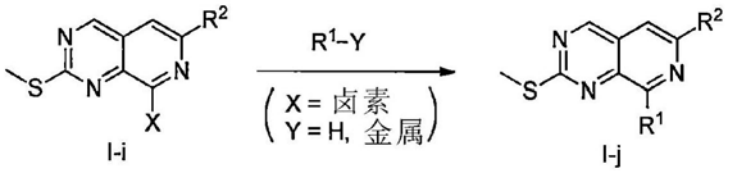
[0657] [化学式15]

[0658] 

[0659] 在适当的有机溶剂(例如,二氯甲烷)中或无溶剂条件下,在0℃至140℃的温度范围内,使化合物I-h与适当的卤化剂(例如,亚硫酰氯)反应,由此得到化合物I-i。

[0660] 5)由化合物I-i合成化合物I-j

[0661] [化学式16]

[0662] 

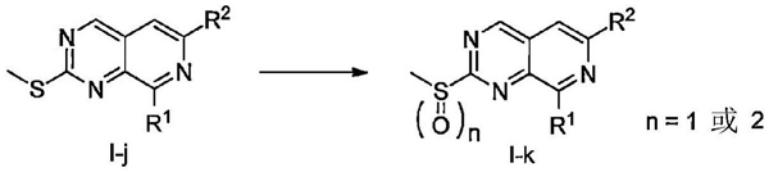
[0663] 在R^1-Y为环状仲胺衍生物的情况下,在适当的碱(例如,三乙胺、碳酸钾、氢化钠)的存在下或非存在下,在适当的有机溶剂(例如,THF,1,4-二噁烷)中或无溶剂条件下,在0℃至溶剂加热回流的温度范围内,使化合物I-i与R^1-Y所表示的环状仲胺衍生物反应,由此得到化合物I-j。

[0664] 在R^1-Y为硼酸衍生物等的有机金属试剂的情况下,在适当的催化剂(例如,乙酸钯、氯化钯)的存在下,在适当的配体(例如,三苯基膦、BINAP、dppf)的存在下或非存在下、适当的碱(例如,三乙胺、碳酸钾、氢化钠)的存在下或非存在下、适当的有机溶剂(例如,THF、1,4-二噁烷)中,在0℃至溶剂加热回流的温度范围内,使化合物I-i与R^1-Y所表示的硼酸衍生物等的有机金属试剂反应,由此得到化合物I-j。

[0665] 而且,在该阶段,可以将R^2根据目标结构使用本领域技术人员所已知的方法进行转换。

[0666] 6)由化合物I-j合成化合物I-k

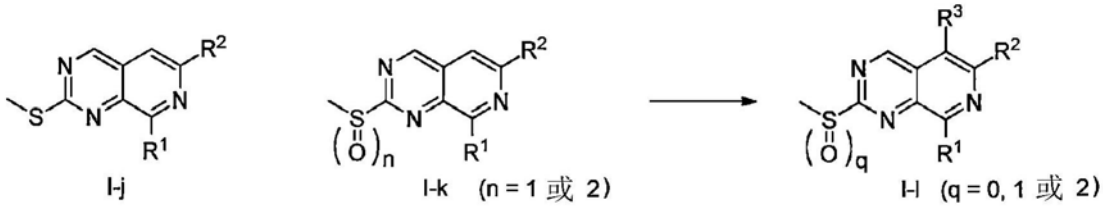
[0667] [化学式17]

[0668] 

[0669] 在适当的有机溶剂(例如,二氯甲烷、水)中,在0℃至溶剂加热回流的温度范围内,使化合物I-j与适当的氧化剂(例如,Oxone(R)、间氯过苯甲酸)反应,由此得到化合物I-k。

[0670] 7)由化合物I-j或化合物I-k合成化合物I-l

[0671] [化学式18]

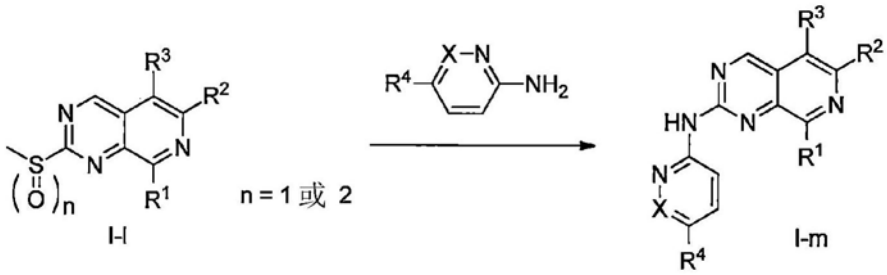
[0672] 

[0673] 在适当的有机溶剂(例如,二氯甲烷、1,2-二氯乙烷)中,在0℃至溶剂加热回流的温度范围内,使化合物I-j或化合物I-k与适当的卤化剂(例如,N-氯代琥珀酰亚胺)反应,由此得到化合物I-l。而且,在该阶段,可以将R^3根据目标结构使用本领域技术人员所已知的方法进行转换。

[0674] 需说明的是,在化合物I-l中q＝0的情况下,接下来,可以按照6)的方法进行硫原子的氧化反应。

[0675] 8)由化合物I-l合成化合物I-m

[0676] [化学式19]

[0677] 

[0678] 在适当的有机溶剂(例如,NMP、THF、甲苯)中或无溶剂条件下、适当的碱(例如,氢化钠、三乙胺、N,N-二异丙基-N-乙胺)的存在下或非存在下,在0℃至溶剂加热回流的温度范围内,使化合物I-l与R^4-(包含X的含氮杂芳基)-NH_2所表示的胺衍生物反应,由此得到化合物I-m。

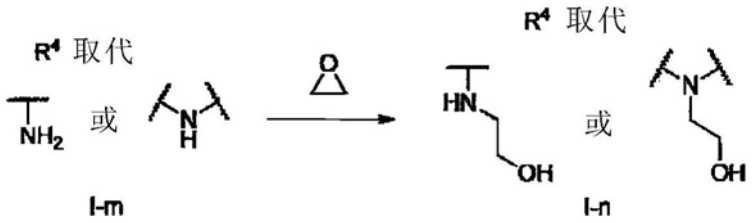
[0679] 需说明的是,在化合物I-m中的R^1、R^2、和R^4为用适当的保护基保护的情况下,可以通过本领域技术人员所熟知的方法进行脱保护。例如,在适当的有机溶剂(例如,二氯甲烷、甲醇、THF)中或无溶剂条件下,在0℃至溶剂加热回流的温度范围内,可以与适当的脱保护试剂(例如,如果保护基为Boc基则为TFA、氯化氢,如果保护基为苯甲酰基则为氢氧化锂,如果保护基为Cbz基在Pd/C存在下则为氢)反应,进行脱保护。(参考文献:Green's Protective Groups in Organic SynthesiS,4版,John Wiley&Sons Inc.)

[0680] 在化合物I-m用多个保护基保护的情况下,可根据化合物I-m的结构以适当的顺序进行脱保护。

[0681] 另外,下述9)～13)所示的反应根据各自的反应条件以使得化合物I-m中的R^1、R^2、和R^4适当被保护的方式来进行,进行各自的反应后,可以以适当的方法进行脱保护。

[0682] 9)由化合物I-m合成化合物I-n

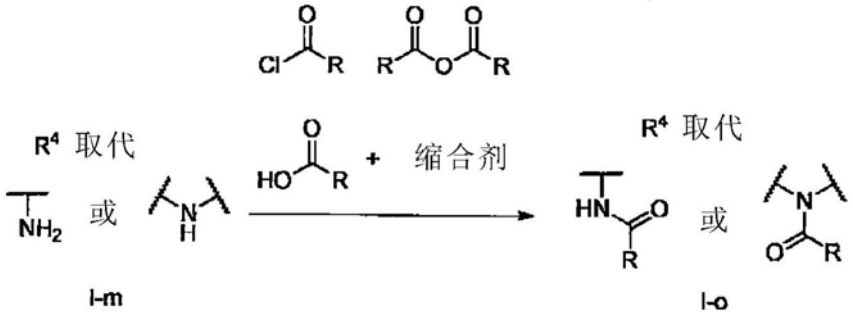
[0683] [化学式20]

[0684] 

[0685] 在适当的有机溶剂(例如,二氯甲烷、NMP、THF)中,在适当的酸(三氟化硼二乙醚络合物)、或适当的碱(例如,碳酸钾、三乙胺)的存在下或非存在下,在0℃至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与可被取代的环氧化物反应,由此得到化合物I-n。

[0686] 10)由化合物I-m合成化合物I-o

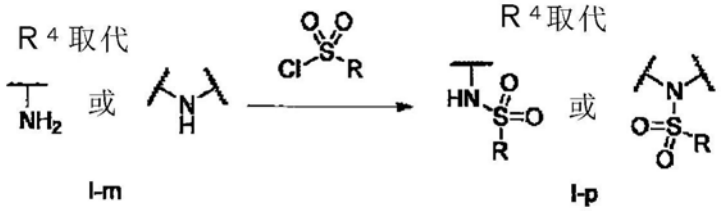
[0687] [化学式21]

[0688] 

[0689] 在适当的有机溶剂(例如,NMP、THF、吡啶)中,在适当的碱(例如,三乙胺、N,N-二异丙基-N-乙胺)的存在下或非存在下,在0℃至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与羧酰氯、羧酸酐、或羧酸和缩合剂反应,由此得到化合物I-o。在本式中,R表示氢原子、C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基。

[0690] 11)由化合物I-m合成化合物I-p

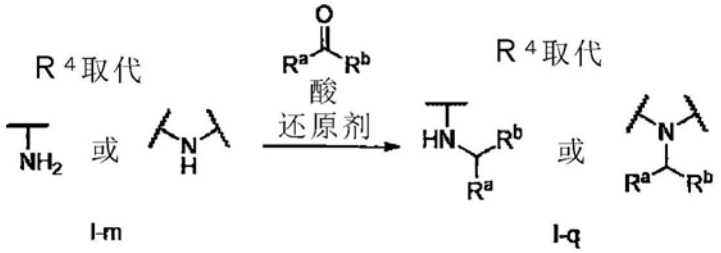
[0691] [化学式22]

[0692] 

[0693] 在适当的有机溶剂(例如,NMP、THF、吡啶)中,在适当的碱(例如,三乙胺、N,N-二异丙基-N-乙胺)的存在下或非存在下,在0℃至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与磺酰氯反应,由此得到化合物I-p。在本式中,R表示C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、C_{6-10}芳基、5～10元的杂芳基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基。

[0694] 12)由化合物I-m合成化合物I-q

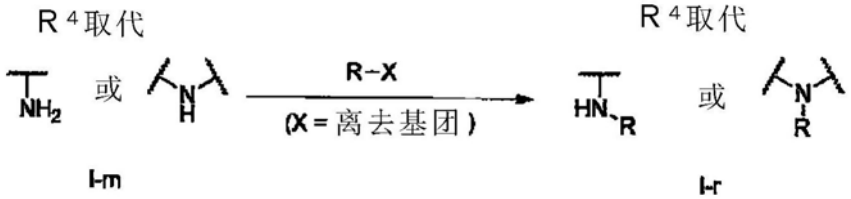
[0695] [化学式23]

[0696] 

[0697] 在适当的有机溶剂(例如,NMP、甲醇)中,在适当的酸(例如,乙酸)的存在下,在室温至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与可被取代的酮、或可被取代的醛和适当的还原剂(例如,三乙酰氧基硼氢化钠、氰基硼氢化钠)反应,由此得到化合物I-q。在本式中,关于R^a、R^b,作为包含它们键合的-CH的-CHR^aR^b整体,表示C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基。

[0698] 13)由化合物I-m合成化合物I-r

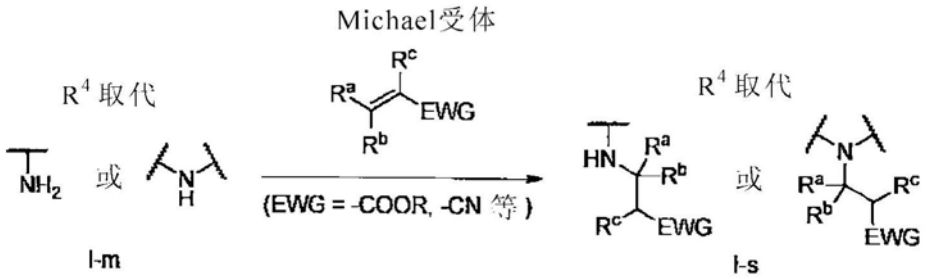
[0699] [化学式24]

[0700] 

[0701] 在适当的有机溶剂(例如,NMP、THF、吡啶)中,在适当的碱(例如,三乙胺、N,N-二异丙基-N-乙胺)的存在下或非存在下,在0℃至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与键合有卤素原子、或磺酰氧基等的离去基团的化合物反应,由此得到化合物I-r。在本式中,R表示C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基。

[0702] 14)由化合物I-m合成化合物I-s

[0703] [化学式25]

[0704] 

[0705] 在适当的有机溶剂(例如,甲醇、THF)中,在0℃至溶剂加热回流的温度范围内,使在R^4中具有伯胺或仲胺结构的化合物I-m与具有Michael受体结构的化合物反应,由此得到化合物I-s。在本式中,关于R^a、R^b、和R^c,作为包含它们键合的-C-CH-结构的-CR^aR^b-CHR^c-整体,表示C_{1-8}烷基、4～12元的杂环基、C_{3-12}环烷基、(4～12元的杂环基)C_{1-3}烷基、(C_{3-12}环烷基)C_{1-3}烷基、(C_{6-10}芳基)C_{1-3}烷基、或(5～10元的杂芳基)C_{1-3}烷基。

[0706] 由于本发明的化合物具有CDK4/6抑制活性,因此对由CDK4/6介导的疾病的预防或治疗有效。具体而言,对于类风湿性关节炎、动脉硬化、肺纤维化、脑梗塞、癌症的治疗、保护骨髓有效,特别是对于类风湿性关节炎、癌症的治疗、保护骨髓有效。

[0707] 另外，本发明的化合物优选与其他激酶比较对CDK4/6抑制活性具有选择性。例如优选与CDK2抑制活性背离。由于CDK2抑制也参与DNA的复制，因此通过背离，可期待使基因毒性表达的担忧降低的效果。本发明的化合物中，优选相比CDK2而选择性地抑制CDK4。

[0708] 本发明的有效成分可以是固体制剂、半固体制剂、和液状制剂等的任何剂型，口服剂和肠胃外剂(注射剂、经皮剂(透皮剂)、滴眼剂、栓剂、经鼻剂、和吸入剂等)的任何应用制剂均可以使用。

[0709] 含有本发明的有效成分的制剂，可以使用通常制剂化所用的添加剂进行调制。作为这些添加剂，可举出：在固体制剂的情况下，乳糖、蔗糖、葡萄糖、玉米淀粉、马铃薯淀粉、结晶纤维素、轻质无水硅酸、合成硅酸铝、偏硅酸铝镁、和磷酸氢钙等的赋形剂；结晶纤维素、羧甲基纤维素、羟丙基纤维素、羧甲基纤维素钠、和聚乙烯吡咯烷酮等的粘合剂；淀粉、羧甲基纤维素钠、羧甲基纤维素钙、交联羧甲基纤维素钠、和羧甲基淀粉钠等的崩解剂；滑石、和硬脂酸类等的润滑剂；羟甲基丙基纤维素、羟丙基甲基纤维素邻苯二甲酸酯、和乙基纤维素等的包衣剂；着色剂；在半固体制剂的情况下，白色凡士林等的基剂，在液状制剂的情况下，乙醇等的溶剂、乙醇等的增溶剂、对羟基苯甲酸酯类等的保存剂、葡萄糖等的等渗剂、柠檬酸类等的缓冲剂、L-抗坏血酸等的抗氧化剂、EDTA等的螯合剂、和聚山梨醇酯80等的悬浮化剂/乳化剂等。

[0710] 本发明的有效成分的给予量，通常为1～1000mg/天左右，给予次数通常为1～3次/天。

[0711] 实施例

[0712] 以下，基于具体的实施例说明本发明。然而，本发明并不限于这些的实施例。

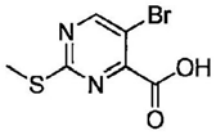
[0713] 关于所分离的新型化合物的结构，通过^{1}H-NMR和/或使用配备有电喷雾源的单四极杆仪器(single quadrupole instrumentation)的质谱分析、其他适当的分析法进行确认。

[0714] 关于^{1}H-NMR光谱(400MHz、DMSO-d_6、CD_3OD、或$CDCl_3$)，显示其化学位移(δ:ppm)和偶合常数(J:Hz)。需说明的是，以下的缩写分别表示以下的内容。s＝单重态(singlet)、d＝双重态(doublet)、t＝三重态(triplet)、q＝四重态(quartet)、brs＝宽单重态(broad singlet)、m＝多重态(multiplet)。关于质谱分析的结果，显示$(M+H)^+$、即作为在化合物的分子质量(M)中附加有质子(H^+)而得的值所观测到的测定值。

[0715] [参考例1]

[0716] 5-溴-2-(甲硫基)嘧啶-4-甲酸的合成

[0717] [化学式26]

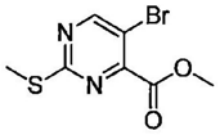
[0718] 

[0719] 在室温下向2-甲基-2-假硫脲硫酸盐(324g，1.16mol)的水溶液(2.5L)中添加粘溴酸(300g，1.16mol)。边搅拌该悬浮液边冷却至0℃，花费4小时滴加三乙胺(486mL，3.49mol)。将反应溶液搅拌过夜，用硅胶TLC确认反应完成之后，将反应溶液用浓盐酸(约250mL)制成酸性。过滤收集所产生的黄色固体，用水(500mL)洗涤2次之后，用二乙醚(500mL)洗涤2次。减压干燥所得的固体，得到标题化合物(160g，收率55％)。

[0720] [参考例2]

[0721] 5-溴-2-甲硫基嘧啶-4-甲酸甲酯的合成

[0722] [化学式27]

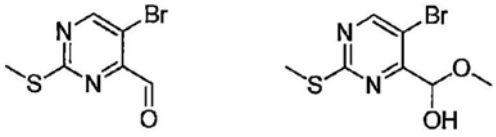
[0723] 

[0724] 边搅拌5-溴-2-(甲硫基)嘧啶-4-甲酸(110g,0.44mol)的甲醇溶液(1.1L)边冷却至0℃,滴加亚硫酰氯(50mL,0.66mol)。将反应溶液缓慢加热,在加热回流下反应4小时。用LC/MS和TLC确认反应完成,将反应溶液在室温下冷却。将挥发成分在减压下馏去,使残渣溶解于乙酸乙酯(1L),用10%碳酸钠水溶液(200mL)洗涤3次、用饱和食盐水(200mL)洗涤2次,使所得的有机相用无水硫酸镁干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的粗体用硅胶柱色谱进行纯化,得到标题化合物(88g,收率75%)。

[0725] [参考例3]

[0726] 5-溴-2-甲硫基嘧啶-4-甲醛和(5-溴-2-甲硫基嘧啶-4-基)甲氧基甲醇的混合物的合成

[0727] [化学式28]

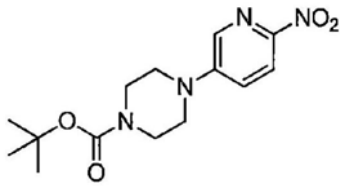
[0728] 

[0729] 将5-溴-2-甲基硫烷基嘧啶-4-甲酸甲酯(25g,95mmol)的THF溶液(375mL)在氮气氛下冷却至-78℃,进行搅拌。向该溶液中滴加DIBAL-H(84mL,143mmol,1.7M甲苯溶液),在-78℃下搅拌4小时,用TLC确认反应完成后,在-78℃下滴加甲醇使反应停止,使反应溶液缓慢升温至0℃。将反应溶液用乙酸乙酯稀释,通过硅藻土进行吸引过滤。将滤液用饱和食盐水(200mL)洗涤2次,使所得的有机相用无水硫酸镁干燥,过滤除去固体。浓缩滤液,由此得到标题化合物的混合物(25g,粗体)。该粗体无需进一步纯化即可用于下一步的反应。

[0730] [参考例4]

[0731] 4-(6-硝基吡啶-3-基)哌嗪-1-甲酸叔丁酯的合成

[0732] [化学式29]

[0733] 

[0734] 将5-溴-2-硝基吡啶(203g,1.37mol)、哌嗪(153g,1.77mol)、四丁基碘化铵(25.2g,0.068mol)、碳酸钾(207g,1.50mol)在二甲亚砜(2.6L)中、在80℃下搅拌过夜。将反应溶液冷却至室温之后,将反应溶液倒入水(7L)中,过滤收集所产生的固体。将所得的固体用二氯甲烷(1L×2次)洗涤,进行干燥。对于滤液,用氯仿萃取(2L×7次),将所得的有机相用水(2L)洗涤,然后用饱和食盐水(2L)洗涤,在减压下进行浓缩,得到固体。混合所得的固体,无需进一步纯化即可用于下一步的反应。

[0735] 使固体(490g)溶解于THF(2L)和水(500mL)中,添加碳酸氢钠(119g,1.42mol)。向

该悬浮液中添加二甲酸二叔丁酯(262g,1.2mol),在室温搅拌3小时。在减压下浓缩反应溶液,将残渣用水(1L)进行稀释,用二氯甲烷(1L×3次)萃取,将所得的有机相混合之后,用水(1L)洗涤。将该水相用二氯甲烷(300mL)萃取。混合所得的有机相,用无水硫酸镁进行干燥。

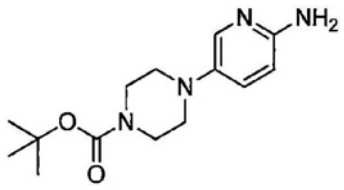
[0736] 过滤除去固体,在减压下进行浓缩。使所产生的固体悬浮于乙酸乙酯(2L)中,加热至60℃,在60℃下过滤除去固体。在减压下干燥所得的固体,由此得到标题化合物(191g,收率62%)。

[0737] APCI-MS(M+H)$^+$309.1、$C_{14}H_{20}N_4O_4$=308.15^{1}H-NMRδ(400MHz,$CDCl_3$):8.16(d,J=9Hz,1H),8.11(d,J=3Hz,1H),7.19(dd,J=9.3Hz,1H),3.64-3.61(m,4H),3.45-3.42(m,4H),1.47(s,9H).

[0738] [参考例5]

[0739] 4-(6-氨基吡啶-3-基)哌嗪-1-甲酸叔丁酯的合成

[0740] [化学式30]

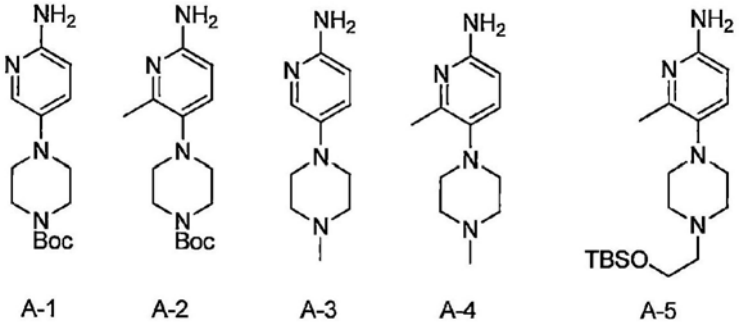
[0741] 

[0742] 使参考例4中所得的4-(6-硝基吡啶-3-基)哌嗪-1-甲酸叔丁酯(83g,269mmol)在Parr Shacker中溶解于甲醇(1.3L),添加雷尼镍(15g,50%水悬浮液)。将反应溶液在氢气氛下(50psi)搅拌5小时。将反应溶液通过硅藻土垫,过滤除去固体,在减压下浓缩滤液。使所得的固体悬浮于二乙醚(120mL)中搅拌4小时,加入庚烷在0℃下冷却45分钟。过滤除去固体,在减压下进行干燥,由此得到标题化合物(62.5g,收率83%)。

[0743] ESI-MS(M+H)$^+$279、$C_{14}H_{22}N_4O_2$=278.17

[0744] 以下的中间体A-1～A-5如下进行合成:按照参考例4和5的方法,使用对应的卤代吡啶衍生物和胺衍生物,根据需要进行适当的保护、脱保护的反应。

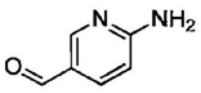
[0745] [化学式31]

[0746] 

[0747] [参考例6]

[0748] 6-氨基吡啶-3-甲醛的合成

[0749] [化学式32]

[0750] 

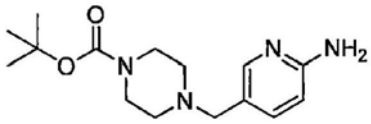
[0751] 使6-氨基吡啶-3-甲腈(1.9g,16mmol)溶解于THF(160mL),边搅拌边冷却至-78℃。

在-78℃下向该溶液中缓慢滴加氢化二异丁基铝(106.5mL,1.5M甲苯溶液),边搅拌边升温至20℃之后,继续搅拌2小时。向反应溶液中加入冰水(100mL)使反应停止,在二氯甲烷(50mL)中萃取3次。混合所得的有机相之后,用食盐水(100mL)洗涤1次,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,将残渣用硅胶柱色谱进行粗纯化,得到标题化合物的粗体(1.7g)。该粗体无需进一步纯化即可用于下一步的反应。

[0752] [参考例7]

[0753] 4-[(6-氨基吡啶-3-基)甲基]哌嗪-1-甲酸叔丁酯的合成

[0754] [化学式33]

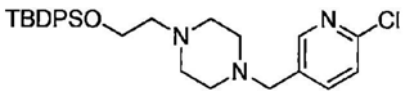
[0755] 

[0756] 使参考例6中合成的6-氨基吡啶-3-甲醛的粗体(1.7g,13.9mmol)和哌嗪-1-甲酸叔丁酯(3.2g,17.2mmol)溶解于二氯甲烷(50mL),在室温下搅拌8小时。向该反应溶液中添加三乙酰氧基硼氢化钠(8.84g,40.9mmol),在室温下搅拌2小时。用LC/MS跟踪反应的进行,反应结束后,加入饱和碳酸钠水溶液(50mL)使反应停止,用乙酸乙酯(50mL)萃取3次。混合所得的有机相,用食盐水(100mL)洗涤1次,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,将残渣用硅胶柱色谱进行粗纯化,得到标题化合物(3.3g,收率81%)。

[0757] [参考例8]

[0758] 1-(2-((叔丁基二苯基甲硅烷基)氧基)乙基)-4-((6-氯吡啶-3-基)甲基哌嗪的合成

[0759] [化学式34]

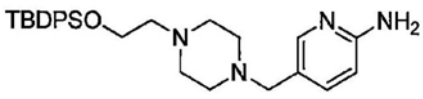
[0760] 

[0761] 向2-氯-5-(氯甲基)吡啶(1.62g,10mmol)、1-(2-((叔丁基二苯基甲硅烷基)氧基)乙基)哌嗪(3.87g,10.5mmol)、碳酸钾(4.15g,30mmol)、和碘化钠(150mg,1.0mmol)中添加DMF(33.3mL)。将该反应溶液在60℃下搅拌2小时。向反应溶液中加入水,用乙酸乙酯(80mL)萃取2次。使有机相用无水硫酸钠进行干燥,过滤除去固体,浓缩滤液。将残渣用硅胶柱色谱进行纯化,由此得到标题化合物(3.26g,收率66%)。

[0762] [参考例9]

[0763] 5-((4-(2-((叔丁基二苯基甲硅烷基)氧基)乙基)哌嗪-1-基)甲基)吡啶-2-胺的合成

[0764] [化学式35]

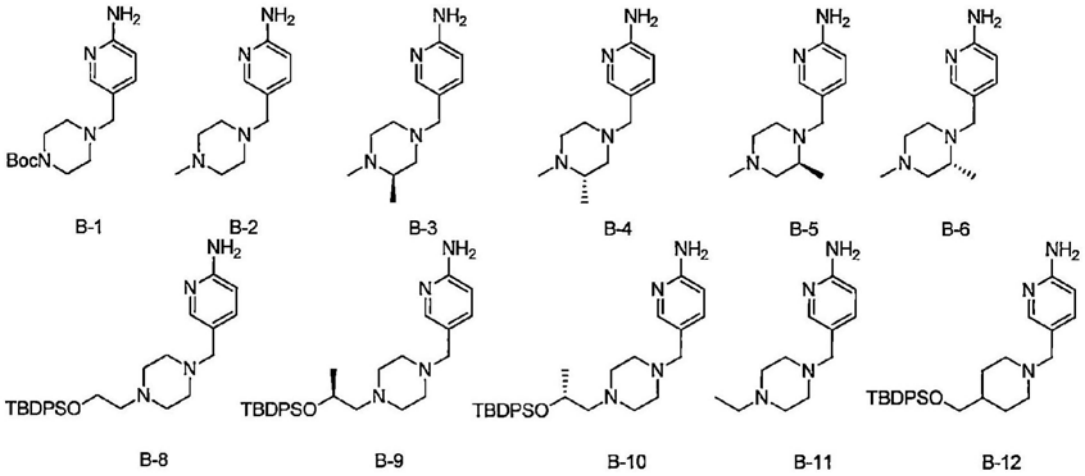
[0765] 

[0766] 向参考例8中合成的1-(2-((叔丁基二苯基甲硅烷基)氧基)乙基)-4-((6-氯吡啶-3-基)甲基哌嗪(3.26g,6.6mmol)、二苯甲酮亚胺(1.33mL,7.92mmol)、三(二亚苄基丙酮)二钯(0)(302mg,0.33mmol)、BINAP(411mg,0.66mmol)、和叔丁氧基钠(1.27g,13.2mmol)中添加甲苯(33mL),在氮气氛下、120℃下搅拌过夜。将反应溶液在室温下冷却,将反应溶液通过硅藻土垫过滤,将硅藻土垫用乙酸乙酯(80mL)洗涤。将滤液用水洗涤,进一步用饱和食盐水

洗涤。使有机相用无水硫酸钠干燥，过滤除去固体，浓缩滤液。使残渣溶解于THF(66mL)，添加柠檬酸水溶液(16mL，2.0mol/L)。将反应溶液在室温下搅拌过夜。使该反应溶液通过填充有强酸性阳离子交换树脂的柱以吸附目标物质，将该树脂用甲醇洗涤之后，通过流动氨(2.0mol/L，甲醇溶液)使目标物质洗脱。浓缩所得的洗脱液，得到标题化合物(1.17g，收率37％)。

[0767] 以下的中间体B-1～B-12如下进行合成：按照参考例6和7、或者参考例8和9的任一项的方法或组合的方法，使用对应的醛衍生物、或对应的烷基卤衍生物、和对应的胺衍生物，根据需要进行适当的保护、脱保护的反应。

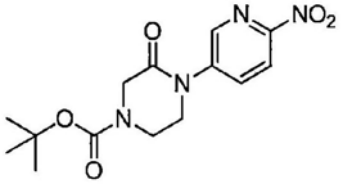
[0768] [化学式36]

[0769] 

[0770] [参考例10]

[0771] 4-(6-硝基吡啶-3-基)-3-氧代哌嗪-1-甲酸叔丁酯的合成

[0772] [化学式37]

[0773] 

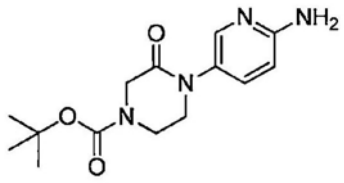
[0774] 参考WO2012/031004中所记载的方法，使2-硝基-5-溴吡啶(1.01g，5.0mmol)、2-氧代-4-哌嗪甲酸叔丁酯(1.00g，5.0mmol)和碳酸铯(3.26g，10.0mmol)悬浮于1,4-二噁烷中，使氮气鼓泡30分钟。向该悬浮液中添加Xantphos(246mg，0.43mmol)和三(二亚苄基丙酮)二钯(229mg，0.25mmol)，在加热回流下搅拌2小时。将反应溶液在室温下冷却之后，加入水和乙酸乙酯，通过硅藻土通进行过滤。分离滤液的有机相，将水相用乙酸乙酯萃取。混合所得的有机相，用无水硫酸钠进行干燥后，过滤除去固体，在减压下进行浓缩。将所得的残渣用硅胶柱色谱进行纯化，得到标题化合物(1.08g，收率67％)。

[0775] ^{1}H-NMR($CDCl_3$)δ：8.67(1H，d，J＝2.4Hz)，8.32(1H，d，J＝8.8Hz)，8.15(1H，dd，J＝8.8，2.4Hz)，4.33(2H，s)，3.93-3.83(4H，m)，1.51(9H，s)。

[0776] [参考例11]

[0777] 4-(6-氨基吡啶-3-基)-3-氧代哌嗪-1-甲酸叔丁酯的合成

[0778] [化学式38]

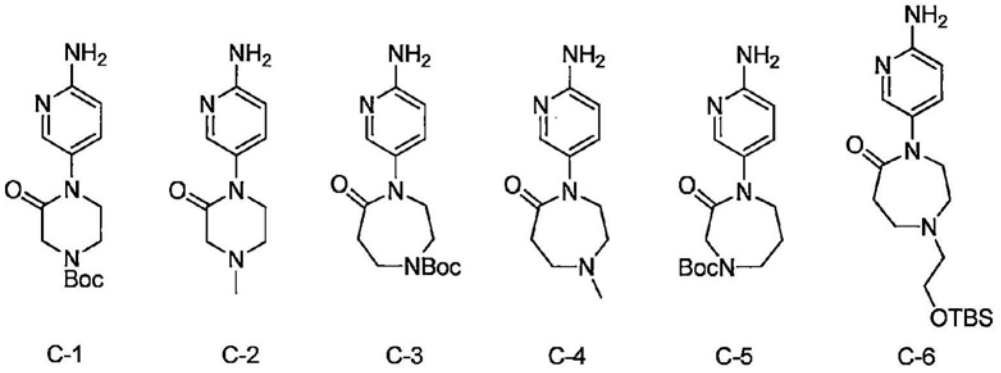
[0779] 

[0780] 使参考例10中所得的化合物(1.08g,3.34mmol)溶解于乙醇(45mL)和THF(22mL)中。向该溶液中加入钯碳(108mg),在氢气氛下搅拌24小时。将反应溶液通过硅藻土进行过滤,在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化,得到标题化合物(0.928g,收率95%)。

[0781] ^{1}H-NMR($CDCl_3$)δ:7.99(1H,d,J=2.4Hz),7.38(1H,dd,J=8.8,2.4Hz),6.53(1H,d,J=8.8Hz),4.50(2H,brs),4.24(2H,s),3.78(2H,t,J=5.1Hz),3.67(2H,t,J=5.4Hz),1.50(9H,s).

[0782] 以下的中间体C-1～C-6如下进行合成:按照参考例13和14的方法,使用对应的卤代吡啶衍生物、和对应的酰胺衍生物,根据需要进行适当的保护、脱保护的反应。

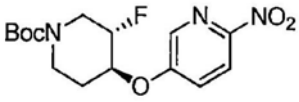
[0783] [化学式39]

[0784] 

[0785] [参考例12]

[0786] 反式-3-氟-4-((6-硝基吡啶-3-基)氧基)哌啶-1-甲酸叔丁酯的合成

[0787] [化学式40]

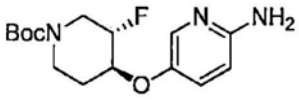
[0788] 

[0789] 使氢化钠(48mg,1.2mmol)悬浮于THF(2mL),添加反式-3-氟-4-羟基哌啶-1-甲酸叔丁酯(263mg,1.2mmol)的THF溶液(2mL),在室温下搅拌1小时。在室温下向该悬浮液中加入5-氟-2-硝基吡啶(142mg,1.0mmol)的THF溶液(1mL)之后,在室温下搅拌过夜。反应用LC/MS跟踪,反应结束后,向反应溶液中加入水(10mL),由此使反应停止,用乙酸乙酯(10mL)萃取3次。混合所得的有机相,用饱和食盐水洗涤之后,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化,由此得到标题化合物(310mg,收率91%)。

[0790] [参考例13]

[0791] 反式-4-((6-氨基吡啶-3-基)氧基)-3-氟哌啶-1-甲酸叔丁酯的合成

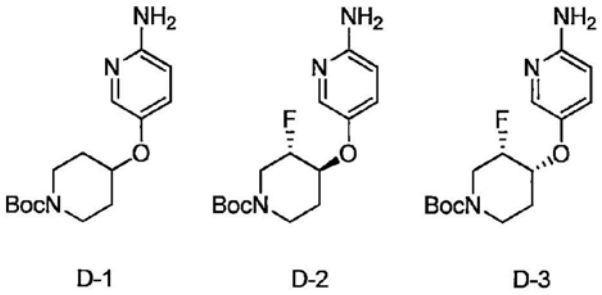
[0792] [化学式41]

[0793] 

[0794] 使参考例12中所得的反式-3-氟-4-((6-硝基吡啶-3-基)氧基)哌啶-1-甲酸叔丁酯(310mg,0.908mmol)溶解于THF(9mL)和甲醇(9mL)中。向该溶液中添加氯化铵(486mg,9.08mmol)和锌粉末(594mg,9.08mmol),在室温下搅拌1小时。将反应溶液通过硅藻土过滤,在减压下浓缩滤液。向残渣中添加饱和碳酸氢钠水溶液(30mL),将水相用二氯甲烷(30mL)萃取2次。混合所得的有机相,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,得到标题化合物的粗体。所得的粗体无需纯化即可用于下一步的反应。

[0795] 以下的中间体D-1～D-3如下进行合成:按照参考例15和16的方法,使用对应的卤代吡啶衍生物、和对应的醇衍生物,根据需要进行适当的保护、脱保护的反应。

[0796] [化学式42]

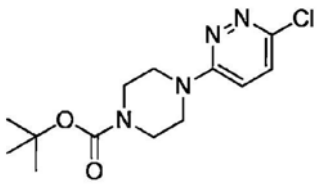
[0797] 

D-1 D-2 D-3

[0798] [参考例14]

[0799] 4-(6-氯哒嗪-3-基)哌嗪-1-甲酸叔丁酯的合成

[0800] [化学式43]

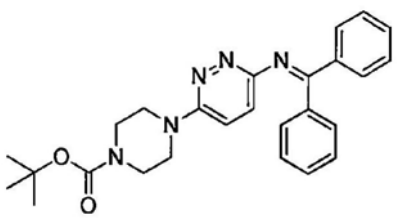
[0801] 

[0802] 使3,6-二氯哒嗪(5.01g,33.6mmol)和哌嗪-1-甲酸叔丁酯(6.88g,37.0mmol)溶解于DMF(50mL),添加三乙胺(11.7mL,50.4mmol),在80℃下搅拌过夜。将反应溶液冷却至室温,加入水之后,用二氯甲烷与甲醇的95:5混合溶液(50mL)萃取3次。将已混合的有机相用无水硫酸镁进行干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的粗体用二乙醚洗涤,由此得到标题化合物(7.0g,收率70%)。

[0803] [参考例15]

[0804] 4-(6-((二苯基亚甲基)氨基)哒嗪-3-基)哌嗪-1-甲酸叔丁酯的合成

[0805] [化学式44]

[0806] 

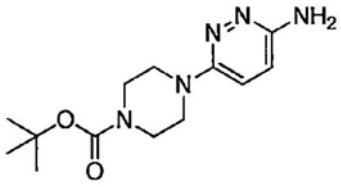
[0807] 使参考例14中所得的4-(6-氯哒嗪-3-基)哌嗪-1-甲酸叔丁酯(59.8mg,

0.20mmol)、二苯甲酮亚胺(43.5mg,0.24mmol)、三(二亚苄基丙酮)二钯(9.2mg,0.010mmol)、BINAP(12.5mg,0.020mmol)和碳酸铯(130.3mg,0.40mmol)悬浮于甲苯(1.0mL),在100℃下搅拌过夜。在室温下冷却之后,将反应溶液通过硅藻土进行过滤,用乙酸乙酯洗涤硅藻土。将所得的滤液用饱和食盐水洗涤,用无水硫酸镁进行干燥之后,过滤除去固体,在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化,得到标题化合物(67mg,收率76%)。

[0808] [参考例16]

[0809] 4-(6-氨基哒嗪-3-基)哌嗪-1-甲酸叔丁酯的合成

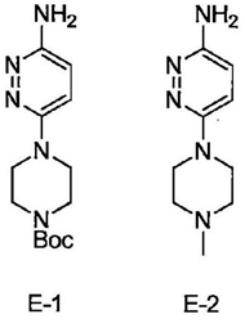
[0810] [化学式45]

[0811] 

[0812] 使参考例15中所得的4-(6-((二苯基亚甲基)氨基)哒嗪-3-基)哌嗪-1-甲酸叔丁酯(67mg,0.151mmol)溶解于THF(0.76mL),加入柠檬酸水溶液(0.378mL,0.755mmol,2mol/L),在室温下搅拌过夜。向反应溶液中加入饱和碳酸氢钠水溶液(5mL)进行中和,用乙酸乙酯(5mL)萃取2次。混合有机相,用无水硫酸镁进行干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的粗体用叔丁基甲基醚(5mL)洗涤,由此得到标题化合物(30mg,收率71%)。

[0813] 以下的中间体E-1、和E-2如下进行合成:按照参考例17～19的任一种方法或组合的方法,使用对应的卤代杂芳基衍生物、和对应的胺衍生物,根据需要进行适当的保护、脱保护的反应。

[0814] [化学式46]

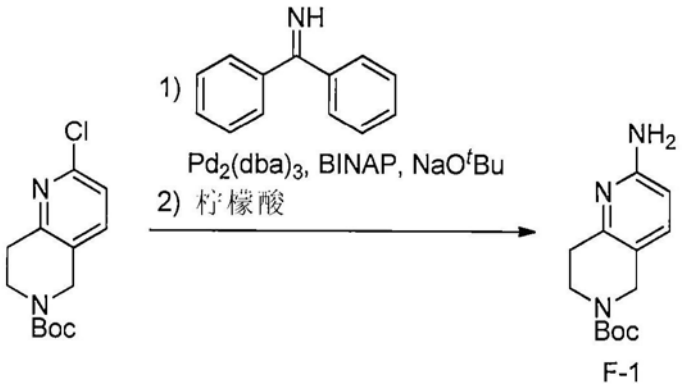
[0815] 

E-1 E-2

[0816] [参考例17]

[0817] 中间体F-1通过按照参考例9的方法,在Pd催化剂存在下,使二苯甲酮亚胺、叔丁氧基钠与2-氯-7,8-二氢-1,6-萘啶-6(5H)-甲酸叔丁酯反应,进行脱保护来合成。

[0818] [化学式47]

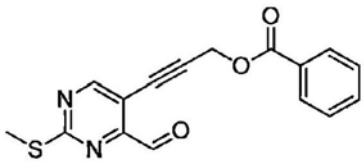
[0819] 

F-1

[0820] [实施例1]

[0821] 3-(4-甲酰基-2-甲硫基嘧啶-5-基)-2-丙炔基苯甲酸酯的合成

[0822] [化学式48]

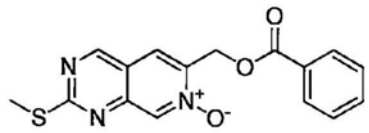
[0823] 

[0824] 将Pd(PhCN)$_2$Cl$_2$(2.4g,6.4mmol)、碘化铜(0.82g,4.3mmol)和[(t-Bu)$_3$P]HBF$_4$(4g,13.9mmol)的1,4-二噁烷溶液(55mL)进行脱气、氩置换,在室温下添加二异丙胺(18.5mL,128.8mmol)。将该反应溶液在室温下搅拌5分钟,缓慢滴加参考例3中所记载的5-溴-2-甲基硫烷基嘧啶-4-甲醛与(5-溴-2-甲基硫烷基嘧啶-4-基)甲氧基甲醇的混合物(25g,粗体)和炔丙基苯甲酸酯(20g,128.8mmol)的1,4-二噁烷溶液(55mL)之后,将反应溶液在室温下搅拌5小时。用LC/MS跟踪反应的进行,反应完成时,将反应混合物用乙酸乙酯(1L)稀释,通过硅藻土进行吸引过滤,将硅藻土用乙酸乙酯洗涤。在减压下浓缩所得的滤液,将所得的粗体直接用于进一步的反应。

[0825] [实施例2]

[0826] 6-((苯甲酰氧基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶7-氧化物(Int-1)的合成

[0827] [化学式49]

[0828] 

[0829] 使实施例1中合成的3-(4-甲酰基-2-甲硫基嘧啶-5-基)-2-丙炔基苯甲酸酯的粗体溶解于乙醇(500mL),在室温下添加盐酸羟胺(8.3g,120mmol)和乙酸钠(10g,120mmol)。将该反应溶液在室温下搅拌6小时之后,用乙醇(1L)进行稀释,加入碳酸钾(27.8g,200mmol)之后,在50℃下搅拌3小时。用LC/MS跟踪反应的进行,反应完成时,将反应溶液通过硅藻土进行吸引过滤,用乙酸乙酯洗涤硅藻土。将所得的滤液用无水硫酸钠进行干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的粗体用硅胶柱色谱进行纯化,得到标题化合物(5.0g,收率16%)。

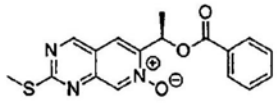
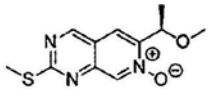
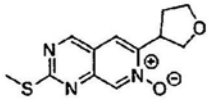
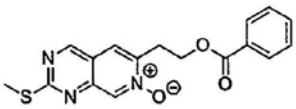
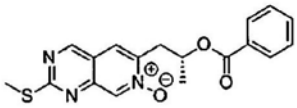
[0830] 1H-NMR(DMSO-d6)δ:9.46(1H,s),8.93(1H,s),8.31(1H,s),8.13(2H,d,J=7.6Hz),7.73(1H,t,J=7.3Hz),7.60(2H,t,J=7.7Hz),5.54(2H,5),2.62(3H,s).

[0831] LC/MS:(M+H)$^+$=328.2、$C_{16}H_{13}N_3O_3S$=327.07

[0832] 以下所记载的化合物Int-2～Int-9按照实施例1～2中所记载的方法来合成。

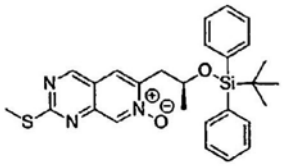
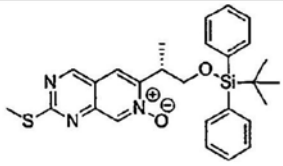
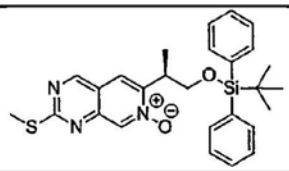
[0833] [表1]

[0834]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-2		1H-NMR (CDCl3) δ: 9.04 (1H, s), 8.79 (1H, s), 8.14 (2H, d, J = 7.5 Hz), 7.77-7.40 (4H, m), 6.66 (1H, q, J = 6.3 Hz), 2.65 (3H, s), 1.79 (3H, d, J = 6.6 Hz).	342.0	341.08
Int-3		1H-NMR (DMSO-d6) δ: 9.44 (1H, d, J = 0.4 Hz), 8.85 (1H, s), 8.09 (1H, s), 4.87 (1H, q, J = 6.4 Hz), 3.32 (3H, s), 2.61 (3H, s), 1.41 (3H, d, J = 6.4 Hz).	252.1	251.07
Int-4		1H-NMR (CDCl3) δ: 9.04 (1H, s), 8.79 (1H, s), 7.65 (1H, s), 4.25-3.90 (5H, m), 2.65 (3H, s), 2.62-2.46 (1H, m), 2.13-2.03 (1H, m).	264.1	263.07
Int-5		1H-NMR (CDCl3) δ: 8.99 (1H, s), 8.81 (1H, s), 7.98-7.93 (2H, m), 7.70-7.38 (4H, m), 4.78 (2H, t, J = 6.2 Hz), 3.48 (2H, t, J = 6.0 Hz), 2.65 (3H, s).	342.1	341.08
Int-6		1H-NMR (CDCl3) δ: 8.89 (1H, s), 8.78 (1H, s), 7.96-7.91 (2H, m), 7.58-7.50 (2H, m), 7.45-7.36 (2H, m), 5.75-5.62 (1H, m), 3.55-3.45 (1H, m), 3.34-3.22 (1H, m), 2.63 (3H, s), 1.53 (3H, d, J = 6.4 Hz).	356.1	355.1

[0835] [表2]

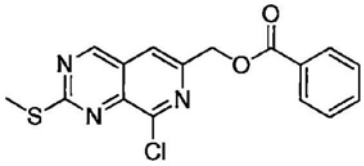
[0836]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-7		1H-NMR (CDCl3) δ: 8.72 (1H, s), 8.49 (1H, s), 7.52-7.20 (11H, m), 4.58-4.50 (1H, m), 3.28-3.20 (1H, m), 2.98-2.89 (1H, m), 2.65 (3H, s), 1.30 (3H, d, J = 6.4 Hz), 0.96 (9H, s).	490.2	489.19
Int-8		1H-NMR (CDCl3) δ: 8.91 (1H, s), 8.65 (1H, s), 7.56-7.24 (11H, m), 4.05-3.92 (3H, m), 2.66 (3H, s), 1.42 (3H, d, J = 7.2 Hz), 0.99 (9H, s).	490.2	489.19
Int-9			490.30	489.19

[0837] [实施例3]

[0838] 8-氯-2-甲硫基吡啶并[3,4-d]嘧啶-6-基苯甲酸酯(Int-10)的合成

[0839] [化学式50]

[0840] 

[0841] 使实施例2中合成的6-((苯甲酰氧基)甲基)-2-(甲硫基)吡啶并[3,4-d]嘧啶7-氧化物(5.0g,15.3mmol)溶解于二氯甲烷(60mL),冷却至0℃。在0℃下向该溶液中滴加亚硫酰氯(25mL,343mmol),在室温下搅拌16小时。用TLC跟踪反应的进行,反应完成时,在减压下浓缩反应溶液,进一步与甲苯(20mL)进行共沸2次,由此馏去亚硫酰氯。将所得的残渣用中性氧化铝柱色谱进行粗纯化,得到标题化合物(2.75g,收率52%)。

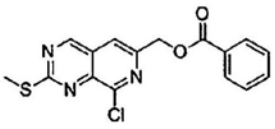
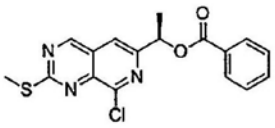
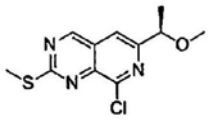
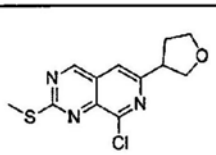
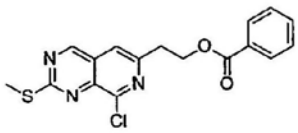
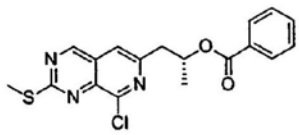
[0842] 1H-NMR(DMSO-d6)δ:9.64(1H,s),8.14(1H,s),8.13-8.06(2H,m),7.75-7.68(1H,m),7.59(2H,t,J=7.7Hz),5.56(2H,s),2.69(3H,s).

[0843] LC/MS:$(M+H)^+$=346.0、$C_{16}H_{12}ClN_3O_2S$=345.03

[0844] 以下所记载的化合物Int-11～Int-19按照实施例3中所记载的方法来合成。

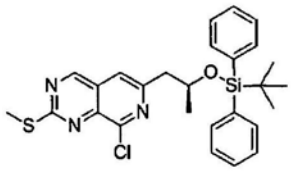
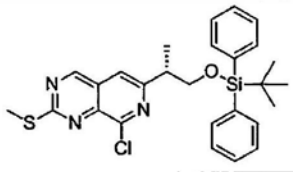
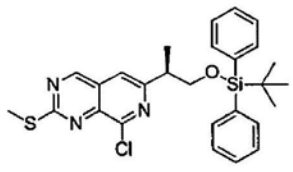
[0845] [表3]

[0846]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-11		1H-NMR (DMSO-d6) δ: 9.64 (1H, s), 8.14 (1H, s), 8.13-8.06 (2H, m), 7.75-7.68 (1H, m), 7.59 (2H, t, J = 7.7 Hz), 5.56 (2H, s), 2.69 (3H, s).	346.0	345.03
Int-12		1H-NMR (CDCl3) δ: 9.19 (1H, s), 8.16-8.12 (2H, m), 7.68 (1H, s), 7.64-7.58 (1H, m), 7.53-7.46 (2H, m), 6.27 (1H, q, J = 6.8 Hz), 2.74 (3H, s), 1.81 (3H, d, J = 6.4 Hz).	360.15	359.05
Int-13		1H-NMR (DMSO-d6) δ: 9.62 (1H, s), 8.00 (1H, s), 4.52 (2H, q, J = 6.3 Hz), 3.30 (3H, s), 2.68 (3H, s), 1.38 (3H, d, J = 6.3 Hz).	269.9	269.04
Int-14		1H-NMR (CDCl3) δ: 9.17 (1H, s), 7.48 (1H, s), 4.25-3.90 (4H, m), 3.76-3.66 (1H, m), 2.74 (3H, s), 2.48-2.22 (2H, m).	282.1	281.04
Int-15		1H-NMR (CDCl3) δ: 9.15 (1H, s), 7.98-7.93 (2H, m), 7.58-7.37 (4H, m), 4.78 (2H, t, J = 6.4 Hz), 3.38 (2H, t, J = 6.4 Hz), 2.74 (3H, s).	360.1	359.05
Int-16		1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.00-7.93 (2H, m), 7.58-7.50 (1H, m), 7.48 (1H, s), 7.47-7.36 (2H, m), 5.66-5.54 (1H, m), 3.39-3.20 (2H, m), 2.72 (3H, s), 1.48 (3H, d, J = 6.4 Hz).		

[0847] [表4]

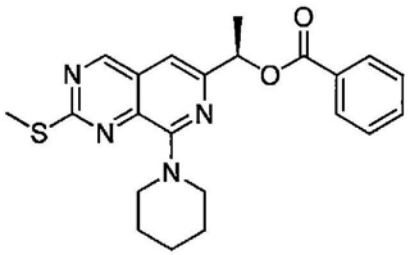
[0848]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-17		1H-NMR (CDCl3) δ: 8.93 (1H, s), 7.52-7.17 (11H, m), 4.49-4.37 (1H, m), 2.99 (2H, d, J = 6.4 Hz), 2.74 (3H, s), 1.25 (3H, d, J = 6.0 Hz), 0.91 (9H, s).	508.2	507.16
Int-18		1H-NMR (CDCl3) δ: 9.09 (1H, s), 7.52-7.26 (11H, m), 4.00-3.92 (2H, m), 3.29-3.22 (1H, m), 2.75 (3H, s), 1.36 (3H, d, J = 7.6 Hz), 0.93 (9H, s).	508.2	507.16
Int-19		1H-NMR (CDCl3) δ: 9.09 (1H, s), 7.52-7.44 (4H, m), 7.42-7.34 (3H, m), 7.33-7.26 (4H, m), 4.00-3.92 (2H, m), 3.29-3.22 (1H, m), 2.75 (3H, s), 1.36 (3H, d, J = 7.2 Hz), 0.93 (9H, s).	508.20	507.16

[0849] [实施例4]

[0850] (R)-1-(2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-20)的合成

[0851] [化学式51]

[0852] 

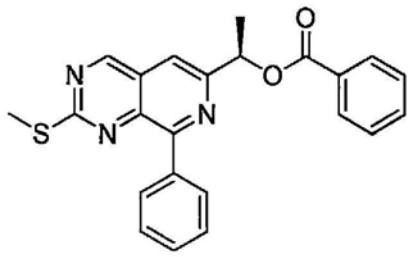
[0853] 将按照实施例1～3中所记载的方法合成的(R)-1-(8-氯-2-(甲硫基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-2,720mg,2.0mmol)和哌啶(2.0mL)在1,4-二噁烷(6.0mL)中、在100℃下搅拌过夜。用TLC跟踪反应的进行,反应结束后,将反应溶液冷却至室温。向反应溶液中添加饱和碳酸氢钠水溶液(40mL),用乙酸乙酯(40mL)萃取3次。将所得的有机相用食盐水洗涤,用无水硫酸钠进行干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的残渣用硅胶柱色谱进行纯化,由此得到标题化合物(808mg,收率99%)。

[0854] LC/MS:$(M+H)^+$=409.2、$C_{22}H_{24}N_4O_2S$=408.16

[0855] [实施例5]

[0856] (R)-1-(2-(甲硫基)-8-苯基吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-21)的合成

[0857] [化学式52]

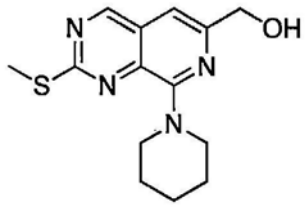
[0858] 

[0859] 向按照实施例1～3中所记载的方法合成的(R)-1-(8-氯-2-(甲硫基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-2,290mg,0.80mmol)、苯基硼酸(150mg,1.2mmol)、和四(三苯基膦)钯(0)(55mg,0.048mmol)中添加1,4-二噁烷(2.7mL)和饱和碳酸钠水溶液(1.67mL),在氮气氛下、在90℃下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,将反应溶液冷却至室温。将反应溶液用水进行稀释,用乙酸乙酯萃取。将所得的有机相用食盐水洗涤,用无水硫酸钠进行干燥,过滤除去固体之后,在减压下浓缩滤液。将所得的残渣用硅胶柱色谱进行粗纯化,直接用于下一步的反应。

[0860] [实施例6]

[0861] (2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)甲醇的合成

[0862] [化学式53]

[0863] 

[0864] 使按照实施例1～4中所记载的方法合成的(2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸甲酯(1.3g)溶解于甲醇(30mL)、THF(30mL)和水(20mL)中,在冰冷下滴加氢氧化钠水溶液(8.2mL,2mol/L)。将反应溶液在室温下搅拌15小时。用LC/MS跟踪反应的进行,反应结束后,浓缩反应溶液。向残渣中加入冰水,通过滴加盐酸(1mol/L)使pH为5～6之后,用乙酸乙酯萃取3次。混合有机相,用饱和食盐水洗涤,用无水硫酸钠进行干燥。过滤除去固体,在减压下干燥滤液。将残渣用硅胶柱色谱进行纯化,由此得到标题化合物(0.96g)。

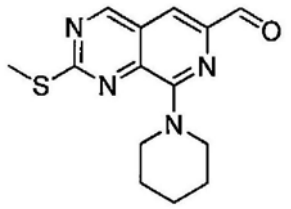
[0865] LC/MS:$(M+H)^+$=291.0、$C_{14}H_{18}N_4OS$=290.12

[0866] ^{1}H-NMR($CDCl_3$):δ9.32(s,1H),7.19(s,1H),5.40(brs,1H),4.50(s,2H),3.89(brs,4H),2.58(s,3H),1.67(brs,6H).

[0867] [实施例7]

[0868] 2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲醛的合成

[0869] [化学式54]

[0870] 

[0871] 使实施例6中合成的(2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)甲醇

(0.20g,0.689mmol)溶解于二氯甲烷(3.0mL),在0℃下搅拌。在氩气氛下,在0℃下向该溶液中添加Death-Martin Peryoginan(1.02g,2.0mmol),将反应溶液在室温下搅拌15小时。用TLC和LC/MS跟踪反应,反应结束后,将反应溶液用水进行稀释。加入碳酸氢钠水溶液(1mol/L)将pH调节为7～8,用二氯甲烷萃取2次。混合所得的有机相,用食盐水洗涤之后,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,得到标题化合物(0.19g)。

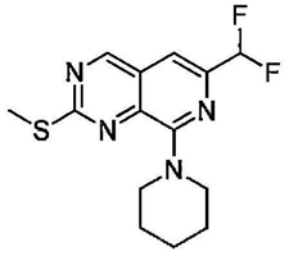
[0872] LC/MS:$(M+H)^+$=289.2、$C_{14}H_{16}N_4OS$=288.10

[0873] ^{1}H-NMR($CDCl_3$):δ9.89(s,1H),9.49(s,1H),7.80(s,1H),4.02(brs,4H),2.62(s,3H),1.71(brs,6H).

[0874] [实施例8]

[0875] 6-(二氟甲基)-2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶(Int-22)的合成

[0876] [化学式55]

[0877] 

[0878] 使实施例7中合成的2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲醛(0.19g,0.66mmol)溶解于二氯甲烷(5.0mL),在0℃下搅拌。在氩气氛下,在0℃下向该溶液中添加DAST(0.85mL,3.92mmol),将反应溶液在室温下搅拌12小时。用TLC和LC/MS跟踪反应,将反应溶液用水进行稀释,用二氯甲烷萃取2次。混合所得的有机相,用饱和食盐水洗涤之后,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,将残渣用硅胶柱色谱进行纯化,由此得到标题化合物(65mg,三个阶段收率32%)。

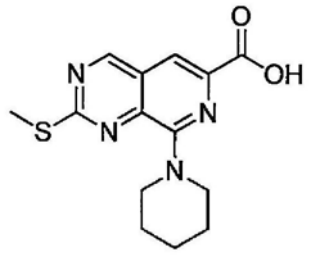
[0879] LC/MS:$(M+H)^+$=311.4、$C_{14}H_{16}F_2N_4S$=310.11

[0880] ^{1}H-NMR($CDCl_3$):δ9.40(s,1H),7.43(s,1H),6.85(t,J=55Hz,1H),3.99(brs,4H),2.60(s,3H),1.70(brs,6H).

[0881] [实施例9]

[0882] 2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基甲酸的合成

[0883] [化学式56]

[0884] 

[0885] 使实施例7中合成的2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲醛(50mg,0.173mmol)溶解于叔丁醇(7.5mL),添加2-甲基-2-丁烯(0.3mL,3.47mmol)。在室温下向该溶液中添加$NaClO_2$(157mg,1.74mmol)与磷酸二氢钠(162mg,1.04mmol)的水溶液(2.5mL)。将反应溶液在室温下搅拌16小时。用TLC跟踪反应,反应结束后,在减压下浓缩反

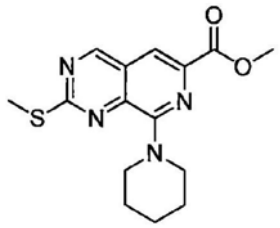
应溶液。使残渣溶解于乙酸乙酯(20mL)，用饱和食盐水洗涤之后，用无水硫酸钠进行干燥。过滤除去固体之后，在减压下浓缩滤液，由此得到标题化合物的粗体(50mg)。

[0886] LC/MS：$(M+H)^+$＝305.2、$C_{14}H_{16}N_4O_2S$＝304.10

[0887] [实施例10]

[0888] 2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基甲酸甲酯(Int-23)的合成

[0889] [化学式57]

[0890] 

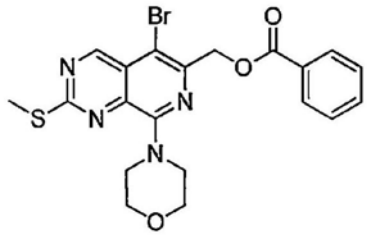
[0891] 使通过实施二次实施例9而合成的2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基甲酸的粗体(100mg)溶解于甲醇(1.5mL)，在0℃下添加亚硫酰氯(0.8mL)。将该反应溶液在室温下搅拌16小时。用TLC跟踪反应，反应结束后，在减压下浓缩反应溶液。向残渣中加入水进行稀释之后，在0℃下加入饱和碳酸氢钠水溶液，将pH调节为8。将水相用乙酸乙酯萃取。将所得的有机相用水洗涤，进一步用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥。过滤除去固体之后，在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化，由此得到标题化合物(50mg，收率48％)。

[0892] LC/MS：$(M+H)^+$＝319.2、$C_{15}H_{18}N_4O_2S$＝318.12

[0893] [实施例11]

[0894] (5-溴-2-(甲硫基)-8-吗啉代吡啶并[3,4-d]嘧啶-6-基)苯甲酸甲酯的合成

[0895] [化学式58]

[0896] 

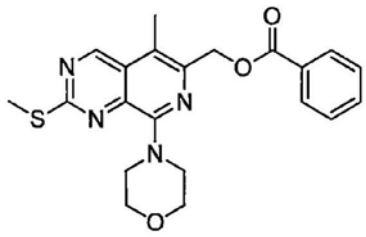
[0897] 使按照实施例1～4中所记载的方法合成的(2-(甲硫基)-8-吗啉代吡啶并[3,4-d]嘧啶-6-基)苯甲酸甲酯(2.0g，5.05mmol)溶解于乙腈(40mL)，在0℃下添加N-溴代琥珀酰亚胺(0.989g，5.56mmol)，在0℃下搅拌1小时。用LC/MS和TLC跟踪反应，反应结束后，将反应溶液用二氯甲烷稀释，用水洗涤之后，用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥，过滤除去固体之后，在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化，由此得到标题化合物(2.0g，收率83％)。

[0898] LC/MS：$(M+H)^+$＝474.8&477.0、$C_{20}H_{19}BrN_4O_3S$＝474.04&476.03

[0899] [实施例11]

[0900] (5-甲基-2-(甲硫基)-8-吗啉代吡啶并[3,4-d]嘧啶-6-基)苯甲酸甲酯(Int-24)的合成

[0901] [化学式59]

[0902] 

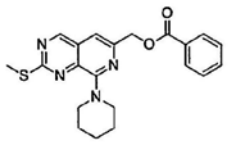
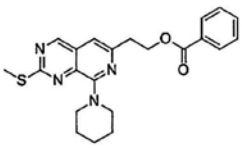
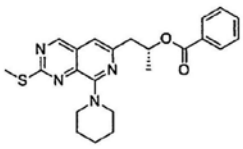
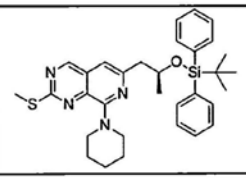
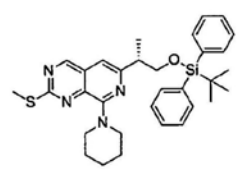
[0903] 使实施例10中合成的(5-溴-2-(甲硫基)-8-吗啉代吡啶并[3,4-d]嘧啶-6-基)苯甲酸甲酯(2.0g,4.21mmol)溶解于1,4-二噁烷(50mL)。在室温下向该溶液中添加碳酸钾(1.16g,8.42mmol)、2,4,6-三甲基硼氧环烷(2.64g,21.05mmol)、四(三苯基膦)钯(0.438g,0.379mmol),在110℃下搅拌16小时。用LC/MS和TLC跟踪反应,反应结束后,将反应溶液在室温下冷却,在减压下进行浓缩。将残渣用乙酸乙酯稀释,用水洗涤之后,用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥,过滤除去固体之后,在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化,由此得到标题化合物(1.0g,收率58%)。

[0904] LC/MS:$(M+H)^+$=411.2、$C_{21}H_{22}N_4O_3S$=410.14

[0905] 以下所记载的化合物Int-25～Int-43按照实施例4～11中所记载的方法来合成。

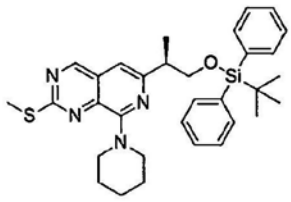
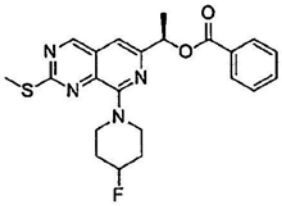
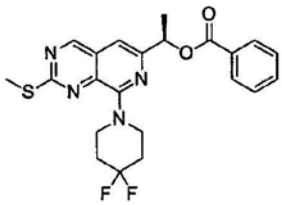
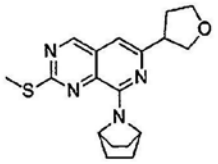
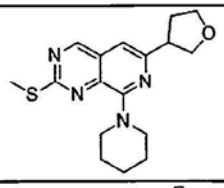
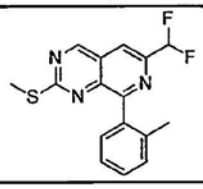
[0906] [表5]

[0907]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-25		1H-NMR (DMSO-d6) δ: 9.33 (1H, s), 8.09 (2H, d, J = 7.3 Hz), 7.71 (1H, t, J = 7.4 Hz), 7.58 (2H, t, J = 7.7 Hz), 7.22 (1H, s), 5.37 (2H, s), 4.00-3.85 (4H, m), 2.67 (3H, s), 1.75-1.50 (6H, m).	395.2	394.15
Int-26		1H-NMR (CDCl3) δ: 8.97 (1H, s), 8.00-7.94 (2H, m), 7.57-7.48 (1H, m), 7.44-7.35 (2H, m), 6.85 (1H, s), 4.75 (2H, t, J = 6.4 Hz), 4.00-3.91 (4H, m), 3.19 (2H, t, J = 6.8 Hz), 2.63 (3H, s), 1.79-1.70 (6H, m).	409.2	408.16
Int-27		1H-NMR (CDCl3) δ: 8.94 (1H, s), 8.00-7.93 (2H, m), 7.57-7.48 (1H, m), 7.44-7.34 (2H, m), 6.83 (1H, s), 5.70-5.58 (1H, m), 4.00-3.85 (4H, m), 3.24-3.14 (1H, m), 3.09-2.99 (1H, m), 2.62 (3H, s), 1.79-1.68 (6H, m), 1.43 (3H, d, J = 6.4 Hz).	423.2	422.18
Int-28			557.3	556.27
Int-29		1H-NMR (CDCl3) δ: 8.95 (1H, s), 7.58-7.49 (4H, m), 7.42-7.27 (6H, m), 6.79 (1H, s), 4.00-3.75 (6H, m), 3.13-3.04 (1H, m), 2.63 (3H, s), 1.79-1.69 (6H, m), 1.32 (3H, d, J = 6.8 Hz), 0.96 (9H, s).	557.30	556.27

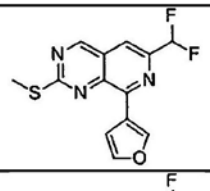
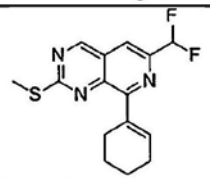
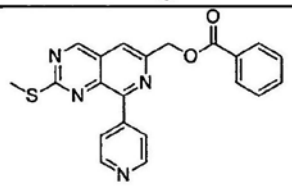
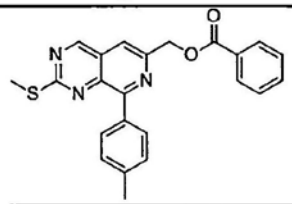
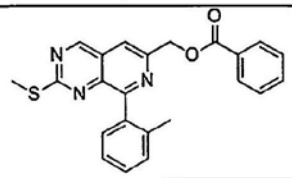
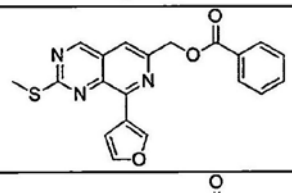
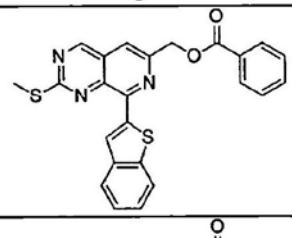
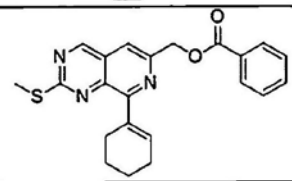
[0908] [表6]

[0909]

化合物编号	结构	NMR	(M+H)+	精确质量
Int-30		1H-NMR (CDCl3) δ: 8.95 (1H, s), 7.58-7.49 (4H, m), 7.42-7.27 (6H, m), 6.79 (1H, s), 4.00-3.75 (6H, m), 3.13-3.04 (1H, m), 2.63 (3H, s), 1.79-1.69 (6H, m), 1.32 (3H, d, J = 6.8 Hz), 0.96 (9H, s).	557.30	556.27
Int-31		1H-NMR (CDCl3) δ: 9.03 (1H, s), 8.18-8.13 (2H, m), 7.64-7.56 (1H, m), 7.53-7.44 (2H, m), 7.05 (1H, d, J = 0.8 Hz), 6.18-6.09 (1H, m), 5.00-4.83 (1H, m), 4.25-4.06 (4H, m), 2.62 (3H, s), 2.23-1.95 (4H, m), 1.73 (3H, d, J = 6.8Hz).	427.2	426.15
Int-32		1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.18-8.11 (2H, m), 7.65-7.56 (1H, m), 7.53-7.44 (2H, m), 7.10 (1H, s), 6.19-6.09 (1H, m), 4.25-4.15 (4H, m), 2.61 (3H, s), 2.23-2.06 (4H, m), 1.73 (3H, d, J = 6.4Hz).	445.2	444.14
Int-33		1H-NMR (CDCl3) δ: 8.97 (1H, s), 6.83 (1H, s), 5.34 (2H, brs), 4.25-3.85 (4H, m), 3.58-3.44 (1H, m), 2.67 (3H, s), 2.25-2.21 (2H, m), 1.95-1.82 (4H, m), 1.60-1.48 (4H, m).	343.2	342.15
Int-34		1H-NMR (CDCl3) δ: 8.97 (1H, s), 6.81 (1H, s), 4.25-3.85 (8H, m), 3.58-3.44 (1H, m), 2.62 (3H, s), 2.35-2.21 (2H, m), 1.85-1.70 (6H, m).	331.2	330.15
Int-35			318.0	317.08

[0910] [表7]

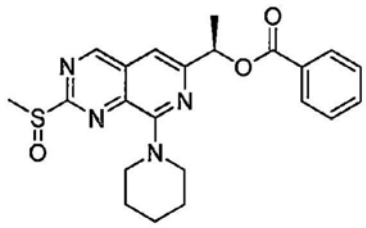
[0911]

化合物编号	结构	NMR	$(M+H)^+$	精确质量
Int-36			294.2	293.04
Int-37			308.2	307.10
Int-38			389.2	388.10
Int-39			402.0	401.12
Int-40			402.0	401.12
Int-41			378.0	377.08
Int-42			444.0	443.08
Int-43			392.0	391.14

[0912] [实施例12]

[0913] (R)-1-(2-(甲基亚磺酰基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-44)的合成

[0914] [化学式60]

[0915] 

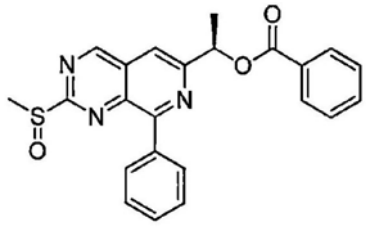
[0916] 使实施例4中合成的(R)-1-(2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-20,808mg,1.98mmol)溶解于二氯甲烷(20mL),冷却至0℃。在0℃下向该反应溶液中添加间氯过苯甲酸(488mg,1.98mmol),在室温下搅拌1小时。用LC/MS跟踪反应的进行,反应结束后,加入饱和碳酸氢钠水溶液(30mL)进行稀释,用二氯甲烷(30mL)萃取3次。混合所得的有机相,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,得到标题化合物的粗体。所得的粗体无需纯化即可用于下一步的反应。

[0917] LC/MS:$(M+H)^+$=441.2、$C_{22}H_{24}N_4O_4S$=440.52

[0918] [实施例13]

[0919] (1R)-1-(2-(甲基亚磺酰基)-8-苯基吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-45)的合成

[0920] [化学式61]

[0921] 

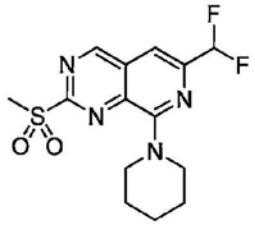
[0922] 使实施例5中合成的(R)-1-(2-(甲硫基)-8-苯基吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-21)的粗体溶解于二氯甲烷(7.1mL),冷却至0℃。向该溶液中添加间氯过苯甲酸(184mg,0.745mmol),在0℃下搅拌20分钟。用LC/MS跟踪反应的进行,反应结束后,将反应溶液进行硅藻土过滤。用大量过度的乙酸乙酯洗涤硅藻土,将所得的滤液用饱和碳酸氢钠水溶液洗涤之后,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,将残渣用硅胶柱色谱进行纯化,由此得到标题化合物的粗体(172mg,两个阶段收率58%)。

[0923] LC/MS:$(M+H)^+$=418.2、$C_{23}H_{19}N_3O_3S$=417.11

[0924] [实施例14]

[0925] 6-(二氟甲基)-2-(甲基磺酰基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶(Int-46)的合成

[0926] [化学式62]

[0927] 

[0928] 使实施例8中合成的6-(二氟甲基)-2-(甲硫基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧

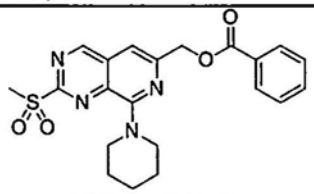
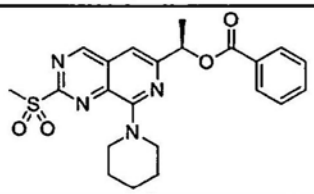
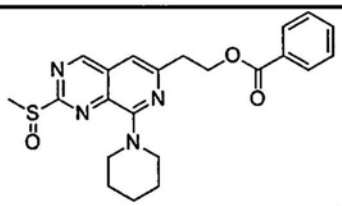
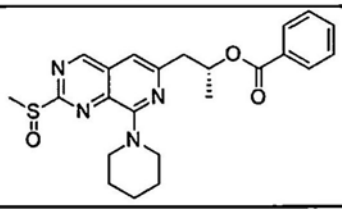
啶(Int-22,195mg,0.63mmol)溶解于THF(10mL)和水(3mL)中,在0℃下添加Oxone(R)(967mg,1.572mmol),在室温下搅拌5小时。用TLC跟踪反应的进行,反应结束后,将反应溶液用水进行稀释,将水相用乙酸乙酯萃取2次。混合所得的有机相,用饱和食盐水洗涤之后,用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,得到标题化合物的粗体(120mg)。该粗体无需进一步纯化即可用于下一步的反应。

[0929] LC/MS:$(M+H)^+$=343.2、$C_{14}H_{16}F_2N_4O_2S$=342.10

[0930] 以下所记载的化合物Int-45～Int-71按照实施例12～14中所记载的方法来合成。

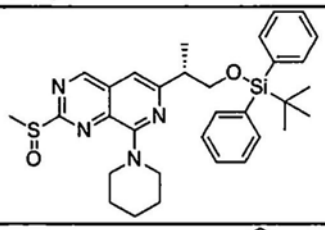
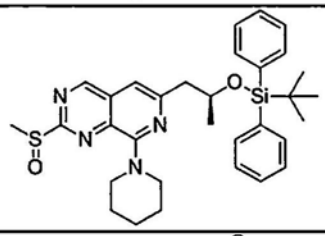
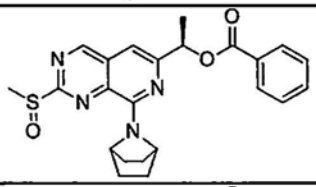
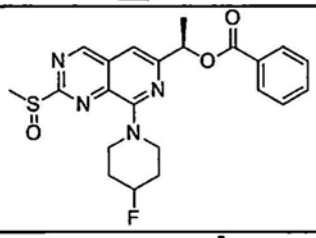
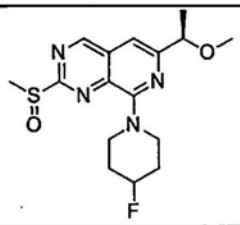
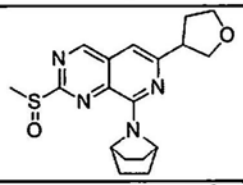
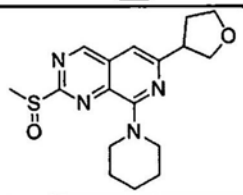
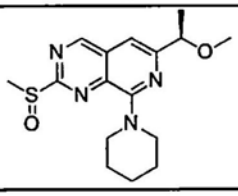
[0931] [表8]

[0932]

化合物编号	结构	$(M+H)^+$	精确质量
Int-47		427.1	426.14
Int-48		441.2	440.52
Int-49		425.2	424.16
Int-50		439.2	438.17

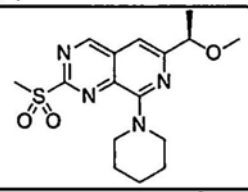
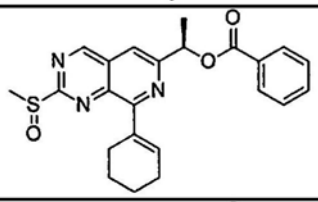
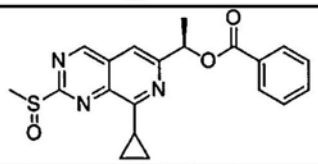
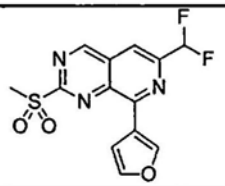
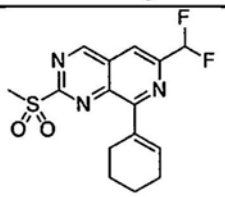
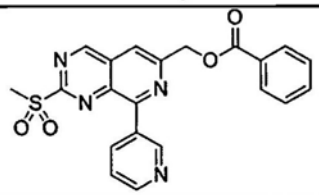
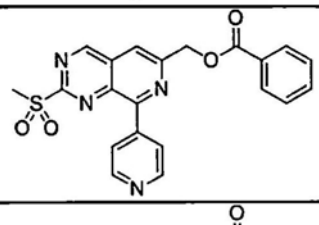
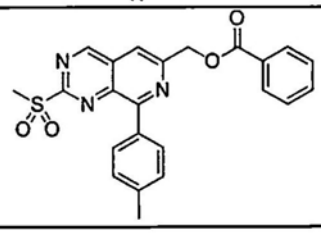
[0933] [表9]

[0934]

化合物编号	结构	$(M+H)^+$	精确质量
Int-51		573.3	572.26
Int-52		573.3	572.26
Int-53		437.2	436.16
Int-54		443.2	442.15
Int-55		353.2	352.14
Int-56		359.2	358.15
Int-57		347.2	346.15
Int-58		335.2	334.15

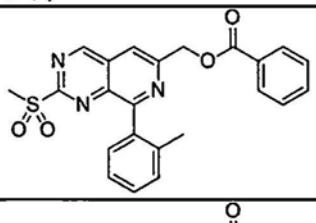
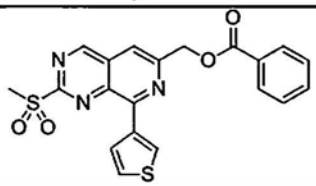
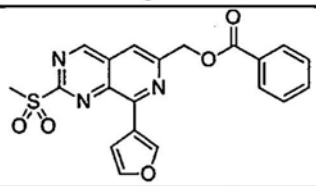
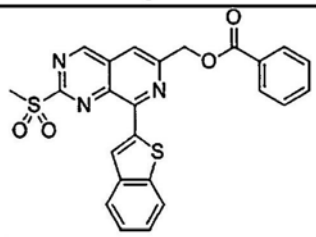
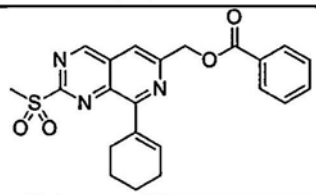
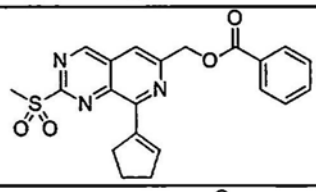
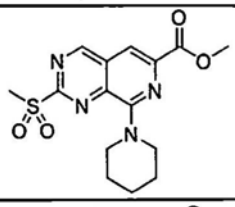
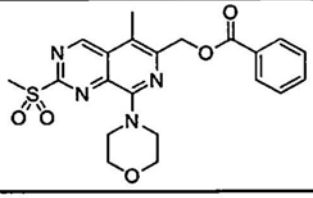
[0935] [表10]

[0936]

化合物编号	结构	(M+H)+	精确质量
Int-59		351.9	350.14
Int-60		422.2	421.15
Int-61		382.1	381.11
Int-62		326.2	325.03
Int-63		340.2	339.09
Int-64		421.0	420.09
Int-65		421.2	420.09
Int-66		433.8	433.11

[0937] [表11]

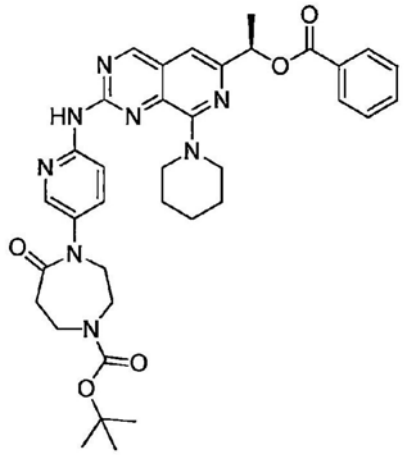
[0938]

化合物编号	结构	(M+H)+	精确质量
Int-67		433.8	433.11
Int-68		425.8	425.05
Int-69		410.2	409.07
Int-70		476.0	475.07
Int-71		424.0	423.13
Int-72		410.0	409.11
Int-73		351.0	350.10
Int-74		443.0	442.13

[0939] [实施例15]

[0940] (R)-4-(6-((6-(1-(苯甲酰氧基)乙基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)-5-氧代-1,4-二氮杂环庚烷-1-甲酸叔丁酯的合成

[0941] [化学式63]

[0942] 

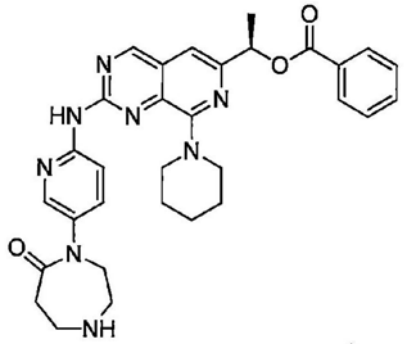
[0943] 向实施例14所记载的方法中合成的(R)-1-(2-(甲基磺酰基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-48,110.9mg,0.252mmol)和按照参考例10～11的方法合成的4-(6-氨基吡啶-3-基)-5-氧代-1,4-二氮杂环庚烷-1-甲酸叔丁酯(C-3,154.3mg,0.504mmol)中添加甲苯(0.63mL),在120℃下搅拌4天。用LC/MS跟踪反应的进行,冷却至室温。将该反应混合物用硅胶柱色谱进行纯化,由此得到标题化合物(19.3mg,收率11.5%)。

[0944] LC/MS:$(M+H)^+$=667.4、$C_{36}H_{42}N_8O_5$=666.77

[0945] [实施例16]

[0946] (R)-1-(2-((5-(7-氧代-1,4-二氮杂环庚烷-1-基)吡啶-2-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯的合成

[0947] [化学式64]

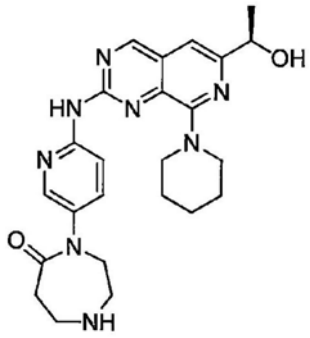
[0948] 

[0949] 使实施例15中所得的(R)-4-(6-((6-(1-(苯甲酰氧基)乙基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)-5-氧代-1,4-二氮杂环庚烷-1-甲酸叔丁酯(19.3mg)溶解于二氯甲烷(1.0mL)和TFA(1.0mL)中,在室温搅拌2小时。用LC/MS跟踪反应的进行,反应结束后,在减压下浓缩反应溶液。所得的粗体无需纯化即可用于下一步的反应。

[0950] [实施例17]

[0951] (R)-4-(6-((6-(1-(羟乙基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)-1,4-二氮杂环庚烷-5-酮(化合物89)的合成

[0952] [化学式65]

[0953] 

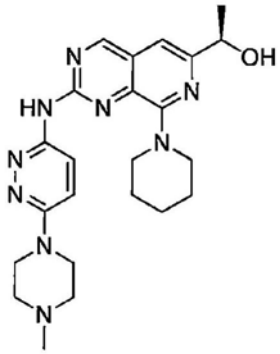
[0954] 使实施例16中所得的(R)-1-(2-((5-(7-氧代-1,4-二氮杂环庚烷-1-基)吡啶-2-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯的粗体溶解于甲醇(1.0mL)和THF(1.0mL)中。向该溶液中添加碳酸钾(12.3mg,0.089mmol),在室温下搅拌。用LC/MS跟踪反应的进行,反应结束后,过滤反应溶液,在减压下浓缩滤液。将所得的粗体用制备型HPLC(乙腈/水/TFA系)进行纯化。使包含目标物质的馏分通过强酸性阳离子交换树脂(SCX)的柱,由此使目标物质在树脂上吸附。该SCX柱用二氯甲烷洗涤。进一步使氨(2mol/L,甲醇溶液)在SCX柱中流动,由此使目标物质洗脱。在减压下浓缩所得的洗脱液,由此得到标题化合物(13.6mg)。

[0955] LC/MS:$(M+H)^+$=463.3、$C_{24}H_{30}N_8O_2$=462.55

[0956] [实施例18]

[0957] (R)-1-(2-((6-(4-甲基哌嗪-1-基)哒嗪-3-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)乙醇(化合物123)的合成

[0958] [化学式66]

[0959] 

[0960] 向按照实施例14所记载的方法合成的(R)-1-(2-(甲基磺酰基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(Int-48,44mg,0.10mmol)和按照参考例15～17的方法合成的6-(4-甲基哌嗪-1-基)哒嗪-3-胺(E-2,38.7mg,0.20mmol)中添加甲苯(0.25mL),在120℃下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,冷却至室温。将该反应混合物用硅胶柱色谱进行纯化,由此得到粗体。所得的粗体无需纯化即可用于下一步的反应。

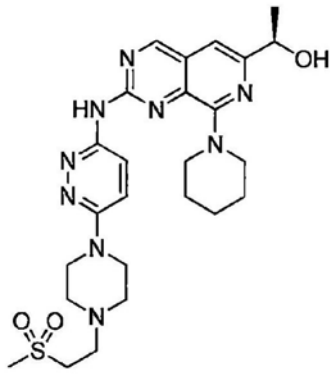
[0961] 使所得的粗体溶解于甲醇(1.0mL)和THF(1.0mL)中。向该溶液中滴加氢氧化锂水溶液(0.075mL,3.0mmol,4mol/L),在室温下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,在减压下浓缩反应溶液。将所得的粗体用制备型HPLC(乙腈/水/TFA系)进行纯化。将包含目标物质的馏分在强酸性阳离子交换树脂(SCX)的柱上通过,使目标物质在树脂上吸附。将该SCX柱用甲醇洗涤。进一步使氨(2mol/L,甲醇溶液)在SCX柱上流动,由此使目标物质洗脱。在减压下浓缩所得的洗脱液,由此得到标题化合物(20.7mg)。

[0962] LC/MS：$(M+H)^+$＝450.3、$C_{23}H_{31}N_9O$＝449.55

[0963] [实施例19]

[0964] (R)-1-(2-((6-(4-(2-(甲基磺酰基)乙基)哌嗪-1-基)哒嗪-3-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)乙醇(化合物114)的合成

[0965] [化学式67]

[0966] 

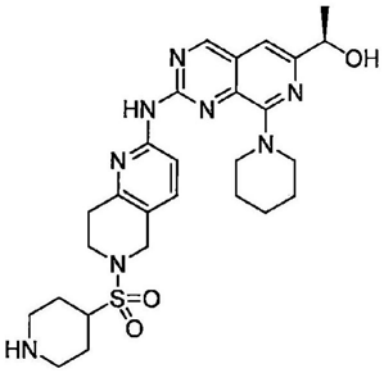
[0967] 使实施例15～17所记载的方法中合成的(R)-1-(2-((6-(哌嗪-1-基)哒嗪-3-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-基)乙醇(13.6mg,0.0312mmol)溶解于氯仿(0.31mL),添加2-(甲基磺酰基)4-甲基苯磺酸乙酯(9.6mg,0.0344mmol)和N-乙基二异丙胺(6.1μL,0.0344mmol)之后,将反应溶液在80℃下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,将反应溶液恢复至室温,在减压下浓缩反应溶液。将所得的残渣用制备型HPLC进行纯化,将包含目标物质的馏分在强酸性阳离子交换树脂(SCX)的柱上通过,由此使目标物质在树脂上吸附。将该SCX柱用甲醇洗涤之后,用氨(2mol/L,甲醇溶液)洗脱目标物质。在减压下浓缩所得的洗脱液,由此得到标题化合物(8.6mg,收率51％)。

[0968] LC/MS：$(M+H)^+$＝542.3、$C_{25}H_{35}N_9O_3S$＝541.26 ^{1}H-NMR($CDCl_3$)δ：9.08(1H,s),8.60(1H,d,J＝9.6Hz),8.42(1H,brs),7.06(1H,d,J＝9.6Hz),6.93(1H,s),4.83(1H,m),3.98(1H,m),3.82(4H,m),3.61(4H,m),3.20(2H,t,J＝6.4Hz),3.05(3H,s),2.95(2H,t,J＝6.4Hz),2.68(4H,m),1.85-1.52(6H,m),1.51(3H,d,J＝6.4Hz).

[0969] [实施例20]

[0970] (R)-1-(8-(哌啶-1-基)-2-((6-(哌啶-4-基磺酰基)-5,6,7,8-四氢-1,6-萘啶-2-基)氨基)吡啶并[3,4-d]嘧啶-6-基)乙醇(化合物163)的合成

[0971] [化学式68]

[0972] 

[0973] 使按照实施例15、和16所记载的方法合成的(R)-1-(8-(哌啶-1-基)-2-((5,6,7,8-四氢-1,6-萘啶-2-基)氨基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(51mg,0.10mmol)溶

解于二氯甲烷(1mL)和三乙胺(21μL,0.012mmol)中,在0℃下添加4-(氯磺酰基)哌啶-1-甲酸叔丁酯(34.1mg,0.12mmol)之后,在室温下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,添加饱和碳酸氢钠水溶液(10m)使反应停止,用二氯甲烷(10mL)萃取3次。混合所得的有机相,用无水硫酸钠进行干燥。过滤除去固体,浓缩滤液。将所得的残渣用胺修饰硅胶柱色谱进行粗纯化。所得的粗体无需进一步纯化即可用于下一步的反应。

[0974] 使所得的粗体溶解于二氯甲烷(3mL)和TFA(1mL)中,在室温下搅拌2小时。用LC/MS跟踪反应的进行,反应结束后,添加饱和碳酸氢钠水溶液(10m)使反应停止,用二氯甲烷(10mL)萃取3次。混合所得的有机相,用无水硫酸钠进行干燥。过滤除去固体,浓缩滤液。将所得的残渣用胺修饰硅胶柱色谱进行粗纯化。所得的粗体无需进一步纯化即可用于下一步的反应。

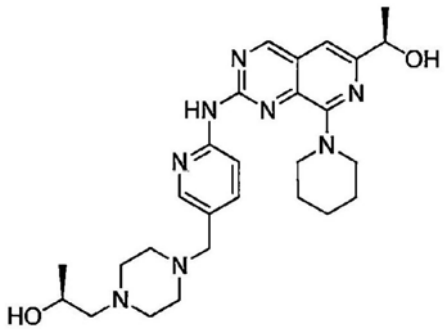
[0975] 使所得的粗体溶解于甲醇(2.0mL)和THF(2.0mL)中,添加碳酸钾(138mg,1.0mmol),在室温下搅拌5小时。用LC/MS跟踪反应的进行,反应结束后,添加水(10m)之后,用二氯甲烷(10mL)萃取3次。混合所得的有机相,用无水硫酸钠进行干燥。过滤除去固体,在减压下浓缩滤液。将所得的残渣用制备型HPLC进行纯化。将包含目标物质的馏分在强酸性阳离子交换树脂(SCX)的柱上通过,由此使目标物质在树脂上吸附。将该SCX柱用甲醇洗涤之后,用氨(2mol/L,甲醇溶液)洗脱目标物质。在减压下浓缩所得的洗脱液,由此得到标题化合物(38.4mg,收率70%)。

[0976] LC/MS:$(M+H)^+$=553.3、$C_{27}H_{36}N_8O_3S$=552.26^{1}H-NMR(DMSO-d6)δ:10.12(1H,s),9.31(1H,s),8.27(1H,d,J=8.2Hz),7.63(1H,d,J=8.7Hz),),7.25(1H,s),5.27(1H,d,J=4.1Hz),4.70-4.60(1H,m),4.46(2H,s),3.84-3.68(4H,m),3.64(2H,t,J=5.9Hz),2.99(2H,d,J=11.9Hz),2.87(2H,t,J=5.5Hz),2.50-2.39(2H,m),1.91-1.81(2H,m),1.77-1.60(6H,m),1.56-1.42(2H,m),1.38(3H,d,J=6.9Hz).

[0977] [实施例21]

[0978] (S)-1-(4-((6-((6-((R)-1-羟乙基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)甲基)哌嗪-1-基)丙烷-2-醇(化合物183)的合成

[0979] [化学式69]

[0980] 

[0981] 使按照实施例15和16所记载的方法合成的(R)-1-(2-((5-(哌嗪-1-基甲基)吡啶-2-基)氨基)-8-(哌嗪-1-基)吡啶并[3,4-d]嘧啶-6-基)苯甲酸乙酯(72mg,0.13mmol)溶解于甲醇(1mL),添加(S)-环氧丙烷(7.6mg,0.13mmol)之后,将反应溶液在55℃下搅拌过夜。用LC/MS跟踪反应的进行,反应结束后,在减压下浓缩溶液。将所得的粗体用硅胶柱色谱进行粗纯化。所得的粗体无需进一步纯化即可用于下一步的反应。

[0982] 使所得的粗体溶解于甲醇(1.0mL)和THF(1.0mL)中,添加氢氧化锂水溶液(0.2mL,

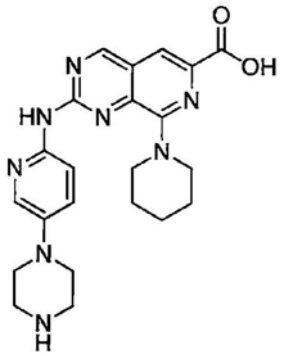
0.80mmol,4mol/L),在室温下搅拌。用LC/MS跟踪反应的进行,反应结束后,过滤除去固体,在减压下浓缩滤液。将所得的残渣用制备型HPLC进行纯化,将包含目标物质的馏分在强酸性阳离子交换树脂(SCX)的柱通过,由此使目标物质在树脂上吸附。将该SCX柱用甲醇洗涤之后,用氨(2mol/L,甲醇溶液)洗脱目标物质。在减压下浓缩所得的洗脱液,由此得到标题化合物(30.6mg,收率62%)。

[0983] LC/MS:$(M+H)^+$=507.4、$C_{27}H_{38}N_8O_2$=506.31

[0984] [实施例22]

[0985] 2-((5-(哌嗪-1-基)吡啶-2-基)氨基-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲酸(化合物23)的合成

[0986] [化学式70]

[0987] 

[0988] 使按照实施例15所记载的方法合成的2-((5-(4-(叔丁氧基羰基)哌嗪-1-基)吡啶-2-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲酸甲酯(100mg,0.182mmol)溶解于甲醇(5mL)、THF(4mL)、和水(1mL)中,在0℃下添加氢氧化锂一水合物(23mg,0.546mmol)。将反应溶液在室温下搅拌16小时。用LC/MS跟踪反应的进行,反应结束后,在减压下浓缩反应溶液。使残渣溶解于二氯甲烷,用水洗涤,进一步用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥。过滤除去固体之后,在减压下浓缩滤液,由此得到粗体(100mg)。所得的粗体无需纯化即可用于下一步的反应。

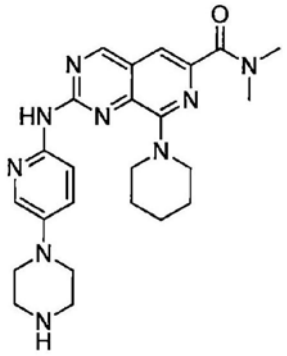
[0989] 使所得粗体中的一部分(15mg,0.028mmol)溶解于二氯甲烷(3mL),在0℃下添加HCl/1,4-二噁烷溶液(0.5mL,4mol/L)。将反应溶液在0℃下搅拌1小时。用LC/MS跟踪反应的进行,反应结束后,在减压下浓缩反应溶液,由此得到标题化合物的HCl盐(10mg)。

[0990] LC/MS:$(M+H)^+$=435.3、$C_{22}H_{26}N_8O_2$=434.22

[0991] [实施例23]

[0992] N,N-二甲基-2-((5-(哌嗪-1-基)吡啶-2-基)氨基-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲酰胺(化合物27)的合成

[0993] [化学式71]

[0994] 

[0995] 按照实施例22所记载的方法，使2-((5-(4-(叔丁氧基羰基)哌嗪-1-基)吡啶-2-基)氨基)-8-(哌啶-1-基)吡啶并[3,4-d]嘧啶-6-甲酸甲酯(100mg，0.182mmol)与氢氧化锂一水合物(23mg，0.546mmol)反应，使由此所得的粗体的一部分(50mg，0.0936mmol)溶解于THF(2mL)中。在0℃下向该溶液中添加二异丙基乙胺(0.05mL，0.280mmol)和HATU(53mg，0.140mmol)。将该反应溶液在0℃下搅拌15分钟之后，加入二甲胺/THF溶液(0.25mL，2mol/L)。将反应溶液在室温下搅拌16小时。用LC/MS跟踪反应的进行。在减压下浓缩反应溶液，使残渣溶解于乙酸乙酯中。将有机相用水洗涤、进一步用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥，过滤除去固体之后，在减压下浓缩滤液，由此得到粗体(50mg)。所得的粗体无需纯化即可用于下一步的反应。

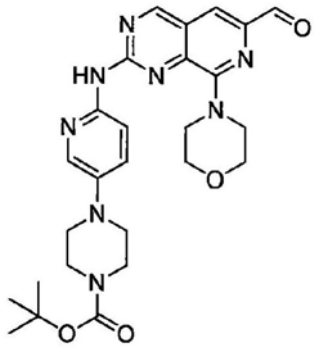
[0996] 使所得的粗体溶解于二氯甲烷(3mL)，在0℃下添加HCl/1,4-二噁烷溶液(0.5mL，4mol/L)。将反应溶液在0℃下搅拌1小时。用LC/MS跟踪反应的进行，反应结束后，在减压下浓缩反应溶液。将残渣用制备型HPLC进行纯化，由此得到标题化合物(2.0mg)。

[0997] LC/MS：$(M+H)^+$＝462.41、$C_{24}H_{31}N_9O$＝461.27

[0998] [实施例24]

[0999] 4-(6-((6-甲酰基-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)哌嗪-1-甲酸叔丁酯的合成

[1000] [化学式72]

[1001] 

[1002] 使按照实施例15所记载的方法合成的4-(6-((6-((苯甲酰氧基)甲基)-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)哌嗪-1-甲酸叔丁酯(300mg，0.256mmol)溶解于THF(2mL)，加入甲醇镁(25mL，7～8％甲醇溶液)，在室温下搅拌16小时。用TLC跟踪反应的进行，反应结束后，浓缩反应溶液。将残渣用水(20mL)稀释，用甲醇/二氯甲烷混合溶剂(1：9，75mL)萃取3次。将有机相用无水硫酸钠进行干燥，过滤除去固体之后，在减压下浓缩滤液，由此得到粗体(270mg)。所得的粗体无需纯化即可用于下一步的反应。

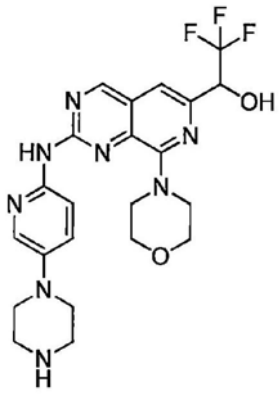
[1003] 使所得的粗体(270mg)溶解于乙酸乙酯(30mL)，在室温下加入2-碘代苯甲酸(162mg，0.576mmol)。将该反应溶液在60℃下搅拌16小时。用TLC跟踪反应的进行，反应结束后，过滤反应溶液。将滤液用水洗涤、进一步用饱和食盐水洗涤。将有机相用无水硫酸钠进行干燥，过滤除去固体之后，在减压下浓缩滤液。将残渣用硅胶柱色谱进行纯化，由此得到标题化合物的粗体(130mg，收率48％)。

[1004] LC/MS：$(M+H)^+$＝521.0、$C_{26}H_{32}N_8O_4$＝520.25

[1005] [实施例25]

[1006] 2,2,2-三氟-1-(8-吗啉代-2-((5-(哌嗪-1-基)吡啶-2-基)氨基)吡啶并[3,4-d]嘧啶-6-基)乙醇(化合物35)的合成

[1007] [化学式73]

[1008] 

[1009] 使实施例24中合成的4-(6-((6-甲酰基-8-吗啉代吡啶并[3,4-d]嘧啶-2-基)氨基)吡啶-3-基)哌嗪-1-甲酸叔丁酯的粗体(25mg，0.048mmol)溶解于THF(0.5mL)，在0℃下冷却。在0℃下向该溶液中加入(三氟甲基)三甲基硅烷(23μL，0.143mmol)，然后在0℃下加入催化量的四丁基氟化铵(1滴)之后，在0℃下搅拌2小时。用LC/MS跟踪反应的进行，在减压下浓缩反应溶液。残渣无需纯化即可用于下一步的反应。

[1010] 使残渣溶解于二氯甲烷(1mL)，在0℃下添加HCl/1,4-二噁烷溶液(0.2mL，4mol/L)。将反应溶液在0℃下搅拌30分钟。用LC/MS跟踪反应的进行，反应结束后，在减压下浓缩反应溶液。将残渣用制备型HPLC进行纯化，将所得的馏分用饱和碳酸氢钠水溶液调制成碱性之后，用乙酸乙酯(75mL)萃取2次。混合所得的有机相，在减压下浓缩，由此得到标题化合物(6.0mg，收率25％。

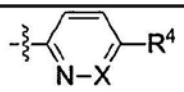
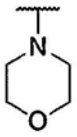
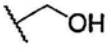
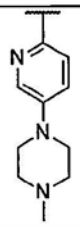
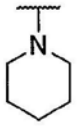
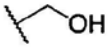
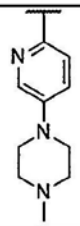
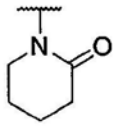
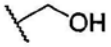
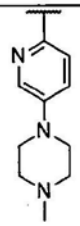
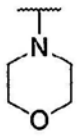
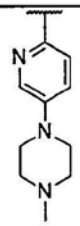
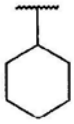
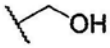
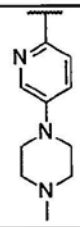
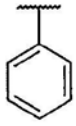
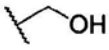
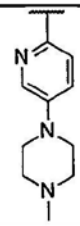
[1011] LC/MS：$(M+H)^+$＝491.39、$C_{22}H_{25}N_8O_2$＝490.21

[1012] [实施例26]

[1013] 以下的化合物1～337通过按照实施例15～25所述的合成法，根据需要适当地进行脱保护来合成。

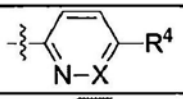
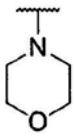
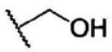
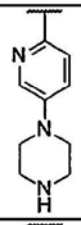
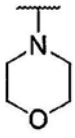
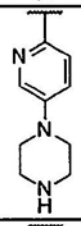
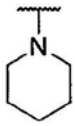
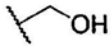
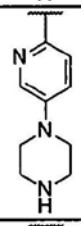
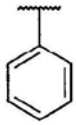
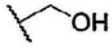
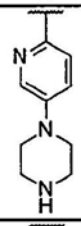
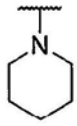
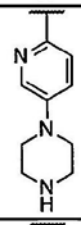
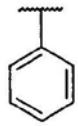
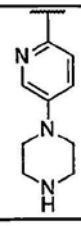
[1014] [表12]

[1015]

实施例编号	R1	R2	R3	
1				
2				
3				
4				
5				
6				

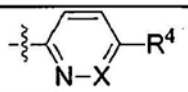
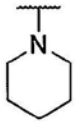
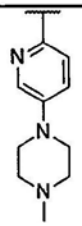
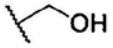
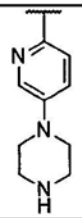
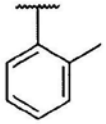
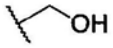
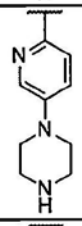
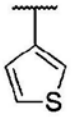
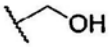
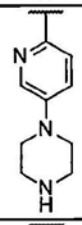
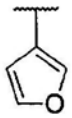
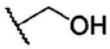
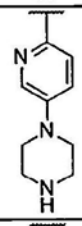
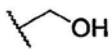
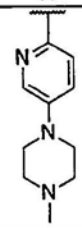
[1016] [表13]

[1017]

实施例编号	R1	R2	R3	
7				
8				
9				
10				
11				
12				

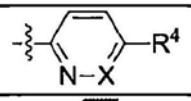
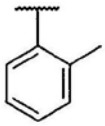
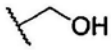
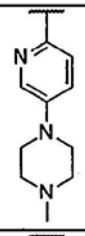
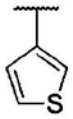
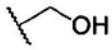
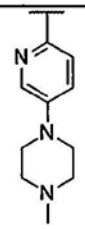
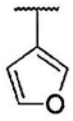
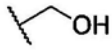
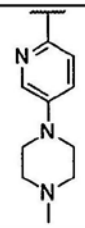
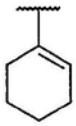
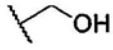
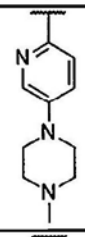
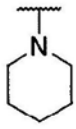
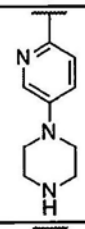
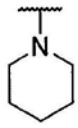
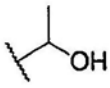
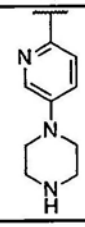
[1018] [表14]

[1019]

实施例编号	R1	R2	R3	
13				
14				
15				
16				
17				
18				

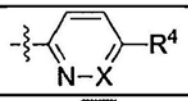
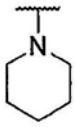
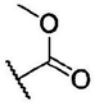
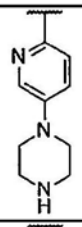
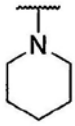
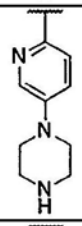
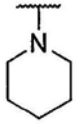
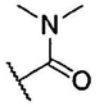
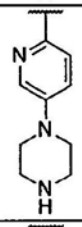
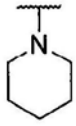
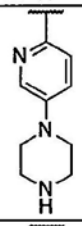
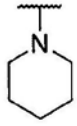
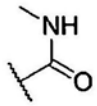
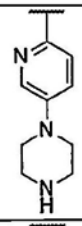
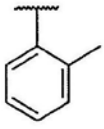
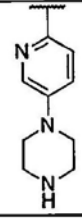
[1020] [表15]

[1021]

实施例编号	R1	R2	R3	
19				
20				
21				
22				
23				
24				

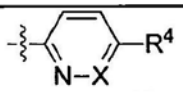
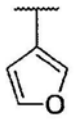
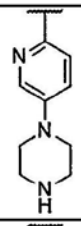
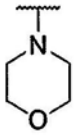
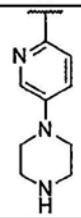
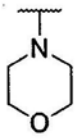
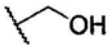
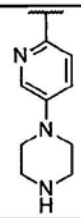
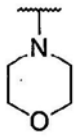
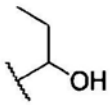
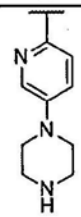
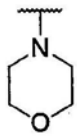
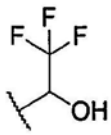
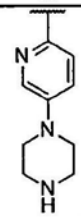
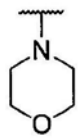
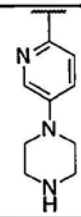
[1022] [表16]

[1023]

实施例编号	R1	R2	R3	
25				
26				
27				
28				
29				
30				

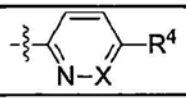
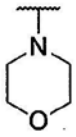
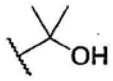
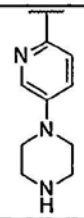
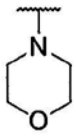
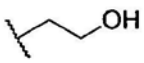
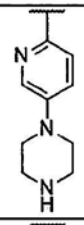
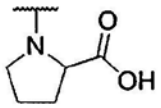
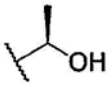
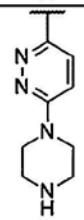
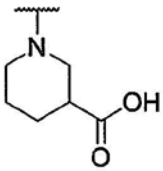
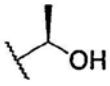
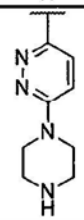
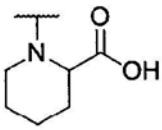
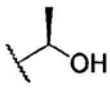
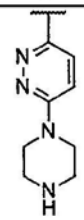
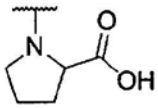
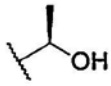
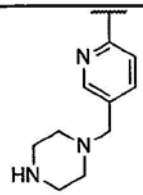
[1024] [表17]

[1025]

实施例编号	R1	R2	R3	
31				
32				
33				
34				
35				
36				

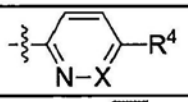
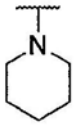
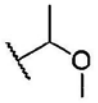
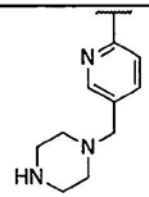
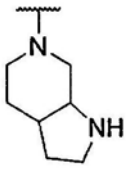
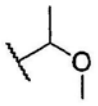
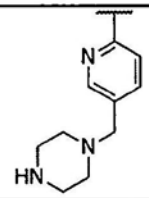
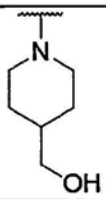
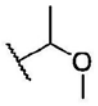
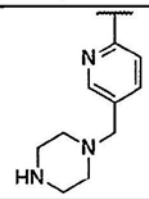
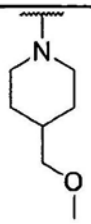
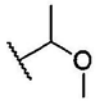
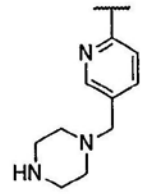
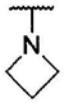
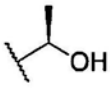
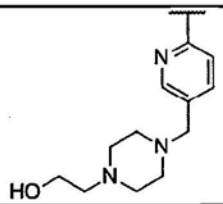
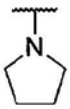
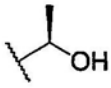
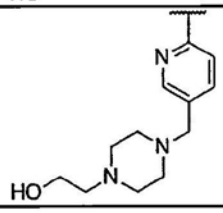
[1026] [表18]

[1027]

实施例编号	R1	R2	R3	
37				
38				
39				
40				
41				
42				

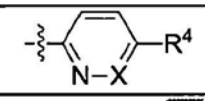
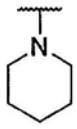
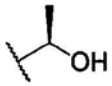
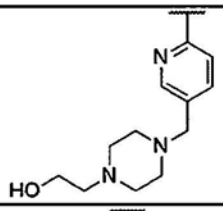
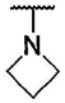
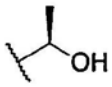
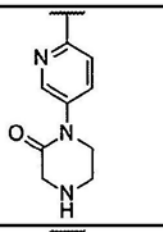
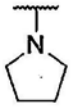
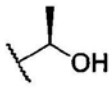
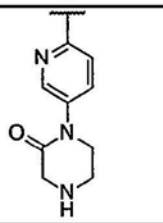
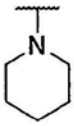
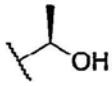
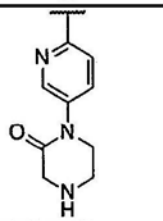
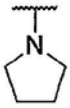
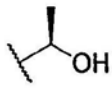
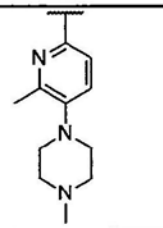
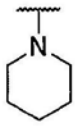
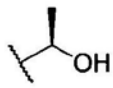
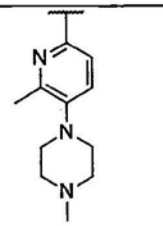
[1028] [表19]

[1029]

实施例编号	R1	R2	R3	
43				
44				
45				
46				
47				
48				

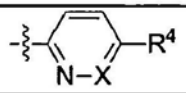
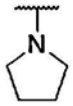
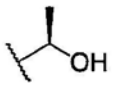
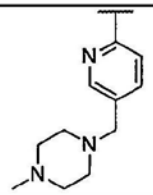
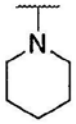
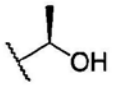
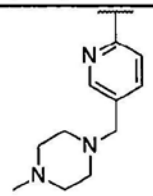
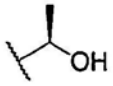
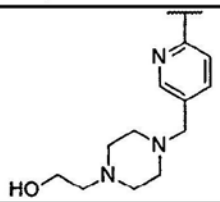
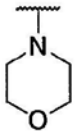
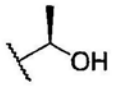
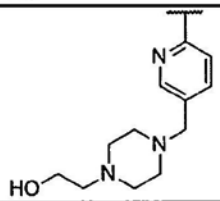
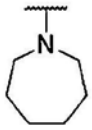
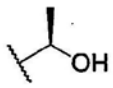
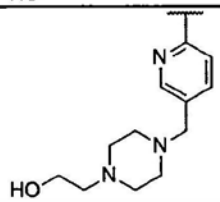
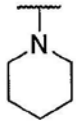
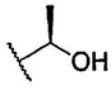
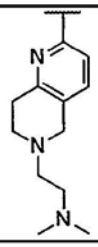
[1030] [表20]

[1031]

实施例编号	R1	R2	R3	
49				
50				
51				
52				
53				
54				

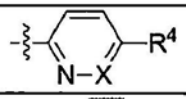
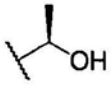
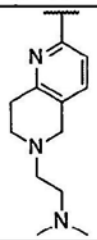
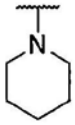
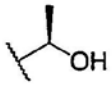
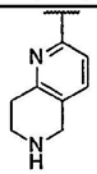
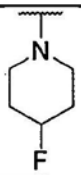
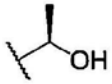
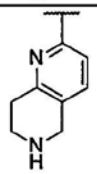
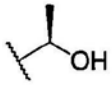
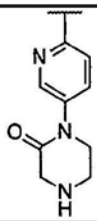
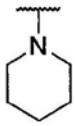
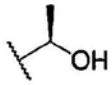
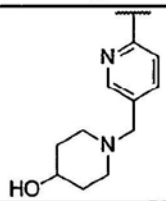
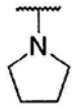
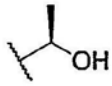
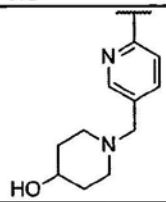
[1032] [表21]

[1033]

实施例编号	R1	R2	R3	
55				
56				
57				
58				
59				
60				

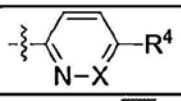
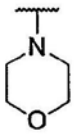
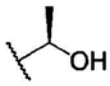
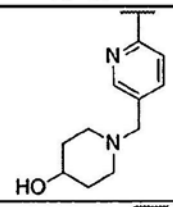
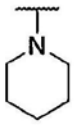
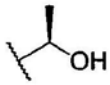
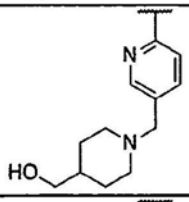
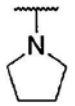
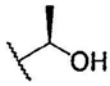
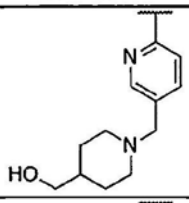
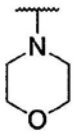
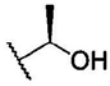
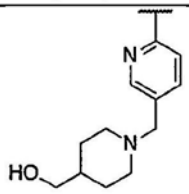
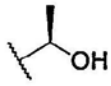
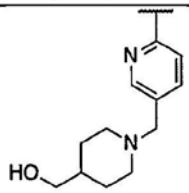
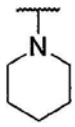
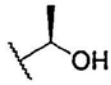
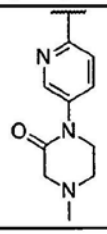
[1034] [表22]

[1035]

实施例编号	R1	R2	R3	
61				
62				
63				
64				
65				
66				

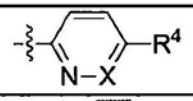
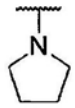
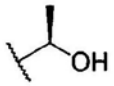
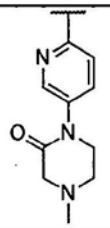
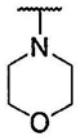
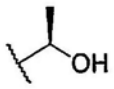
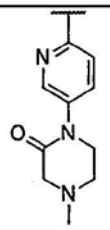
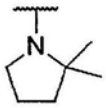
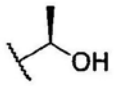
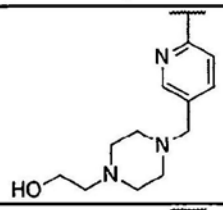
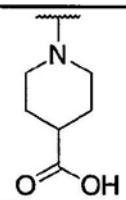
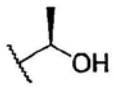
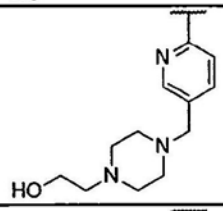
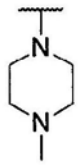
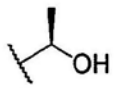
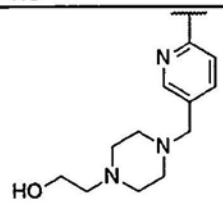
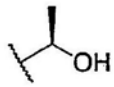
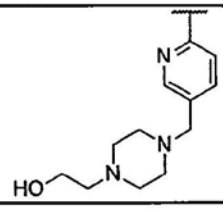
[1036] [表23]

[1037]

实施例编号	R1	R2	R3	
67				
68				
69				
70				
71				
72				

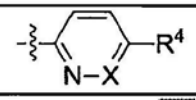
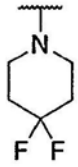
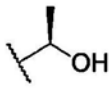
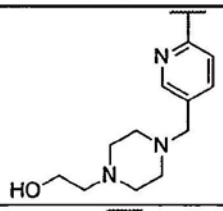
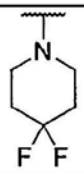
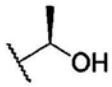
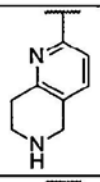
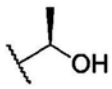
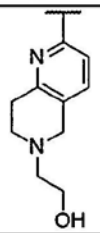
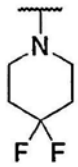
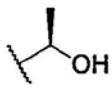
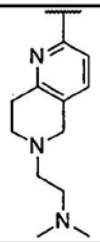
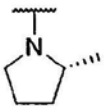
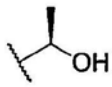
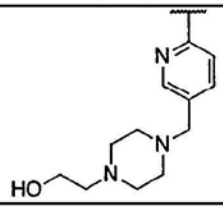
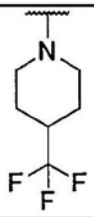
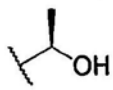
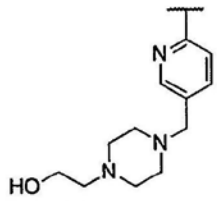
[1038] [表24]

[1039]

实施例编号	R1	R2	R3	
73				
74				
75				
76				
77				
78				

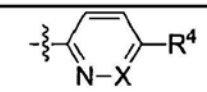
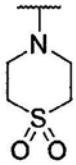
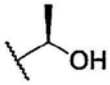
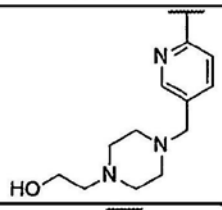
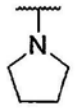
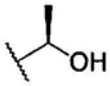
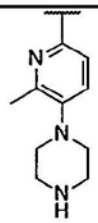
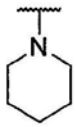
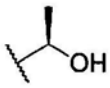
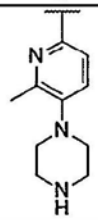
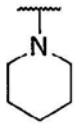
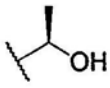
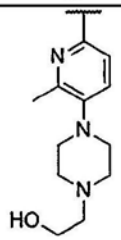
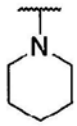
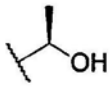
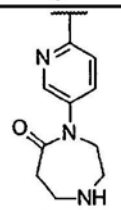
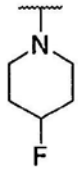
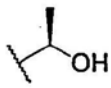
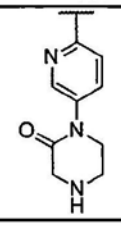
[1040] [表25]

[1041]

实施例编号	R1	R2	R3	
79				
80				
81				
82				
83				
84				

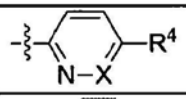
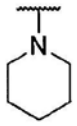
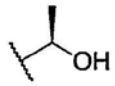
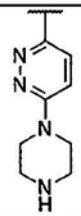
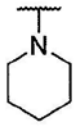
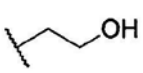
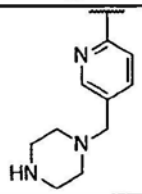
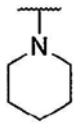
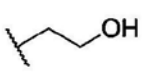
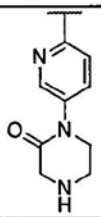
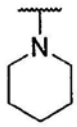
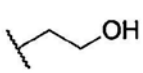
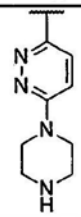
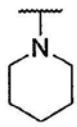
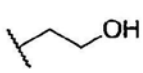
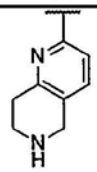
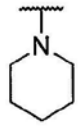
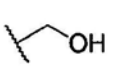
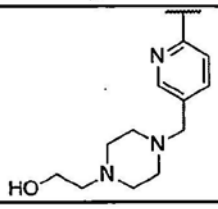
[1042] [表26]

[1043]

实施例编号	R1	R2	R3	
85				
86				
87				
88				
89				
90				

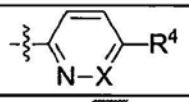
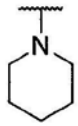
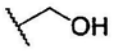
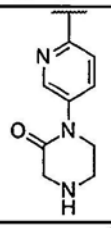
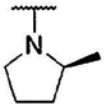
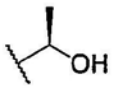
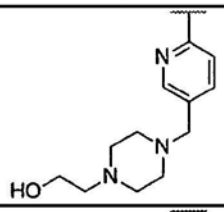
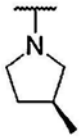
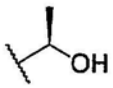
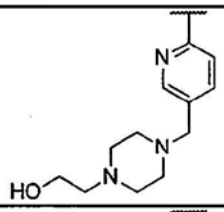
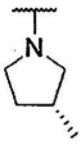
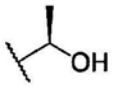
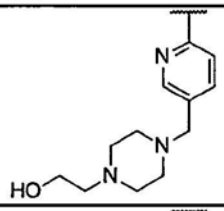
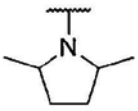
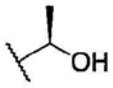
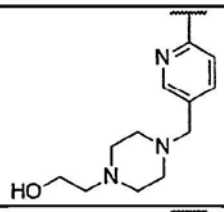
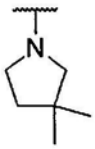
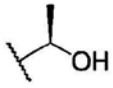
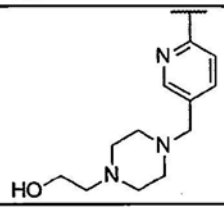
[1044] [表27]

[1045]

实施例编号	R1	R2	R3	
91				
92				
93				
94				
95				
96				

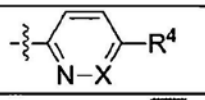
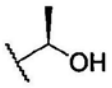
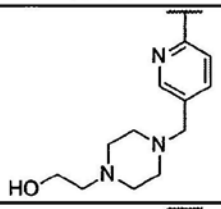
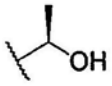
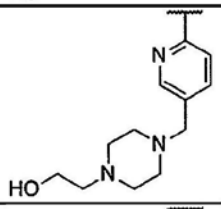
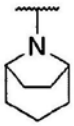
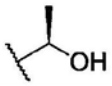
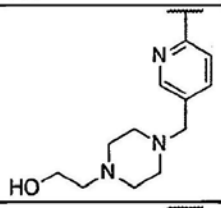
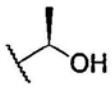
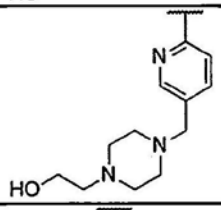
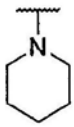
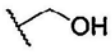
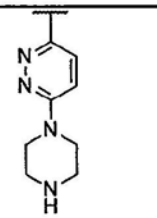
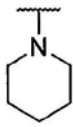
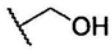
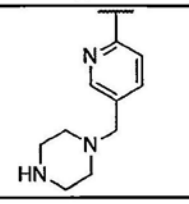
[1046] [表28]

[1047]

实施例编号	R1	R2	R3	
97				
98				
99				
100				
101				
102				

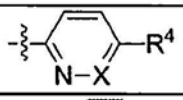
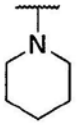
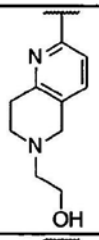
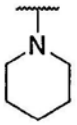
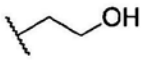
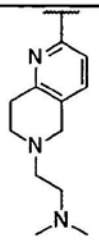
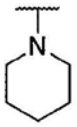
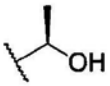
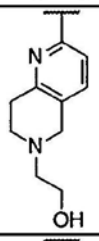
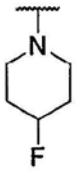
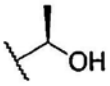
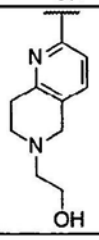
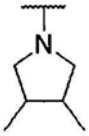
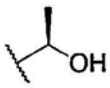
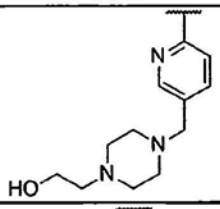
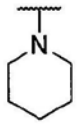
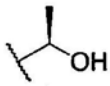
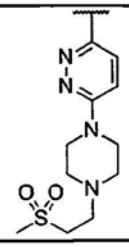
[1048] [表29]

[1049]

实施例编号	R1	R2	R3	
103				
104				
105				
106				
107				
108				

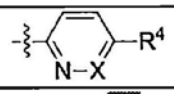
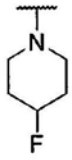
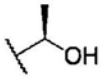
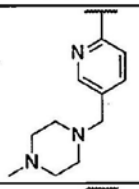
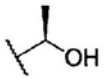
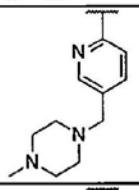
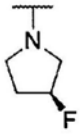
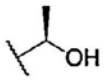
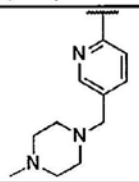
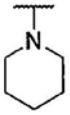
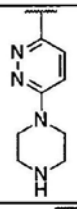
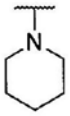
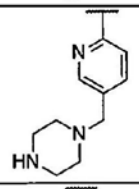
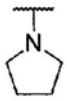
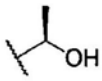
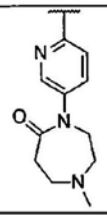
[1050] [表30]

[1051]

实施例编号	R1	R2	R3	
109				
110				
111				
112				
113				
114				

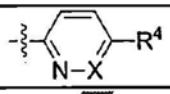
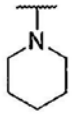
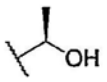
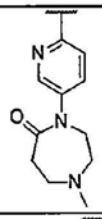
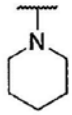
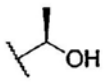
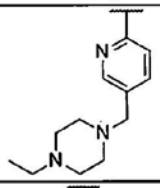
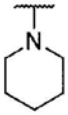
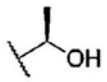
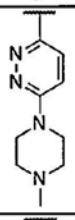
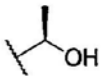
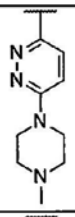
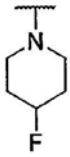
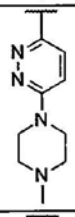
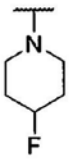
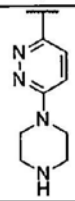
[1052] [表31]

[1053]

实施例编号	R1	R2	R3	
115				
116				
117				
118				
119				
120				

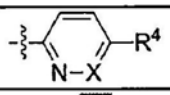
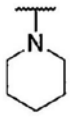
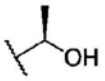
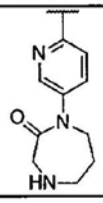
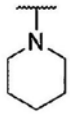
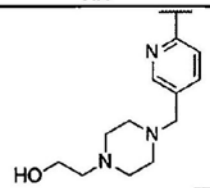
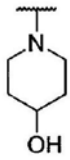
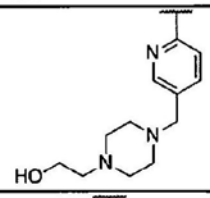
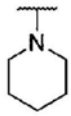
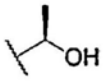
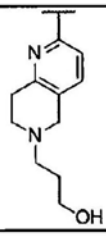
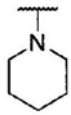
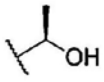
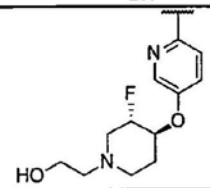
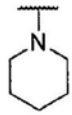
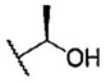
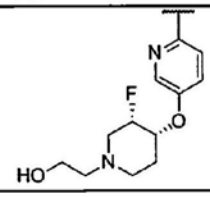
[1054] [表32]

[1055]

实施例编号	R1	R2	R3	
121				
122				
123				
124				
125				
126				

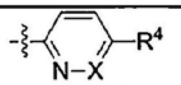
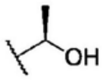
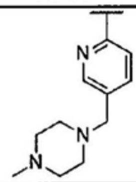
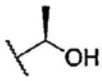
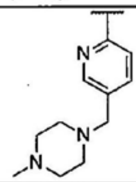
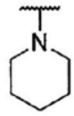
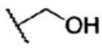
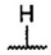
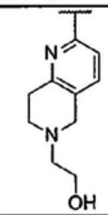
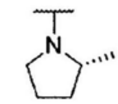
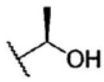
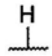
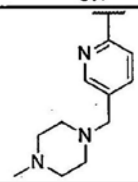
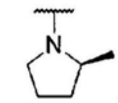
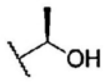
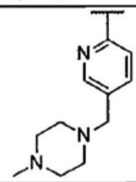
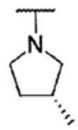
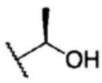
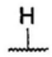
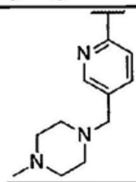
[1056] [表33]

[1057]

实施例编号	R1	R2	R3	
127				
128				
129				
130				
131				
132				

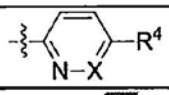
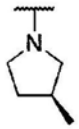
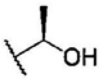
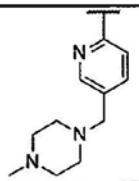
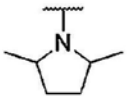
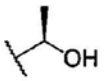
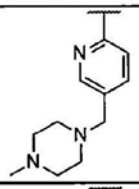
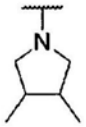
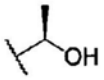
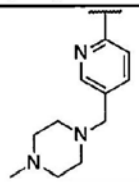
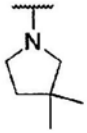
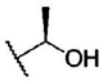
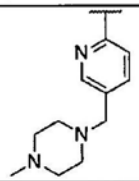
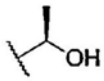
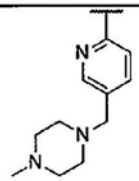
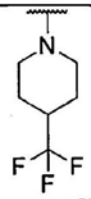
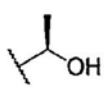
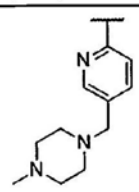
[1058] [表34]

[1059]

实施例编号	R1	R2	R3	
133				
134				
135				
136				
137				
138				

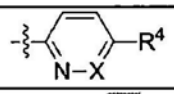
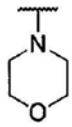
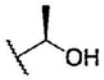
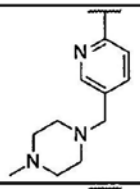
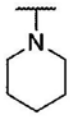
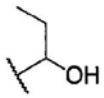
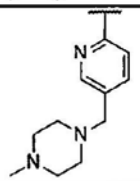
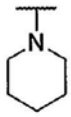
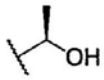
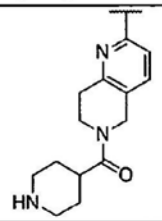
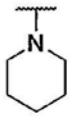
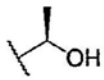
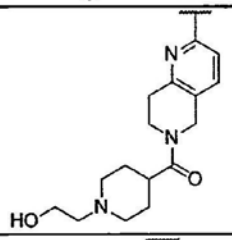
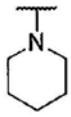
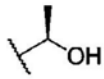
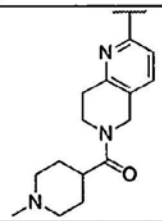
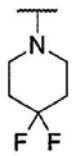
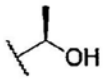
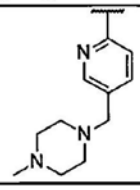
[1060] [表35]

[1061]

实施例编号	R1	R2	R3	
139				
140				
141				
142				
143				
144				

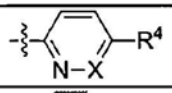
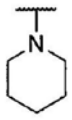
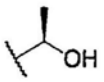
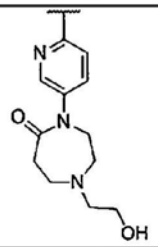
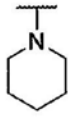
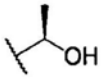
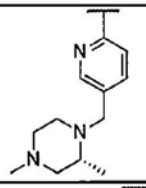
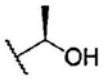
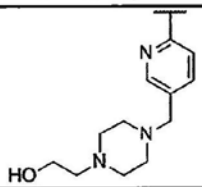
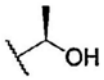
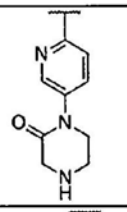
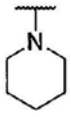
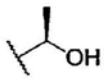
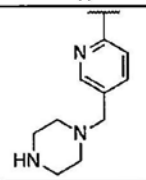
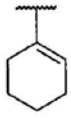
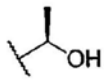
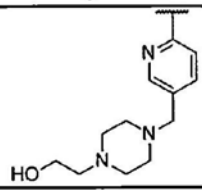
[1062] [表36]

[1063]

实施例编号	R1	R2	R3	
145				
146				
147				
148				
149				
150				

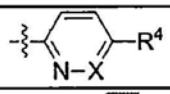
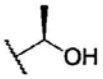
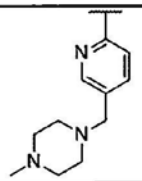
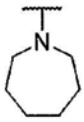
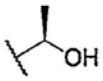
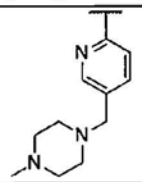
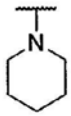
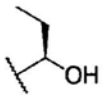
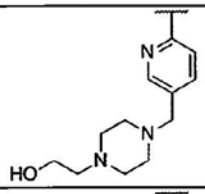
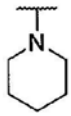
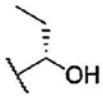
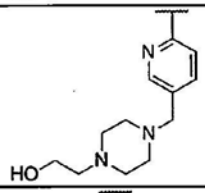
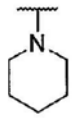
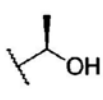
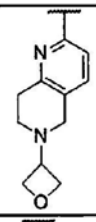
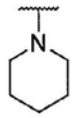
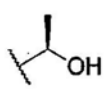
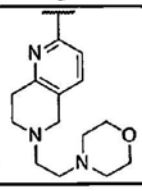
[1064] [表37]

[1065]

实施例编号	R1	R2	R3	
151				
152				
153				
154				
155				
156				

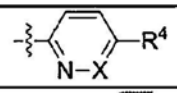
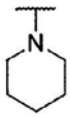
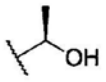
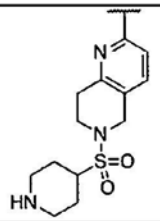
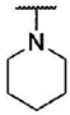
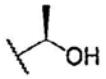
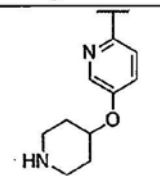
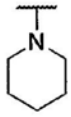
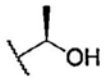
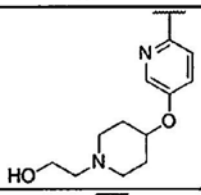
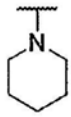
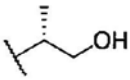
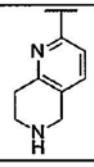
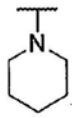
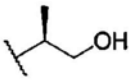
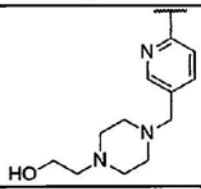
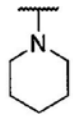
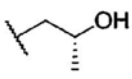
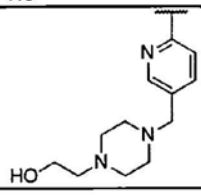
[1066] [表38]

[1067]

实施例编号	R1	R2	R3	
157				
158				
159				
160				
161				
162				

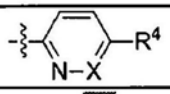
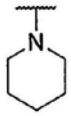
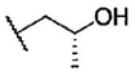
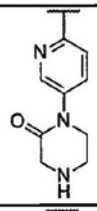
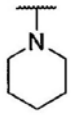
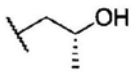
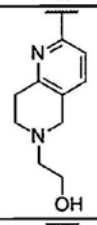
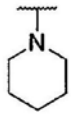
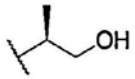
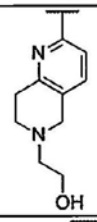
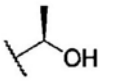
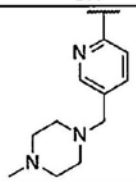
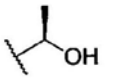
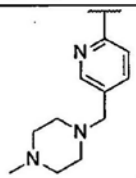
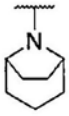
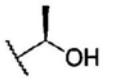
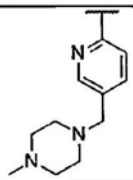
[1068] [表39]

[1069]

实施例编号	R1	R2	R3	
163				
164				
165				
166				
167				
168				

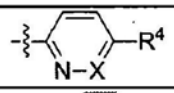
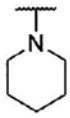
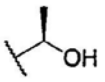
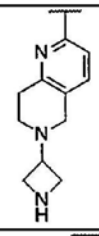
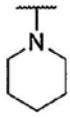
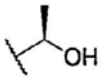
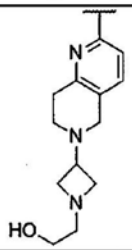
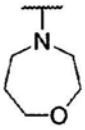
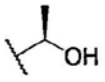
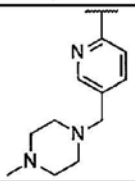
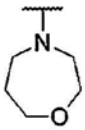
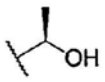
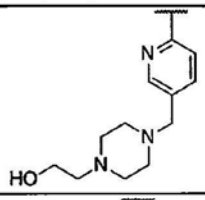
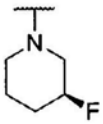
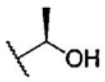
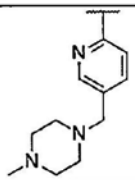
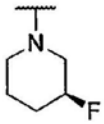
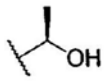
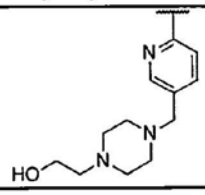
[1070] [表40]

[1071]

实施例编号	R1	R2	R3	
169				
170				
171				
172				
173				
174				

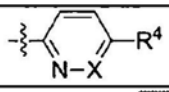
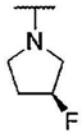
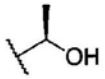
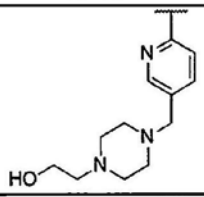
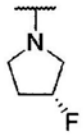
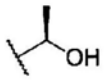
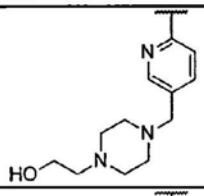
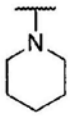
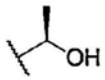
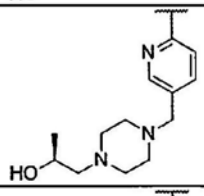
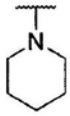
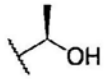
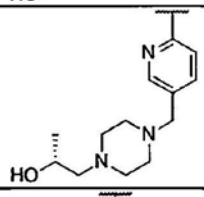
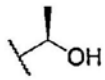
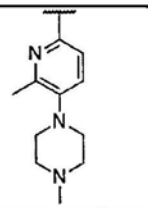
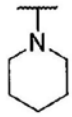
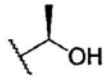
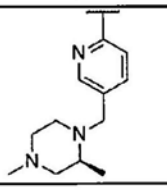
[1072] [表41]

[1073]

实施例编号	R1	R2	R3	
175				
176				
177				
178				
179				
180				

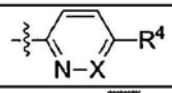
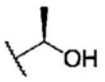
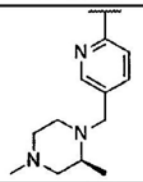
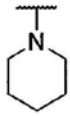
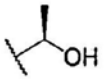
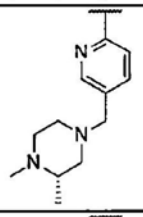
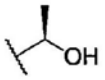
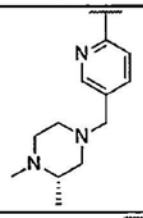
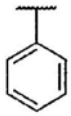
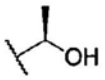
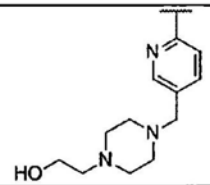
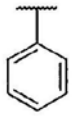
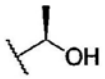
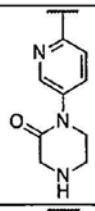
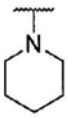
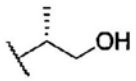
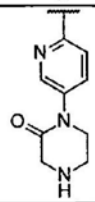
[1074] [表42]

[1075]

实施例编号	R1	R2	R3	
181				
182				
183				
184				
185				
186				

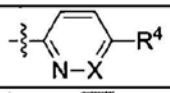
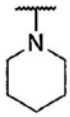
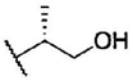
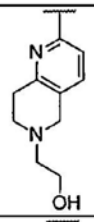
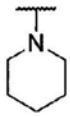
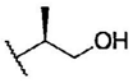
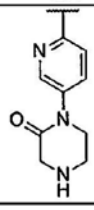
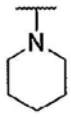
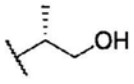
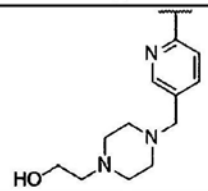
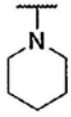
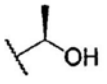
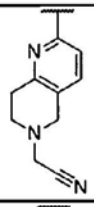
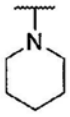
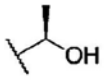
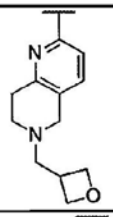
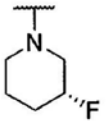
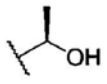
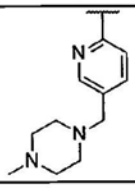
[1076] [表43]

[1077]

实施例编号	R1	R2	R3	
187				
188				
189				
190				
191				
192				

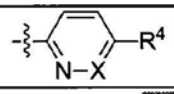
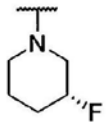
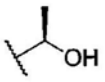
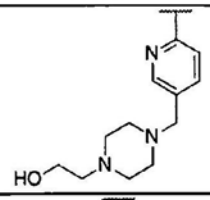
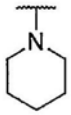
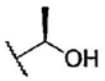
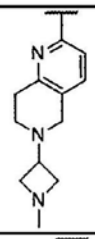
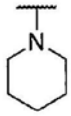
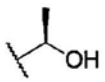
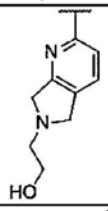
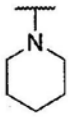
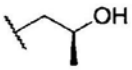
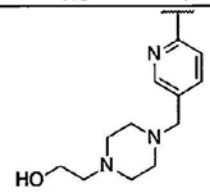
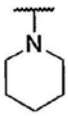
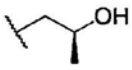
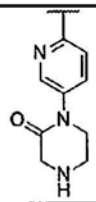
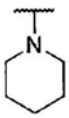
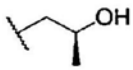
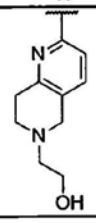
[1078] [表44]

[1079]

实施例编号	R1	R2	R3	
193				
194				
195				
196				
197				
198				

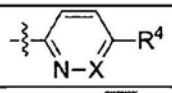
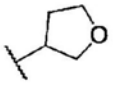
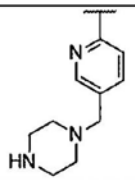
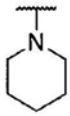
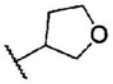
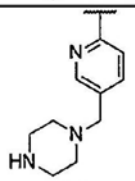
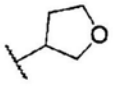
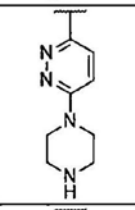
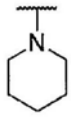
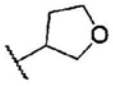
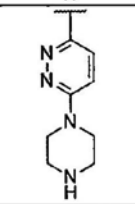
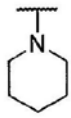
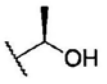
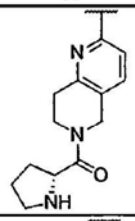
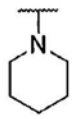
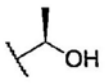
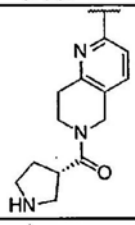
[1080] [表45]

[1081]

实施例编号	R1	R2	R3	
199				
200				
201				
202				
203				
204				

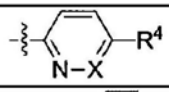
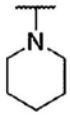
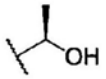
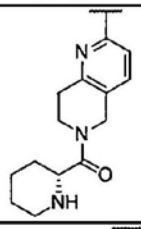
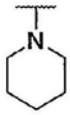
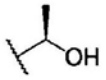
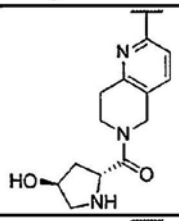
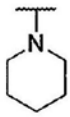
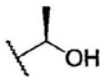
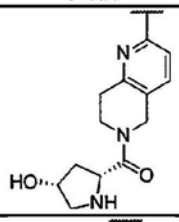
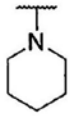
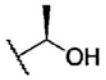
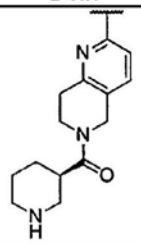
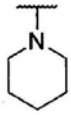
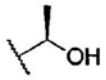
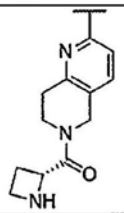
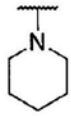
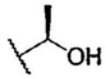
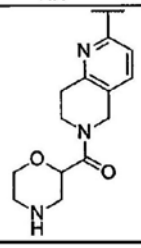
[1082] [表46]

[1083]

实施例编号	R1	R2	R3	
205				
206				
207				
208				
209				
210				

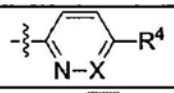
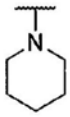
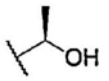
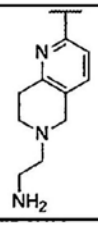
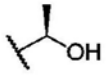
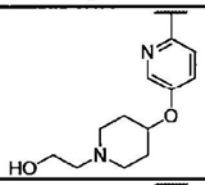
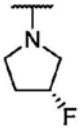
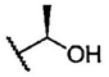
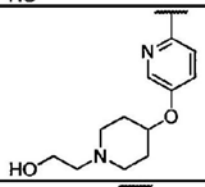
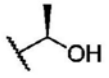
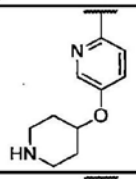
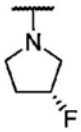
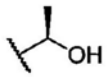
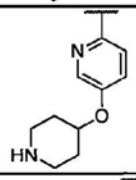
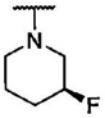
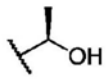
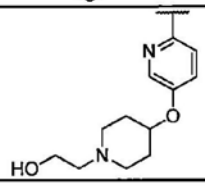
[1084] [表47]

[1085]

实施例编号	R1	R2	R3	
211				
212				
213				
214				
215				
216				

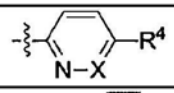
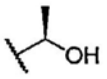
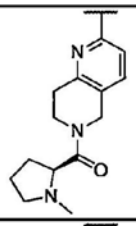
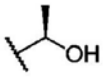
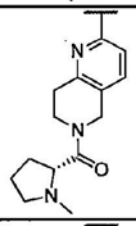
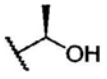
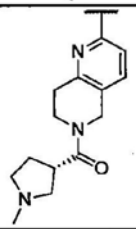
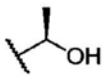
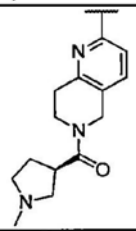
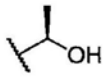
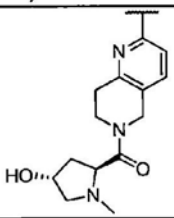
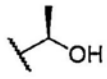
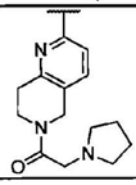
[1086] [表48]

[1087]

实施例编号	R1	R2	R3	
217				
218				
219				
220				
221				
222				

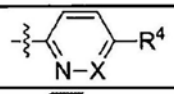
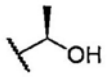
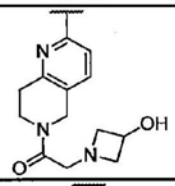
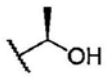
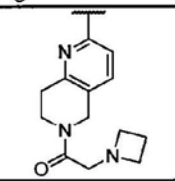
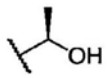
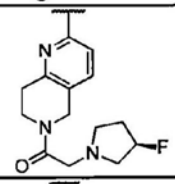
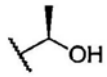
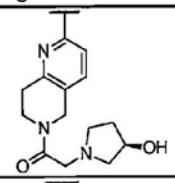
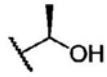
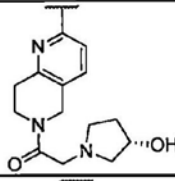
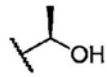
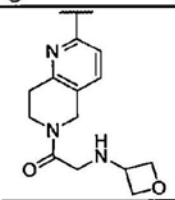
[1088] [表49]

[1089]

实施例编号	R1	R2	R3	
223				
224				
225				
226				
227				
228				

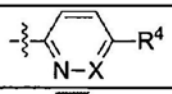
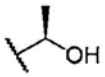
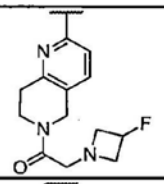
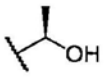
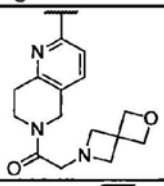
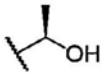
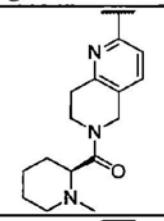
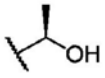
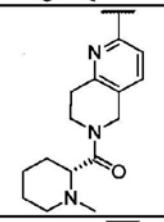
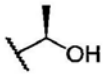
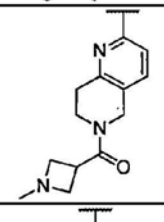
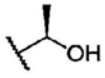
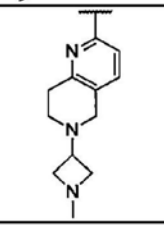
[1090] [表50]

[1091]

实施例编号	R1	R2	R3	
229				
230				
231				
232				
233				
234				

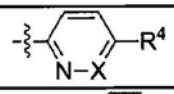
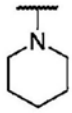
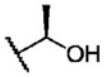
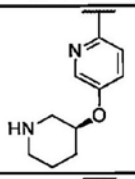
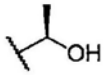
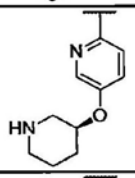
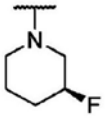
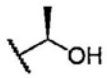
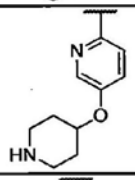
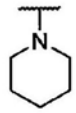
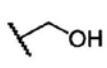
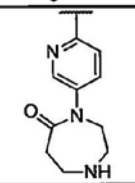
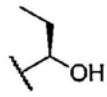
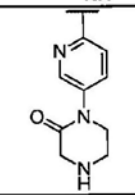
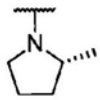
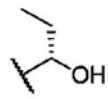
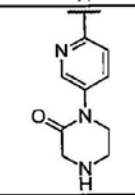
[1092] [表51]

[1093]

实施例编号	R1	R2	R3	
235				
236				
237				
238				
239				
240				

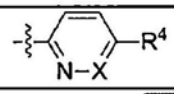
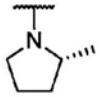
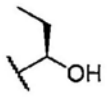
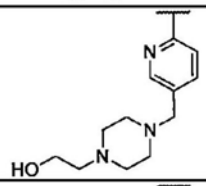
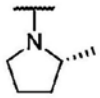
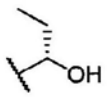
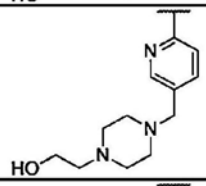
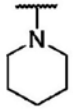
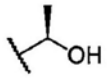
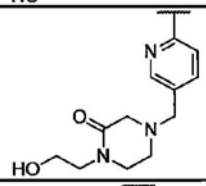
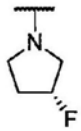
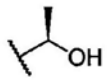
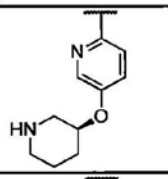
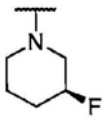
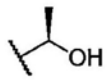
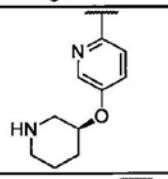
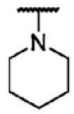
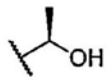
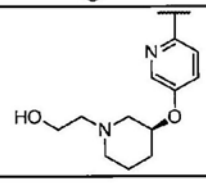
[1094] [表52]

[1095]

实施例编号	R1	R2	R3	
241				
242				
243				
244				
245				
246				

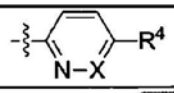
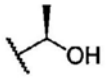
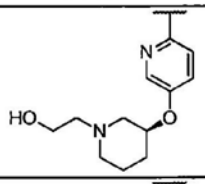
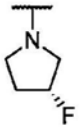
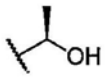
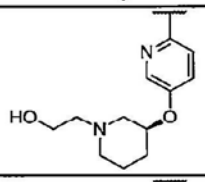
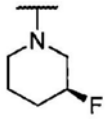
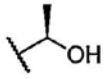
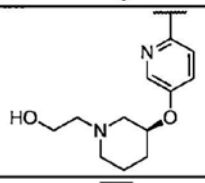
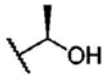
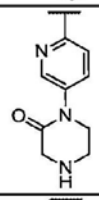
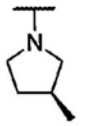
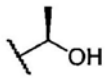
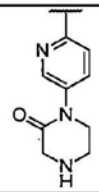
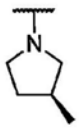
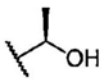
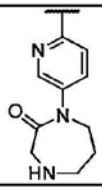
[1096] [表53]

[1097]

实施例编号	R1	R2	R3	
247				
248				
249				
250				
251				
252				

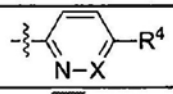
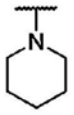
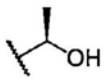
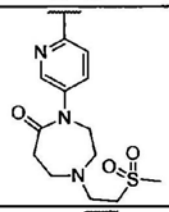
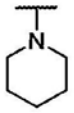
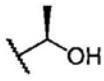
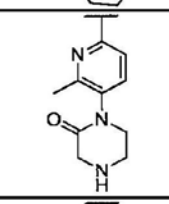
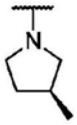
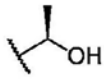
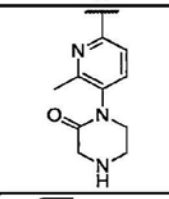
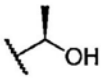
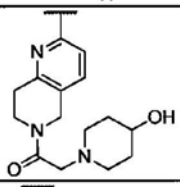
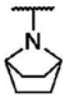
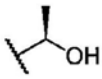
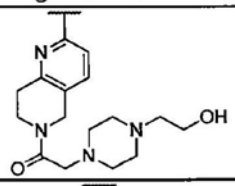
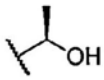
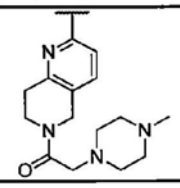
[1098] [表54]

[1099]

实施例编号	R1	R2	R3	
253				
254				
255				
256				
257				
258				

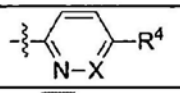
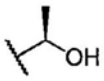
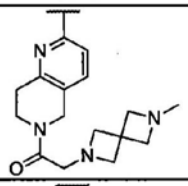
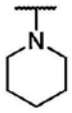
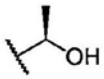
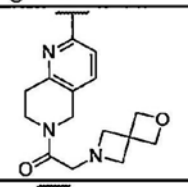
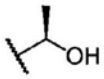
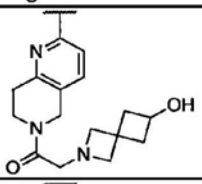
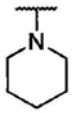
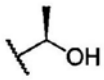
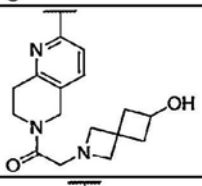
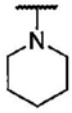
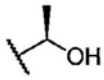
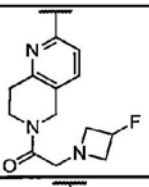
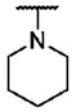
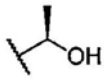
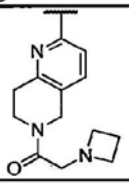
[1100] [表55]

[1101]

实施例编号	R1	R2	R3	
259				
260				
261				
262				
263				
264				

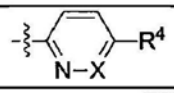
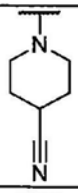
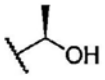
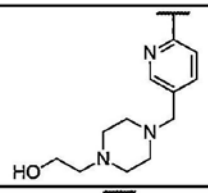
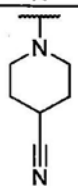
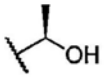
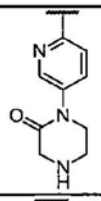
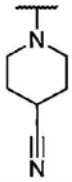
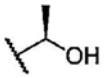
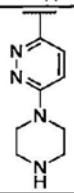
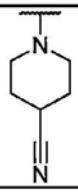
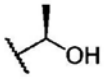
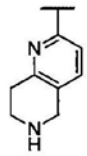
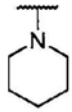
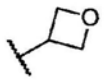
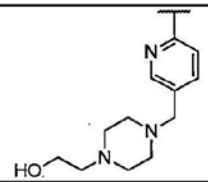
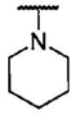
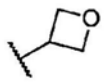
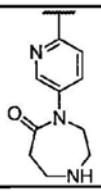
[1102] [表56]

[1103]

实施例编号	R1	R2	R3	
265				
266				
267				
268				
269				
270				

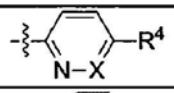
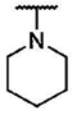
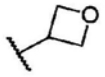
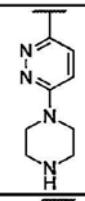
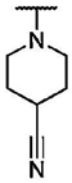
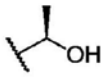
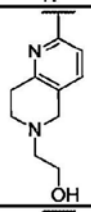
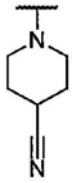
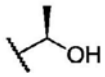
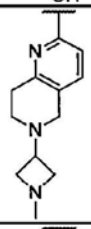
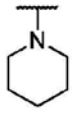
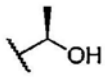
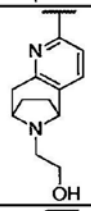
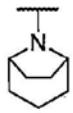
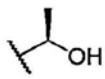
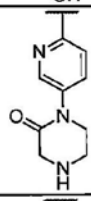
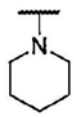
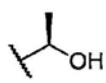
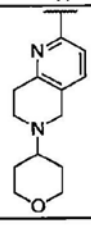
[1104] [表57]

[1105]

实施例编号	R1	R2	R3	
271				
272				
273				
274				
275				
276				

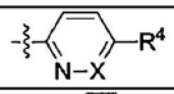
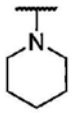
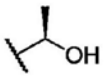
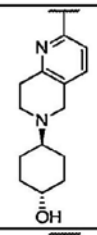
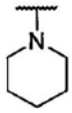
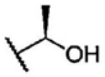
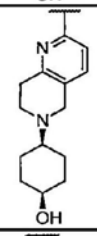
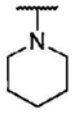
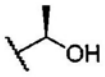
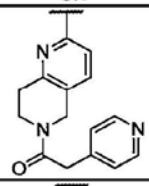
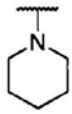
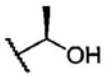
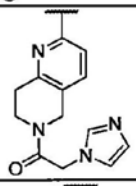
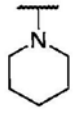
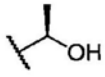
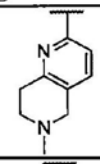
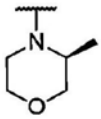
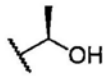
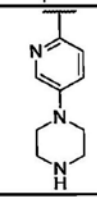
[1106] [表58]

[1107]

实施例编号	R1	R2	R3	
277				
278				
279				
280				
281				
282				

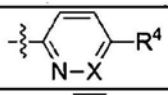
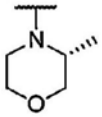
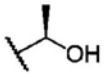
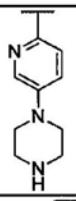
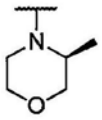
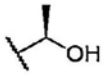
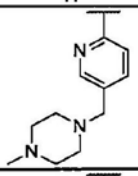
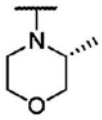
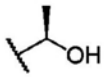
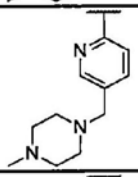
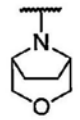
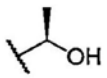
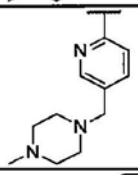
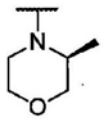
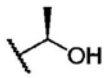
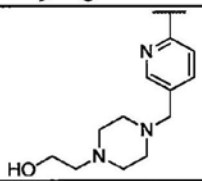
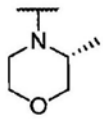
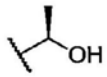
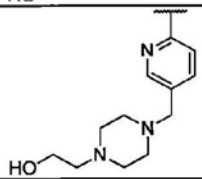
[1108] [表59]

[1109]

实施例编号	R1	R2	R3	
283				
284				
285				
286				
287				
288				

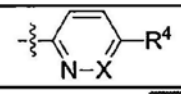
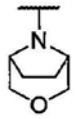
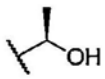
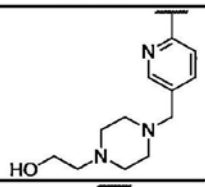
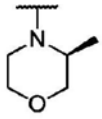
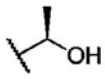
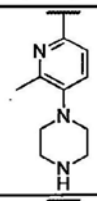
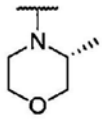
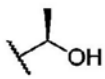
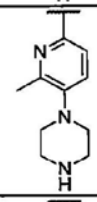
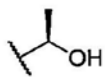
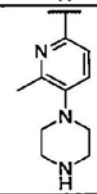
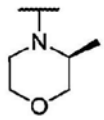
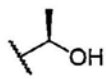
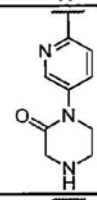
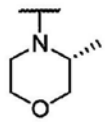
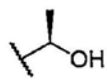
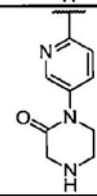
[1110] [表60]

[1111]

实施例编号	R1	R2	R3	
289				
290				
291				
292				
293				
294				

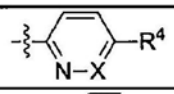
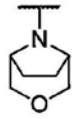
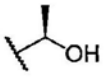
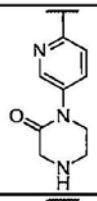
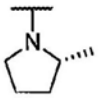
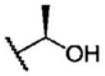
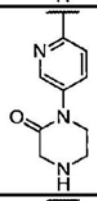
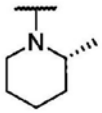
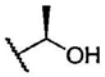
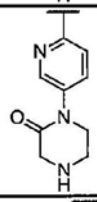
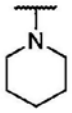
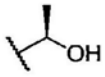
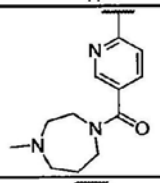
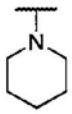
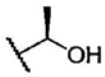
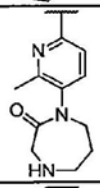
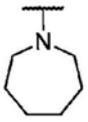
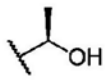
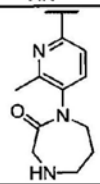
[1112] [表61]

[1113]

实施例编号	R1	R2	R3	
295				
296				
297				
298				
299				
300				

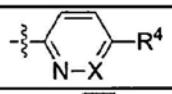
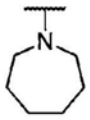
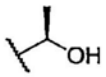
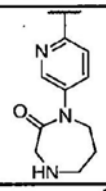
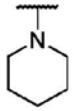
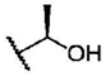
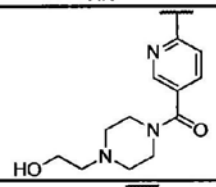
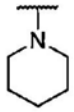
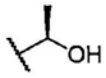
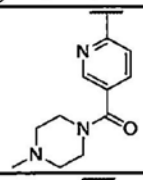
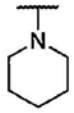
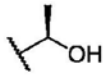
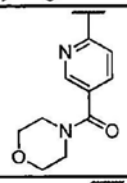
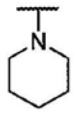
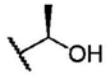
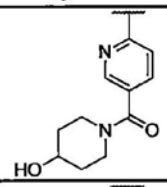
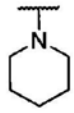
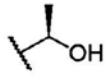
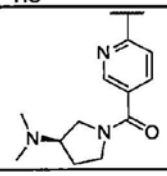
[1114] [表62]

[1115]

实施例编号	R1	R2	R3	
301				
302				
303				
304				
305				
306				

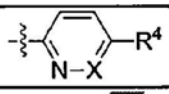
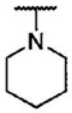
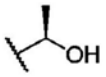
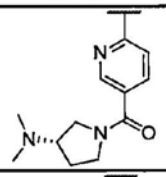
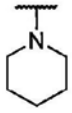
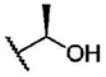
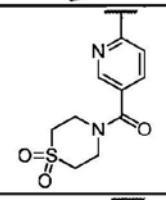
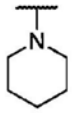
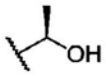
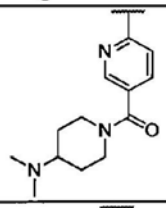
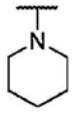
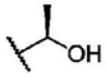
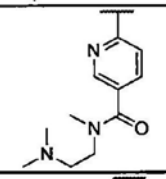
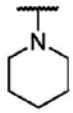
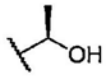
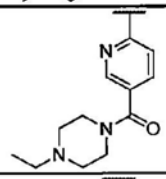
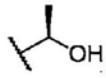
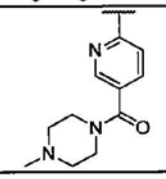
[1116] [表63]

[1117]

实施例编号	R1	R2	R3	
307				
308				
309				
310				
311				
312				

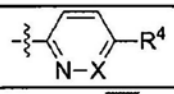
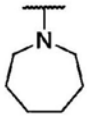
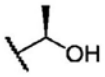
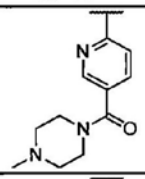
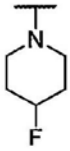
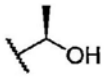
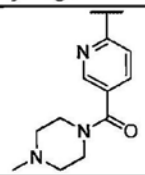
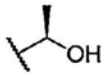
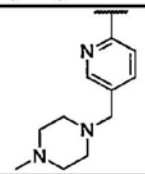
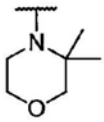
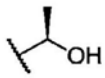
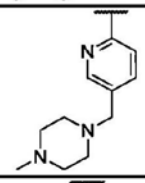
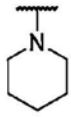
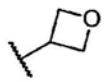
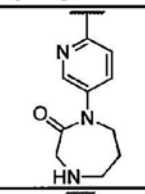
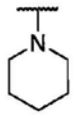
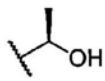
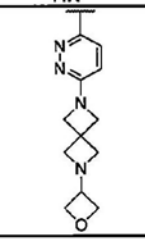
[1118] [表64]

[1119]

实施例编号	R1	R2	R3	
313				
314				
315				
316				
317				
318				

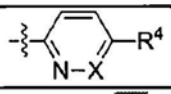
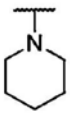
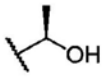
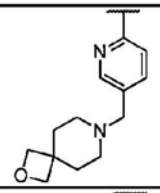
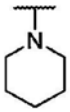
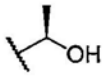
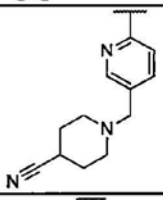
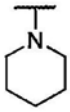
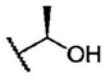
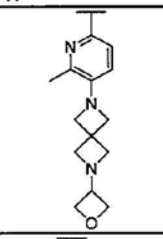
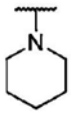
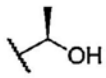
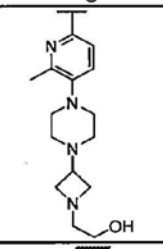
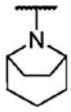
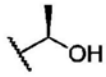
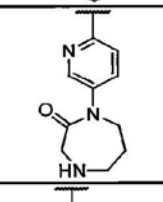
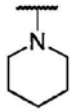
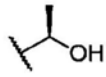
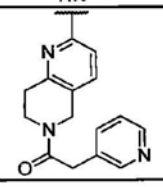
[1120] [表65]

[1121]

实施例编号	R1	R2	R3	
319				
320				
321				
322				
323				
324				

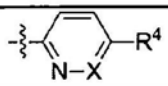
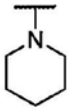
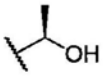
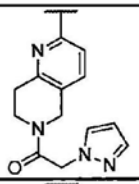
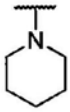
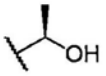
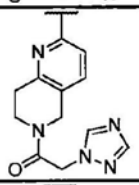
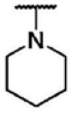
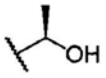
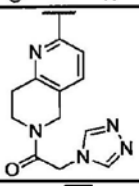
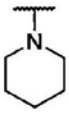
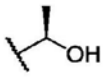
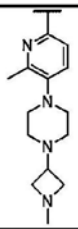
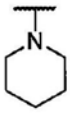
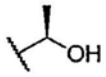
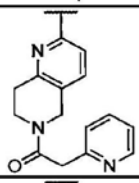
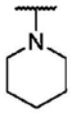
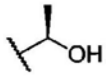
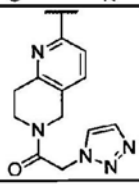
[1122] [表66]

[1123]

实施例编号	R1	R2	R3	
325				
326				
327				
328				
329				
330				

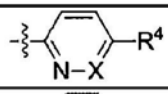
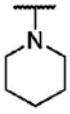
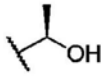
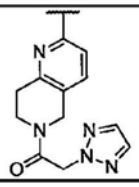
[1124] [表67]

[1125]

实施例编号	R1	R2	R3	
331				
332				
333				
334				
335				
336				

[1126] [表68]

[1127]

实施例编号	R1	R2	R3	
337				

[1128] [表69]

[1129]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
1		437.25	436.23
2	1H-NMR (CD3OD) δ:7.64 (1.0H, d, J=2.9 Hz), 7.32 (1.0H, dd, J = 9.3, 2.9 Hz), 6.98 (1.0H, s), 6.58 (1.0H, d, J = 9.3 Hz), 5.54 (1.0H, s), 4.45 (2.0H, s), 3.08-3.00 (8.0H, m), 2.68-2.64 (4.0H, m), 2.38 (3.0H, s), 1.80-1.74 (4.0H, m), 1.66-1.59 (2.0H, m).	435.25	434.25
3	1H-NMR (CD3OD) δ: 9.29 (1.0H, s), 8.28 (1.0H, d, J=8.8 Hz), 7.94 (1.0H, d, J = 2.9 Hz), 7.78 (1.0H, s), 7.41 (1.0H, dd, J=8.8, 2.9 Hz), 4.69 (2.0H, br s), 3.90-3.40 (2.0H, m), 3.20-3.15 (4.0H, m), 2.67-2.50 (6.0H, m), 2.35 (3.0H, s), 2.03-1.95 (4.0H, m).	449.25	448.23
4	1H-NMR (CDCl3) δ: 9.13 (1.0H, s), 8.27 (1.0H, d, J=9.0 Hz), 8.20 (1.0H, br s), 8.07 (1.0H, d, J = 2.9 Hz), 7.38-7.32 (2.0H, m), 6.57 (1.0H, t, J = 56.0 Hz), 3.99-3.87 (8.0H, br m), 3.29-3.10 (4.0H, m), 2.70-2.60 (4.0H, m), 2.41 (3.0H, s).	457.20	456.22
6		428.37	427.21
7		423.15	422.22
8		443.15	442.20
9		421.31	420.24
10		414.23	413.20
11		441.32	440.22
12		434.15	433.18
13		455.19	454.24
14		428.35	427.21
15		428.32	427.21
16		420.32	419.15
17		404.23	403.18
18		442.0	441.23
19		442.0	441.23
20		434.24	433.17
21		418.27	417.19
22		432.28	431.24
23		435.3	434.22
24		435.33	434.25
25		449.31	448.23
26		433.3	432.24
27		462.41	461.27
28		434.37	433.23
29		448.4	447.25

[1130] [表70]

[1131]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
30		448.37	447.20
31		424.35	423.16
32		437.43	436.23
33		437.40	436.23
34		451.33	450.25
35		491.39	490.21
36		457.39	456.22
37		451.43	450.25
38		437.3	436.23
39		466.3	465.22
40		480.3	479.24
41		480.3	479.24
42		479.3	478.24
43		463.4	462.29
44		504.30	503.31
45		493.25	492.30
46		507.30	506.31
47		465.3	464.26
48	1H-NMR (CDCl3) δ: 9.03 (1H, s), 8.63 (1H, s), 8.28-8.18 (2H, m), 7.66 (1H, dd, J = 8.7, 2.3 Hz), 6.66 (1H, s), 4.78 (1H, q, J = 6.4 Hz), 4.02 (4H, br s), 3.60 (2H, t, J = 5.5 Hz), 3.48 (2H, s), 2.62-2.44 (10H, m), 2.03-1.95 (4H, m), 1.51 (3H, d, J = 6.9 Hz).	479.4	478.28
49	1H-NMR (CDCl3) δ: 9.17 (2H, d, J = 3.7 Hz), 8.54 (1H, d, J = 8.7 Hz), 8.33 (1H, d, J = 1.8 Hz), 7.72 (1H, dd, J = 8.5, 2.1 Hz), 6.94 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 3.85 (4H, t, J = 5.3 Hz), 3.60 (2H, t, J = 5.3 Hz), 3.51 (2H, s), 2.54 (10H, t, J = 5.5 Hz), 1.83 (4H, t, J = 5.3 Hz), 1.75 (2H, d, J = 5.0 Hz), 1.52 (3H, d, J = 6.4 Hz).	493.4	492.30
50		421.3	420.20
51	1H-NMR (CDCl3) δ: 9.01 (1H, s), 8.34-8.25 (3H, m), 7.69 (1H, dd, J = 8.9, 2.5 Hz), 6.67 (1H, s), 4.79 (1H, q, J = 6.4 Hz), 4.03 (4H, br s), 3.71 (4H, d, J = 7.8 Hz), 3.25 (2H, t, J = 5.3 Hz), 2.04-1.96 (4H, m), 1.51 (3H, d, J = 6.4 Hz).	435.3	434.22

[1132] [表71]

[1133]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
52	1H-NMR (CDCl3) δ: 9.67 (1H, s), 9.19 (1H, s), 8.61 (1H, d, J = 9.1 Hz), 8.42 (1H, d, J = 2.7 Hz), 7.70 (1H, dd, J = 8.9, 2.5 Hz), 6.94 (1H, s), 4.83 (1H, q, J = 6.6 Hz), 3.80 (4H, t, J = 5.0 Hz), 3.73 (4H, t, J = 5.3 Hz), 3.25 (2H, t, J = 5.3 Hz), 1.81 (4H, br s), 1.75-1.68 (2H, m), 1.52 (3H, d, J = 6.4 Hz).	449.3	448.23
53		449.3	448.27
54		463.4	462.29
55	1H-NMR (CDCl3) δ: 9.03 (1H, s), 8.60 (1H, s), 8.26 (1H, d, J = 1.8 Hz), 8.19 (1H, d, J = 8.7 Hz), 7.67 (1H, dd, J = 8.7, 2.3 Hz), 6.66 (1H, s), 4.78 (1H, q, J = 6.4 Hz), 4.02 (4H, br s), 3.48 (2H, s), 2.47 (8H, br s), 2.28 (3H, s), 2.01-1.97 (4H, m), 1.51 (3H, d, J = 6.9 Hz).	449.3	448.27
56	1H-NMR (CDCl3) δ: 9.48 (1H, s), 9.19 (1H, s), 8.53 (1H, d, J = 8.2 Hz), 8.36 (1H, d, J = 1.8 Hz), 7.71 (1H, dd, J = 8.5, 2.1 Hz), 6.94 (1H, s), 4.83 (1H, q, J = 6.6 Hz), 3.84 (4H, t, J = 5.3 Hz), 3.49 (2H, s), 2.46 (8H, br s), 2.27 (3H, s), 1.87-1.80 (4H, m), 1.77-1.70 (2H, m), 1.52 (3H, d, J = 6.4 Hz).	463.4	462.29
57	1H-NMR (CDCl3) δ: 9.01 (1H, s), 8.29 (1H, d, J = 9.1 Hz), 8.24 (1H, d, J = 1.8 Hz), 8.20 (1H, s), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 6.69 (1H, s), 4.78 (1H, q, J = 6.4 Hz), 4.47 (4H, br s), 3.60 (2H, t, J = 5.5 Hz), 3.51 (2H, s), 2.59-2.46 (10H, m), 2.25 (4H, t, J = 7.5 Hz), 1.93-1.85 (2H, m), 1.50 (3H, d, J = 6.4 Hz).	505.4	504.30
58	1H-NMR (CDCl3) δ: 9.14 (1H, d, J = 3.7 Hz), 8.57 (1H, s), 8.40 (1H, d, J = 8.7 Hz), 8.28 (1H, d, J = 1.8 Hz), 7.72 (1H, dd, J = 8.2, 2.3 Hz), 7.03 (1H, d, J = 0.9 Hz), 4.87 (1H, q, J = 6.4 Hz), 3.99 (4H, t, J = 4.6 Hz), 3.93 (4H, t, J = 4.6 Hz), 3.61 (2H, t, J = 5.3 Hz), 3.51 (2H, s), 2.60-2.46 (10H, m), 1.54 (3H, d, J = 6.4 Hz).	495.3	494.28
59	1H-NMR (CDCl3) δ: 9.01 (1H, s), 8.22 (1H, d, J = 2.3 Hz), 8.16 (1H, d, J = 8.7 Hz), 8.05 (1H, s), 7.67 (1H, dd, J = 8.7, 2.3 Hz), 6.70 (1H, s), 4.78 (1H, q, J = 6.4 Hz), 4.18 (4H, t, J = 5.9 Hz), 3.60 (2H, t, J = 5.5 Hz), 3.49 (2H, s), 2.59-2.45 (10H, m), 1.87 (4H, s), 1.61-1.55 (4H, m), 1.50 (3H, d, J = 6.4 Hz).	507.4	506.31

[1134] [表72]

[1135]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
60	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J = 8.7 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.24 (1H, s), 5.26 (1H, d, J = 4.6 Hz), 4.70-4.61 (1H, m), 3.84-3.66 (4H, m), 3.57 (2H, s), 2.86-2.73 (4H, m), 2.61-2.53 (2H, m), 2.46-2.38 (2H, m), 2.16 (6H, s), 1.78-1.60 (6H, m), 1.38 (3H, d, J = 6.4 Hz).	477.4	476.30
61	1H-NMR (DMSO-D6) δ: 10.03 (1H, s), 9.31 (1H, s), 8.12 (1H, d, J = 8.2 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.28 (1H, s), 5.28 (1H, d, J = 4.6 Hz), 5.03-4.82 (1H, m), 4.71-4.62 (1H, m), 4.10-3.94 (2H, m), 3.82-3.65 (2H, m), 3.57 (2H, s), 2.86-2.73 (4H, m), 2.62-2.53 (2H, m), 2.46-2.38 (2H, m), 2.22-1.98 (8H, m), 1.95-1.79 (2H, m), 1.39 (3H, d, J = 6.4 Hz).	495.3	494.29
62	1H-NMR (DMSO-D6) δ: 9.93 (1H, s), 9.29 (1H, s), 8.19 (1H, d, J = 8.2 Hz), 7.45 (1H, d, J = 8.2 Hz), 7.24 (1H, s), 5.26 (1H, d, J = 4.6 Hz), 4.70-4.61 (1H, m), 3.86-3.66 (6H, m), 3.05-2.97 (2H, m), 2.75-2.67 (2H, m), 1.79-1.60 (6H, m), 1.38 (3H, d, J = 6.4 Hz).	406.3	405.23
63	1H-NMR (DMSO-D6) δ: 10.00 (1H, s), 9.31 (1H, s), 8.11 (1H, d, J = 8.2 Hz), 7.46 (1H, d, J = 8.2 Hz), 7.27 (1H, s), 5.29 (1H, d, J = 4.6 Hz), 5.03-4.82 (1H, m), 4.71-4.62 (1H, m), 4.09-3.93 (2H, m), 3.86-3.66 (4H, m), 3.06-2.97 (2H, m), 2.75-2.66 (2H, m), 2.16-1.98 (2H, m), 1.95-1.79 (2H, m), 1.39 (3H, d, J = 6.4 Hz).	424.2	423.22
64	1H-NMR (DMSO-D6) δ: 10.36 (1H, s), 9.38 (1H, s), 8.31 (1H, d, J = 2.7 Hz), 8.26 (1H, d, J = 8.7 Hz), 7.82 (1H, dd, J = 8.9, 2.5 Hz), 7.34 (1H, s), 5.32 (1H, d, J = 4.6 Hz), 4.73-4.63 (1H, m), 4.08-3.90 (4H, m), 3.64 (2H, t, J = 5.5 Hz), 3.40 (2H, s), 3.03 (2H, t, J = 5.5 Hz), 2.79 (1H, s), 2.23-2.08 (4H, m), 1.40 (3H, d, J = 6.4 Hz).	485.48	484.21
65	1H-NMR (DMSO-D6) δ: 10.14 (1H, s), 9.32 (1H, s), 8.34 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 2.3 Hz), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 7.25 (1H, s), 5.27 (1H, d, J = 4.6 Hz), 4.69-4.62 (1H, m), 4.54 (1H, d, J = 3.2 Hz), 3.80-3.68 (4H, m), 3.47-3.40 (3H, m), 2.66 (2H, d, J = 11.0 Hz), 2.02 (2H, t, J = 9.8 Hz), 1.74-1.63 (8H, m), 1.41-1.32 (5H, m).	464.25	463.27
66	1H-NMR (DMSO-D6) δ: 9.93 (1H, s), 9.21 (1H, s), 8.17 (1H, s), 7.96 (1H, d, J = 8.7 Hz), 7.68 (1H, d, J = 7.8 Hz), 6.99 (1H, s), 5.17 (1H, d, J = 4.6 Hz), 4.62-4.52 (2H, m), 3.89 (4H, br s), 3.47-3.37 (3H, m), 2.66 (2H, br s), 2.03 (2H, br s), 1.93-1.86 (4H, m), 1.73-1.67 (2H, m), 1.42-1.33 (5H, m).	450.2	449.25

[1136] [表73]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
67	1H-NMR (DMSO-D6) δ: 10.25 (1H, s), 9.35 (1H, s), 8.23-8.15 (2H, m), 7.76-7.72 (1H, m), 7.31 (1H, s), 5.30 (1H, d, J = 4.6 Hz), 4.71-4.64 (1H, m), 4.57 (1H, br s), 3.86-3.74 (8H, m), 3.48-3.41 (3H, m), 2.68 (2H, br s), 2.06 (1H, br s), 1.73-1.67 (2H, m), 1.44-1.34 (5H, m).	466.2	465.25
68	1H-NMR (DMSO-D6) δ: 10.13 (1H, s), 9.32 (1H, s), 8.34 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 2.3 Hz), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 7.26 (1H, s), 5.28 (1H, br s), 4.69-4.62 (1H, m), 4.40 (1H, br s), 3.82-3.70 (4H, m), 3.42 (2H, s), 3.22 (2H, d, J = 5.9 Hz), 2.90 (1H, t, J = 5.5 Hz), 2.80 (2H, d, J = 11.4 Hz), 1.88 (2H, t, J = 10.5 Hz), 1.75-1.55 (9H, m), 1.41-1.30 (5H, m), 1.16-1.06 (2H, m).	478.25	477.29
69	1H-NMR (DMSO-D6) δ: 9.93 (1H, s), 9.22 (1H, s), 8.19 (1H, s), 7.97 (1H, d, J = 8.2 Hz), 7.69 (1H, d, J = 8.2 Hz), 6.99 (1H, s), 5.16 (1H, d, J = 4.6 Hz), 4.63-4.56 (1H, m), 4.42 (1H, br s), 3.89 (4H, br s), 3.47 (2H, br s), 3.22 (2H, br s), 2.85 (2H, br s), 1.95-1.87 (6H, m), 1.63 (2H, d, J = 8.0 Hz), 1.40-1.31 (4H, m), 1.17-1.08 (2H, m).	464.25	463.27
70	1H-NMR (DMSO-D6) δ: 10.35 (1H, s), 9.37 (1H, s), 8.30-8.21 (2H, m), 7.81 (1H, br s), 7.32 (1H, s), 5.31 (1H, d, J = 4.6 Hz), 4.71-4.64 (1H, m), 4.50 (1H, br s), 3.87-3.75 (14H, m), 3.24 (2H, br s), 1.69 (2H, br s), 1.46-1.08 (6H, m).	480.2	479.26
71	1H-NMR (DMSO-D6) δ: 10.15 (1H, s), 9.33 (1H, s), 8.35 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 1.8 Hz), 7.69 (1H, dd, J = 8.7, 2.3 Hz), 7.26 (1H, s), 5.27 (1H, s), 4.75-4.63 (2H, m), 4.45-4.33 (3H, m), 3.75-3.67 (1H, m), 3.26-3.18 (5H, m), 2.80 (2H, d, J = 11.0 Hz), 2.70 (1H, s), 1.94-1.85 (4H, m), 1.65-1.57 (4H, m), 1.46-1.28 (5H, m), 1.15-1.04 (2H, m).	495.25	493.28
72	1H-NMR (DMSO-D6) δ: 10.31 (1H, s), 9.34 (1H, s), 8.44 (1H, d, J = 8.7 Hz), 8.30 (1H, d, J = 2.7 Hz), 7.81 (1H, dd, J = 9.1, 2.7 Hz), 7.27 (1H, s), 5.28 (1H, d, J = 4.6 Hz), 4.69-4.64 (1H, m), 3.83-3.69 (6H, m), 3.19 (2H, br s), 2.80 (2H, br s), 2.33 (3H, s), 1.76-1.64 (6H, m), 1.39 (3H, d, J = 6.9 Hz).	463.25	462.25
73	1H-NMR (DMSO-D6) δ: 10.09 (1H, s), 9.23 (1H, s), 8.27 (1H, d, J = 2.7 Hz), 8.05 (1H, d, J = 9.1 Hz), 7.77 (1H, dd, J = 8.9, 2.5 Hz), 7.00 (1H, s), 5.18 (1H, d, J = 4.6 Hz), 4.63-4.57 (1H, m), 3.90 (4H, br s), 3.69 (2H, t, J = 5.5 Hz), 3.16 (2H, s), 2.77 (2H, br s), 2.31 (3H, s), 1.94-1.88 (4H, m), 1.38 (3H, d, J = 6.4 Hz).	449.2	448.23

[1137]

[1138] [表74]

[1139]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
74	1H-NMR (DMSO-D6) δ: 10.38 (1H, s), 9.37 (1H, s), 8.31 (1H, s), 8.25 (1H, d, J = 8.7 Hz), 7.84 (1H, d, J = 9.1 Hz), 7.32 (1H, s), 5.31 (1H, d, J = 4.6 Hz), 4.71-4.64 (1H, m), 3.86-3.71 (10H, m), 3.19 (2H, s), 2.80 (2H, s), 2.32 (3H, s), 1.39 (3H, d, J = 6.4 Hz).	465.2	464.23
75	1H-NMR (DMSO-D6) δ: 9.90 (1H, s), 9.19 (1H, s), 8.17 (1H, s), 7.91 (1H, d, J = 8.4 Hz), 7.69 (1H, d, J = 8.4 Hz.), 6.99 (1H, s), 5.23 (1H, d, J = 4.4 Hz), 4.62-4.64 (1H, m), 4.41 (1H, br s), 4.28-4.30 (2H, m), 3.47-3.49 (2H, m), 3.34(1H, s), 2.40 (10H, br s), 1.83-1.87 (4H, m), 1.60 (6H, s), 1.31-1.41 (3H, d, J = 6.4 Hz).	507.35	506.31
76	1H-NMR (DMSO-D6) δ: 10.19 (1H, s), 9.34 (1H, s), 8.31 (1H, d, J = 8.4 Hz), 8.21 (1H, s), 7.68 (1H, dd, J1 = 2 Hz, J = 8.4 Hz.), 7.28 (1H, s), 5.28 (1H, br s), 4.56-4.69 (3H, m), 3.45-3.48 (5H, m), 3.03-3.08 (2H, br m), 2.35-2.38 (10H, m), 1.95-1.98 (2H, br m), 1.74-1.84 (2H, br m), 1.40 (3H, d, J = 6.4 Hz).	537.35	536.29
77	1H-NMR (DMSO-D6) δ: 10.21 (1H, s), 9.35 (1H, s), 8.21-8.25 (2H, m), 7.69-7.71 (1H, d, J = 8.8 Hz), 7.29 (1H, s), 5.31 (1H, d, J = 4.8 Hz), 4.66-4.70 (1H, m), 4.35-4.38 (1H, m), 3.79-3.84 (14H, m), 3.46-3.49 (4H, m), 2.54 (6H, s), 2.35-2.37 (8H, m), 2.29 (3H, s), 1.40 (3H, d, J = 6.4 Hz).	508.35	507.31
78	1H-NMR (DMSO-D6) δ: 10.21 (1H, s), 9.36 (1H, s), 8.29 (1H, d, J = 8.4 Hz), 8.21 (1H, s), 7.74 (1H, d, J = 7.2 Hz.), 7.03 (1H, s), 5.32 (1H, d, J = 4.8 Hz), 4.87-5.03 (1H, br d), 4.66-4.69 (1H, m), 3.37 (1H, br s), 4.03 (2H, br s), 3.74-3.71 (2H, br m), 3.44-3.49 (4H, s), 2.35-2.38 (10H, m), 2.06-2.09 (2H, br m), 1.89-1.90 (2H, br m), 1.40 (3H, d, J = 6.4 Hz).	511.35	510.29
79	1H-NMR (DMSO-D6) δ: 10.26 (1H, s), 9.38 (1H, s), 8.19-8.22 (2H, m), 7.75 (1H, d, J = 8.4 Hz.), 7.34 (1H, s), 5.34 (1H, d, J = 4.4 Hz), 4.67-4.70 (1H, m), 4.46-4.50 (1H, br s), 3.98-3.99 (4H, br m), 3.46 (4H, s), 2.33-2.41 (10H, br m), 2.12-2.19 (4H, br m), 1.41 (3H, d, J = 6.4 Hz).	529.3	528.28
80	1H-NMR (DMSO-D6) δ: 10.05 (1H, s), 9.33 (1H, s), 8.04 (1H, d, J = 8.2 Hz), 7.47 (1H, d, J = 8.7 Hz), 7.31 (1H, s), 5.31 (1H, d, J = 4.1 Hz), 4.72-4.62 (1H, m), 4.06-3.90 (4H, m), 3.82 (2H, s), 3.02 (2H, t, J = 5.7 Hz), 2.70 (2H, t, J = 5.3 Hz), 2.22-2.05 (4H, m), 1.39 (3H, d, J = 6.4 Hz).	442.3	441.21

[1140] [表75]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
81	1H-NMR (DMSO-D6) δ: 10.08 (1H, s), 9.34 (1H, s), 8.05 (1H, d, J = 8.7 Hz), 7.51 (1H, d, J = 8.7 Hz), 7.31 (1H, s), 5.30 (1H, d, J = 4.6 Hz), 4.72-4.63 (1H, m), 4.49 (1H, t, J = 5.3 Hz), 4.06-3.90 (4H, m), 3.63-3.55 (4H, m), 2.86-2.74 (4H, m), 2.58 (2H, t, J = 6.2 Hz), 2.22-2.05 (4H, m), 1.39 (3H, d, J = 6.4 Hz).	486.48	485.24
82	1H-NMR (DMSO-D6) δ: 10.08 (1H, s), 9.34 (1H, s), 8.04 (1H, d, J = 8.7 Hz), 7.50 (1H, d, J = 8.2 Hz), 7.31 (1H, s), 5.31 (1H, d, J = 4.1 Hz), 4.73-4.62 (1H, m), 4.06-3.89 (4H, m), 3.57 (2H, s), 2.86-2.73 (4H, m), 2.62-2.54 (2H, m), 2.47-2.39 (2H, m), 2.24-2.05 (10H, m), 1.39 (3H, d, J = 6.4 Hz).	513.4	512.28
83	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.23 (1H, s), 8.19 (1H, d, J = 2 Hz), 7.96 (1H, d, J = 8.4 Hz), 7.70 (1H, dd, J1 = 2 Hz, J2 = 2.4 Hz), 7.03 (1H, s), 5.21 (1H, d, J = 4.0 Hz), 4.84-4.83 (1H,br m), 4.61-4.64 (1H, m), 4.34-4.36 (1H, m), 4.16-4.19 (1H, m), 3.88-3.91 (1H, m), 3.46-3.49 (2H, m), 3.43-3.45 (2H, m), 2.34-2.50 (10H, br m), 2.08-2.11 (1H, m), 1.97-2.06 (1H, m), 1.80-1.83 (1H, m), 1.63-1.67 (1H, m), 1.39 (3H, d, J = 4.0 Hz), 1.17 (3H, d, J = 4.0 Hz).	493.35	492.30
84	1H-NMR (DMSO-D6) δ: 10.22 (1H, s), 9.36 (1H, s), 8.21-8.26 (2H, m), 7.66 (1H, d, J = 8.0 Hz), 7.31 (1H, s), 5.31 (1H, d, J = 8.0 Hz), 4.77-4.87 (2H, m), 4.67-4.70 (1H, m), 4.34-4.37 (1H, m), 3.33-3.49 (4H, m), 2.90-2.98 (2H, m), 2.60-2.67 (1H, m), 2.34-2.37 (10H, m), 1.92-1.95 (2H, m), 1.71-1.74 (2H, m), 1.41 (3H, d, J = 8.0 Hz)	561.30	560.28
85	1H-NMR (DMSO-D6) δ: 10.27 (1H, s), 9.40 (1H, s), 8.22 (1H, d, J = 2 Hz), 8.08 (1H, d, J = 8.4 Hz), 7.76-7.79 (1H, m), 7.38 (1H, s), 5.35 (1H, d, J = 4.8 Hz), 4.69-4.73 (1H, m), 4.42 (4H, br s), 4.34-4.37 (1H, m), 3.45-3.49 (4H, m), 3.28-2.29 (4H, br m), 2.34-2.38 (10H, br m), 1.41 (3H, d, J = 6.8 Hz).	543.30	542.24
86	1H-NMR (CDCl3) δ: 8.97 (1H, s), 8.02-7.95 (2H, m), 7.36 (1H, d, J = 8.7 Hz), 6.62 (1H, s), 4.77 (1H, q, J = 6.4 Hz), 4.01 (4H, br s), 3.46 (1H, s), 3.03 (4H, t, J = 4.6 Hz), 2.85 (4H, t, J = 4.6 Hz), 2.47 (3H, s), 1.98 (4H, t, J = 6.6 Hz), 1.50 (3H, d, J = 6.4 Hz).	435.3	434.25
87	1H-NMR (CDCl3) δ: 9.03 (1H, s), 8.30-8.24 (2H, m), 7.39 (1H, d, J = 8.7 Hz), 6.90 (1H, s), 5.26 (2H, s), 4.81 (1H, q, J = 6.4 Hz), 3.81 (4H, t, J = 5.3 Hz), 3.01 (4H, t, J = 4.8 Hz), 2.85 (4H, t, J = 4.6 Hz), 2.45 (3H, s), 1.83-1.77 (4H, m), 1.75-1.69 (2H, m), 1.49 (3H, d, J = 6.9 Hz).	449.3	448.27

[1141]

[1142] [表76]

[1143]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
88	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.29 (1H, d, J = 8.7 Hz), 8.14 (1H, s), 7.42 (1H, d, J = 9.1 Hz), 6.90 (1H, s), 4.83 (1H, q, J = 6.4 Hz), 3.85 (4H, t, J = 5.3 Hz), 3.67 (2H, t, J = 5.3 Hz), 2.95 (4H, t, J = 4.8 Hz), 2.72 (4H, br s), 2.65 (2H, t, J = 5.3 Hz), 2.48 (3H, s), 1.88-1.80 (4H, m), 1.78-1.72 (2H, m), 1.51 (3H, t, J = 5.9 Hz).	493.3	492.30
89	1H-NMR (CDCl3) δ: 9.09 (1H, d, J = 2.3 Hz), 8.59 (1H, d, J = 9.1 Hz), 8.43 (1H, s), 8.21 (1H, d, J = 2.7 Hz), 7.63 (1H, dd, J = 9.1, 2.7 Hz), 6.93 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 3.88-3.82 (6H, m), 3.17-3.11 (4H, m), 2.89-2.84 (2H, m), 1.88-1.81 (4H, m), 1.77-1.72 (2H, m), 1.52 (3H, d, J = 6.4 Hz).	463.3	462.25
90	1H-NMR (DMSO-D6) δ: 10.75 (1H, s), 9.96 (1H, s), 9.16 (1H, d, J = 7.0 Hz), 9.12 (1H, d, J = 1.8 Hz), 8.71 (1H, dd, J = 7.1, 2.0 Hz), 8.32 (1H, s), 6.72 (1H, d, J = 3.7 Hz), 6.42 (1H, d, J = 39.2 Hz), 6.24-6.18 (1H, m), 5.72-5.63 (2H, m), 5.53-5.44 (2H, m), 5.40 (2H, t, J = 4.0 Hz), 5.22 (2H, s), 4.92 (2H, s), 4.20-4.10 (2H, m), 3.99 (2H, br s), 3.59 (3H, d, J = 5.1 Hz).	467.3	466.22
91	1H-NMR (CDCl3) δ: 9.06 (1H, s), 8.59 (1H, d, J = 10.1 Hz), 8.32 (1H, s), 7.05 (1H, d, J = 9.6 Hz), 6.92 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 3.83 (4H, t, J = 5.3 Hz), 3.57 (4H, t, J = 5.0 Hz), 3.04 (4H, t, J = 5.3 Hz), 1.84-1.70 (6H, m), 1.52 (4H, d, J = 6.9 Hz).	436.3	435.25
92	1H-NMR (CDCl3) δ: 9.06 (1H, s), 8.53 (1H, d, J = 8.2 Hz), 8.36 (1H, s), 8.27 (1H, d, J = 2.3 Hz), 7.75 (1H, dd, J = 8.2, 2.3 Hz), 6.86 (1H, s), 4.03 (2H, t, J = 5.3 Hz), 3.85-3.75 (4H, m), 3.50 (2H, s), 2.98 (2H, t, J = 5.3 Hz), 2.94-2.86 (4H, m), 2.53-2.36 (4H, br m), 1.93-1.83 (4H, m), 1.80-1.71 (2H, m).	449.4	448.27
93	1H-NMR (CDCl3) δ: 9.09 (1H, s), 8.65 (1H, d, J = 9.1 Hz), 8.57 (1H, s), 8.35 (1H, d, J = 2.3 Hz), 7.76 (1H, dd, J = 8.7, 2.7 Hz), 6.87 (1H, s), 4.03 (2H, t, J = 5.3 Hz), 3.84-3.71 (8H, m), 3.27 (2H, t, J = 5.3 Hz), 2.98 (2H, t, J = 5.3 Hz), 1.92-1.82 (4H, m), 1.79-1.68 (2H, m).	449.3	448.23
94	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.61 (1H, d, J = 10.1 Hz), 8.35 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 6.86 (1H, s), 4.03 (2H, t, J = 5.3 Hz), 3.80-3.72 (4H, m), 3.61-3.55 (4H, m), 3.08-3.02 (4H, m), 2.97 (2H, t, J = 5.3 Hz), 1.88-1.78 (4H, m), 1.78-1.68 (2H, m).	436.3	435.25

[1144] [表77]

[1145]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
95	1H-NMR (DMSO-D6) δ: 9.93 (1H, s), 9.21 (1H, s), 8.19 (1H, d, J = 8.2 Hz), 7.45 (1H, d, J = 8.7 Hz), 7.01 (1H, s), 4.60 (1H, t, J = 5.3 Hz), 3.84-3.69 (8H, m), 3.01 (2H, t, J = 5.9 Hz), 2.81 (2H, t, J = 6.9 Hz), 2.70 (2H, t, J = 5.7 Hz), 1.77-1.60 (6H, m).	406.3	405.23
96	1H-NMR (DMSO-D6) δ: 10.15 (1H, s), 9.32 (1H, s), 8.34 (1H, d, J = 8.7 Hz), 8.20 (1H, d, J = 1.8 Hz), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 7.22 (1H, s), 5.36 (1H, s), 4.50 (2H, d, J = 3.7 Hz), 4.35 (1H, s), 3.73 (4H, br s), 3.47-3.41 (4H, m), 2.44-2.32 (10H, m), 1.75-1.63 (6H, m).	479.3	478.28
97	1H-NMR (DMSO-D6) δ: 10.35 (1H, br s), 9.32 (1H, s), 8.42 (1H, d, J = 8.2 Hz), 8.31 (1H, s), 7.77 (1H, d, J = 8.0 Hz), 7.21 (1H, s), 5.36 (1H, s), 4.49 (2H, s), 3.76-3.63 (6H, m), 3.50 (2H, s), 3.12 (2H, s), 1.75-1.61 (6H, m).	435.2	434.22
98	1H-NMR (DMSO-D6) δ: 9.98 (1H, s), 9.23 (1H, s), 8.19 (1H,d, J = 4.0 Hz), 7.94 (1H, d, J = 12 Hz), 7.70 (1H, d, J = 2.0 Hz), 7.00 (1H, s), 5.17 (1H, d, J = 8.0 Hz), 4.89-4.90 (1H, br m), 4.59-4.61 (1H, m), 4.35-4.38 (1H, m), 4.15-4.18 (1H, m), 3.86-3.90 (1H, m), 3.34-3.49 (4H, m), 2.34-2.49 (10H, m), 2.97-1.10 (2H, m), 1.81-1.84 (1H, m), 1.63-1.68 (1H, m), 1.41 (3H, d, J = 4.0 Hz), 1.16 (3H, d, J = 8.0 Hz).	493.30	492.30
99	1H-NMR (DMSO-D6) δ: 9.94 (1H, s), 9.22 (1H, s), 8.18 (1H, d, J = 1.6 Hz), 7.95 (1H, d, J = 8.4 Hz), 7.65-7.68 (1H, m), 6.99 (1H, s), 5.17 (1H, d, J = 4.4 Hz), 4.58-4.63 (1H, m), 4.34-4.37 (1H, m), 4.17-4.21 (1H, br m), 3.92-3.98 (1H, br m), 3.77-3.87 (1H, br m), 3.43-3.49 (5H, m), 2.34-2.37 (11H, br m), 2.05 (1H, br s), 1.45-1.58 (1H, m), 1.38 (3H, d, J = 6.4 Hz), 1.09 (3H, d, J = 6.8 Hz).	493.40	492.30
100	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.22 (1H, s), 8.18 (1H,d, J = 1.6 Hz), 7.97 (1H, d, J = 8.8 Hz), 7.68 (1H, dd, J1 = 2.4 Hz, J2 = 2.0 Hz), 6.99 (1H, s), 5.18 (1H, d, J = 4.0 Hz), 4.58-4.61 (1H, m), 4.34-4.37 (1H, m), 4.10-4.20 (1H, m), 3.91-3.99 (1H, m), 3.79-3.87 (1H, m), 3.43-3.45 (5H, m), 2.27-2.37 (11H, br m), 2.01-2.10 (1H, br m), 1.47-1.52 (1H, m), 1.40 (3H, d, J = 6.4 Hz), 1.10 (3H, d, J = 6.4 Hz)	493.35	492.30

[1146] [表78]

[1147]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
101	1H-NMR (DMSO-D6) δ: 9.80 (1H, s), 9.21 (1H, s), 8.18 (1H, d, J = 1.6 Hz), 7.73 (2H, dd, J1 =2.0 Hz, J2 = 2.0 Hz), 6.98 (1H, s), 5.18 (1H, d, J = 4.0 Hz), 4.98-4.99 (1H, m), 4.88-4.89 (1H, m), 4.59-4.61 (1H, m), 4.35-4.38 (1H, m), 3.50-3.43 (4H, m), 2.34-2.38 (10H, br m), 2.01-2.05 (2H, m), 1.73-1.74 (2H, m), 1.40 (3H, d, J = 4.0 Hz), 1.24-1.25(6H, m).	507.35	506.31
102	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.22 (1H, s), 8.18 (1H, d, J = 2.0 Hz), 7.93 (1H, d, J = 8.0 Hz), 7.67 (1H, dd, J1 = 2.0 Hz, J2 = 2.0 Hz), 6.99 (1H, s), 5.19 (1H, d, J = 4.0 Hz), 4.59-4.62 (1H, m), 4.35-4.38 (1H, m), 3.90-3.94 (2H, m), 3.77 (2H, s), 3.43-3.48 (4H, m), 2.34-2.37 (10H, br m), 1.69-1.73 (2H, m), 1.38-1.39 (3H, m), 1.08-1.09 (6H, s).	507.35	506.31
103	1H-NMR (DMSO-D6) δ: 10.19 (1H, s), 9.32 (1H, s), 8.37 (1H, d, J = 8.0 Hz), 8.22 (1H, d, J = 1.6 Hz), 7.72 (1H, dd, J1 = 1.6 Hz, J2 = 1.6 Hz), 7.24 (1H, s), 5.27 (1H, d, J = 4.0 Hz), 5.20 (2H, s), 4.64-4.67 (1H, m), 4.35-4.37 (1H, br s), 3.45-3.48 (4H, br m), 2.31-2.39 (8H, br s), 1.78-1.80 (4H, br m), 1.49 (4H, d, J = 6.4 Hz), 1.40 (3H, d, J = 6.4 Hz), 1.23 (2H, s).	505.35	504.30
104	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.24 (1H, s), 8.19 (1H,d, J = 1.5 Hz), 7.95 (1H, d, J = 9.0 Hz), 7.71 (1H, d, J = 12 Hz), 7.04 (1H, s), 5.20 (1H, d, J = 3.0 Hz), 4.62-4.58 (1H, m), 4.42-4.49 (2H, m), 4.34-4.38 (1H, m), 3.68-3.72 (2H, m), 3.44-3.50 (4H, m), 2.34-2.38 (10H, br m), 1.64-1.67 (2H, br m), 1.38 (3H, d, J = 6.0 Hz), 0.69-0.71 (1H, m), 0.18-0.22 (1H, m).	491.30	490.28
105	1H-NMR (DMSO-D6) δ: 10.08 (1H, s), 9.27 (1H, s), 8.19 (1H,d, J = 2.0 Hz), 8.06 (1H, d, J = 8.0 Hz), 7.68 (1H, dd, J1 = 2.4 Hz, J2 = 2.4 Hz), 7.10 (1H, s), 5.42 (2H, d, J = 24 Hz), 5.22 (1H, d, J = 4.0 Hz), 4.61-4.64 (1H, m), 4.34-4.37 (1H, m), 3.41-3.44 (4H, m), 2.36-2.37 (10H, br m), 1.96-1.98 (2H, m), 1.84-1.85 (3H, m), 1.78-1.80 (2H, m), 1.41-1.51 (3H, m), 1.39-1.40 (3H, m).	519.40	518.31
106	1H-NMR (DMSO-D6) δ: 10.17 (1H, s), 9.34 (1H, s), 8.38 (1H, d, J = 9.0 Hz), 8.22 (1H, d, J = 3.0 Hz), 7.72 (1H, dd, J1 = 2.1 Hz, J2 = 2.1 Hz), 7.27 (1H, s), 5.29 (1H, d, J = 6.0 Hz), 4.76 (1H, d, 3.0 Hz), 4.63-4.71 (1H, m), 4.34-4.45 (3H, m), 3.71-3.77 (1H, m), 3.45-3.49 (4H, m), 3.18-3.27 (2H, m), 2.27-2.38 (10H, br m), 1.91-1.95 (2H, br m), 1.64-1.67 (2H, br m), 1.39 (3H, d, J = 3.0 Hz).	509.35	508.29

[1148] [表79]

[1149]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
107	1H-NMR (DMSO-D6) δ: 10.27 (1H, s), 9.28 (1H, s), 8.23 (1H, d, J = 10.1 Hz), 7.37 (1H, d, J = 10.1 Hz), 7.18 (1H, s), 5.33 (1H, br s), 4.48 (2H, d, J = 3.7 Hz), 3.70 (4H, br s), 3.43 (4H, t, J = 5.0 Hz), 2.82 (4H, t, J = 5.0 Hz), 1.64 (6H, br s).	422.2	421.23
108	1H-NMR (DMSO-D6) δ: 10.13 (1H, s), 9.32 (1H, s), 8.33 (1H, d, J = 8.2 Hz), 8.20 (1H, d, J = 1.8 Hz), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 7.22 (1H, s), 5.35 (1H, br s), 4.50 (2H, d, J = 4.6 Hz), 3.74 (4H, br s), 3.41 (2H, s), 2.66 (4H, t, J = 4.6 Hz), 2.28 (4H, br s), 1.75-1.63 (6H, m).	435.25	434.25
109	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.22 (1H, s), 8.20 (1H, d, J = 8.2 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.01 (1H, s), 4.60 (1H, t, J = 5.5 Hz), 4.49 (1H, t, J = 5.5 Hz), 3.81-3.70 (6H, m), 3.62-3.54 (4H, m), 2.86-2.74 (6H, m), 2.57 (2H, t, J = 6.2 Hz), 1.77-1.60 (6H, m).	450.3	449.25
110		477.3	476.30
111	1H-NMR (DMSO-D6) δ: 9.96 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J = 8.7 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.24 (1H, d, J = 0.9 Hz), 5.25 (1H, d, J = 4.6 Hz), 4.71-4.60 (1H, m), 4.48 (1H, t, J = 5.3 Hz), 3.84-3.66 (4H, m), 3.64-3.54 (4H, m), 2.86-2.74 (4H, m), 2.58 (2H, t, J = 6.2 Hz), 1.79-1.59 (6H, m), 1.38 (3H, d, J = 6.4 Hz).	450.3	449.25
112		468.3	467.24
113	1H-NMR (DMSO-D6) δ: 9.94 (1H, s), 9.21 (1H, s), 8.18 (1H, s), 7.95 (1H, d, J = 9.0 Hz), 7.64-7.68 (1H, m), 6.98 (1H, s), 5.16 (1H, d, J = 6.0 Hz), 4.56-4.59 (1H, m), 4.33-4.37 (1H, m), 3.96-3.99 (2H, m), 3.66-3.67 (2H, m), 3.43-3.50 (5H, m), 2.27-2.38 (12H, br m), 1.39 (3H, d, J =6.0 Hz), 0.96 (6H, d, J = 6.0 Hz)	507.40	506.31
114	1H-NMR (CDCl3) δ: 9.08 (1H, s), 8.61 (1H, d, J = 9.6 Hz), 8.42 (1H, s), 7.06 (1H, d, J = 9.6 Hz), 6.93 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 3.98 (1H, br s), 3.82 (4H, t, J = 5.3 Hz), 3.61 (4H, t, J = 5.0 Hz), 3.20 (2H, t, J = 6.4 Hz), 3.05 (3H, s), 2.95 (2H, t, J = 6.4 Hz), 2.68 (4H, t, J = 4.8 Hz), 1.83-1.71 (6H, m), 1.52 (3H, d, J = 6.4 Hz).	542.3	541.26
115	1H-NMR (CDCl3) δ: 9.12 (1H, s), 8.51 (1H, s), 8.45 (1H, d, J = 8.2 Hz), 8.28 (1H, d, J = 1.8 Hz), 7.73 (1H, dd, J = 8.7, 2.3 Hz), 7.00 (1H, s), 5.05-4.80 (2H, m), 4.12-4.03 (2H, m), 3.96-3.90 (2H, m), 3.51 (2H, s), 2.55 (8H, s), 2.34 (3H, s), 2.23-2.03 (4H, m), 1.53 (3H, d, J = 6.4 Hz).	481.3	480.28

[1150] [表80]

[1151]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
116	1H-NMR (CDCl3) δ: 9.03 (1H, d, J = 4.1 Hz), 8.22 (1H, d, J = 1.8 Hz), 8.17 (1H, d, J = 8.2 Hz), 8.09 (1H, s), 7.68 (1H, dd, J = 8.7, 2.3 Hz), 6.76 (1H, s), 5.39 (1H, d, J = 53.1 Hz), 4.81 (1H, q, J = 6.4 Hz), 4.46-4.12 (5H, m), 3.50 (2H, s), 2.62-2.38 (10H, m), 2.34 (3H, s), 1.53 (3H, d, J = 6.4 Hz).	467.3	466.26
117		467.3	466.26
118	1H-NMR (CDCl3) δ: 9.18-9.05 (2H, m), 8.61 (1H, d, J = 9.6 Hz), 7.08-7.01 (2H, m), 4.34 (1H, q, J = 6.3 Hz), 3.75 (4H, br s), 3.58 (4H, br s), 3.37 (3H, s), 3.06 (4H, br s), 1.79-1.65 (6H, m), 1.46 (3H, d, J = 6.4 Hz).	450.3	449.27
119		463.3	462.29
120	1H-NMR (CDCl3) δ: 9.01 (1H, s), 8.31-8.26 (2H, m), 8.19 (1H, d, J = 2.7 Hz), 7.58 (1H, dd, J = 8.9, 2.5 Hz), 6.67 (1H, s), 4.79 (1H, q, J = 6.4 Hz), 4.40 (1H, br s), 4.03 (4H, br s), 3.88-3.84 (2H, m), 2.90-2.86 (2H, m), 2.76-2.70 (4H, m), 2.41 (3H, s), 2.03-1.98 (4H, m), 1.51 (3H, d, J = 6.4 Hz).	463.3	462.25
121	1H-NMR (CDCl3) δ: 9.15 (1H, s), 8.96 (1H, s), 8.60 (1H, d, J = 8.7 Hz), 8.27 (1H, d, J = 2.3 Hz), 7.63 (1H, dd, J = 9.1, 2.7 Hz), 6.94 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 4.07 (1H, br s), 3.90-3.82 (6H, m), 2.91-2.87 (2H, m), 2.75 (4H, t, J = 8.9 Hz), 2.42 (3H, s), 1.87-1.80 (4H, m), 1.76-1.71 (2H, m), 1.52 (3H, d, J = 6.4 Hz).	477.3	476.26
122		477.3	476.30
123	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.58 (1H, d, J = 9.6 Hz), 8.51 (1H, s), 7.05 (1H, d, J = 10.1 Hz), 6.93 (1H, s), 4.83 (1H, q, J = 6.4 Hz), 4.02 (1H, s), 3.82 (4H, t, J = 5.3 Hz), 3.63 (4H, t, J = 5.0 Hz), 2.58 (4H, t, J = 5.3 Hz), 2.36 (3H, s), 1.85-1.77 (6H, m), 1.52 (3H, d, J = 6.4 Hz).	450.3	449.27
124	1H-NMR (CDCl3) δ: 9.15 (1H, s), 8.73 (1H, s), 8.50 (1H, d, J = 9.6 Hz), 7.05 (1H, d, J = 9.6 Hz), 7.00 (1H, s), 4.99-4.80 (2H, m), 4.10-4.01 (2H, m), 3.90-3.77 (3H, m), 3.63 (4H, t, J = 5.0 Hz), 2.57 (4H, t, J = 5.0 Hz), 2.36 (3H, s), 2.19-1.95 (4H, m), 1.52 (3H, d, J = 6.4 Hz).	468.3	467.26
125	1H-NMR (CDCl3) δ: 9.18 (1H, s), 8.78 (1H, s), 8.54 (1H, d, J = 10.1 Hz), 7.12 (1H, s), 7.06 (1H, d, J = 10.1 Hz), 4.97-4.80 (1H, m), 4.35 (1H, q, J = 6.6 Hz), 4.13-4.02 (2H, m), 3.83-3.74 (2H, m), 3.63 (4H, t, J = 5.0 Hz), 3.38 (3H, s), 2.57 (4H, t, J = 5.0 Hz), 2.35 (3H, s), 2.18-1.97 (4H, m), 1.47 (3H, d, J = 6.4 Hz).	482.3	481.27

[1152] [表81]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
126	1H-NMR (CDCl3) δ: 9.17 (1H, s), 8.82 (1H, s), 8.53 (1H, d, J = 9.6 Hz), 7.12 (1H, s), 7.05 (1H, d, J = 9.6 Hz), 4.96-4.80 (1H, m), 4.35 (1H, q, J = 6.4 Hz), 4.12-4.02 (2H, m), 3.84-3.75 (2H, m), 3.57 (4H, br s), 3.38 (3H, s), 3.04 (4H, br s), 2.06 (4H, d, J = 48.5 Hz), 1.47 (3H, d, J = 6.9 Hz).	468.3	467.26
127	1H-NMR (CDCl3) δ: 9.14 (1H, s), 8.93 (1H, s), 8.60 (1H, d, J = 9.1 Hz), 8.29 (1H, d, J = 2.3 Hz), 7.65 (1H, dd, J = 8.7, 2.7 Hz), 6.94 (1H, s), 4.84 (1H, q, J = 6.3 Hz), 3.86 (7H, td, J = 9.7, 5.0 Hz), 3.76 (2H, s), 3.18 (2H, t, J = 5.5 Hz), 1.96-1.91 (2H, m), 1.83-1.73 (6H, m), 1.52 (3H, d, J = 6.4 Hz).	463.3	462.25
128		499.3	498.27
129	1H-NMR (CDCl3) δ: 9.15 (1H, s), 8.46-8.43 (2H, m), 8.27 (1H, d, J = 1.8 Hz), 7.75 (1H, dd, J = 8.7, 2.3 Hz), 7.32 (1H, s), 6.56 (1H, t, J = 56.0 Hz), 4.58-4.51 (2H, m), 4.04-3.97 (1H, m), 3.61 (2H, q, J = 5.2 Hz), 3.51 (2H, s), 3.46-3.38 (2H, m), 2.57-2.50 (10H, m), 2.15-2.08 (2H, m), 1.86-1.77 (2H, m).	515.3	514.26
130	1H-NMR (DMSO-D6) δ: 9.96 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J = 8.2 Hz), 7.50 (1H, d, J = 8.2 Hz), 7.24 (1H, s), 5.25 (1H, d, J = 4.6 Hz), 4.71-4.61 (1H, m), 4.51-4.40 (1H, m), 3.84-3.66 (4H, m), 3.57-3.43 (4H, m), 2.86-2.78 (2H, m), 2.77-2.69 (2H, m), 2.56-2.48 (2H, m), 1.79-1.59 (8H, m), 1.38 (3H, d, J = 6.4 Hz).	464.55	463.27
131	1H-NMR (DMSO-D6) δ: 10.00 (1H, s), 9.29 (1H, s), 8.27 (1H, d, J = 9.1 Hz), 8.11 (1H, d, J = 2.7 Hz), 7.55 (1H, dd, J = 9.1, 3.2 Hz), 7.23 (1H, d, J = 0.9 Hz), 5.24 (1H, d, J = 4.6 Hz), 4.73-4.52 (2H, m), 4.49-4.38 (2H, m), 3.83-3.67 (4H, m), 3.54-3.46 (2H, m), 3.22-3.11 (1H, m), 2.82-2.73 (1H, m), 2.54-2.41 (2H, m), 2.34-2.17 (2H, m), 2.13-2.03 (1H, m), 1.77-1.48 (7H, m), 1.38 (3H, d, J = 6.4 Hz).	512.53	511.27
132	1H-NMR (DMSO-D6) δ: 10.00 (1H, s), 9.29 (1H, s), 8.28 (1H, d, J = 9.1 Hz), 8.10 (1H, d, J = 3.2 Hz), 7.55 (1H, dd, J = 8.9, 3.0 Hz), 7.23 (1H, d, J = 0.9 Hz), 5.24 (1H, d, J = 4.6 Hz), 4.93-4.75 (1H, m), 4.70-4.52 (2H, m), 4.41 (1H, t, J = 5.3 Hz), 3.84-3.66 (4H, m), 3.50 (2H, q, J = 5.8 Hz), 3.02-2.88 (1H, m), 2.76-2.40 (4H, m), 2.40-2.28 (1H, m), 1.97-1.60 (8H, m), 1.38 (3H, d, J = 6.4 Hz).	512.57	511.27
133		471.3	470.24

[1153]

[1154] [表82]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
134	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.51-8.45 (2H, m), 8.27 (1H, s), 7.74 (1H, t, J = 4.3 Hz), 6.97 (1H, s), 4.85 (1H, q, J = 6.4 Hz), 4.53-4.47 (2H, m), 4.04-3.97 (1H, m), 3.50-3.39 (4H, m), 2.49 (8H, br s), 2.29 (3H, s), 2.15-1.82 (4H, m), 1.53 (3H, d, J = 6.4 Hz).	479.3	478.28
135	1H-NMR (DMSO-D6) δ: 9.99 (1H, s), 9.29 (1H, s), 8.21 (1H, d, J = 8.2 Hz), 7.52 (1H, d, J = 8.7 Hz), 7.20 (1H, s), 5.33 (1H, t, J = 5.7 Hz), 4.69-4.44 (3H, m), 3.80-3.58 (8H, m), 2.86 (4H, br s), 2.70-2.63 (2H, m), 1.75-1.62 (6H, m).	436.25	435.24
136	1H-NMR (DMSO-D6) δ: 9.91 (1H, s), 9.23 (1H, s), 8.19 (1H, d, J = 2.1 Hz), 7.96 (1H, d, J = 9.7 Hz), 7.05 (1H, dd, J1 = 2.1 Hz, J2 = 8.4 Hz), 7.00 (1H, s), 5.16 (1H, d, 4.5 Hz), 4.87-4.93 (1H, m), 4.58-4.62 (1H, m), 4.14-4.18 (1H, m), 3.86-3.88 (1H, m), 3.46 (2H, s), 2.49 (8H, m), 2.23 (3H, s), , 2.11-1.94 (2H, m), 1.80-1.86 (1H, m), 1.62-1.67 (1H, m), 1.42 (3H, d, J = 6.3 Hz), 1.17 (3H, d, J = 6.0 Hz).	463.30	462.29
137	1H-NMR (DMSO-D6) δ: 9.98 (1H, s), 9.23 (1H, s), 8.19 (1H, s), 7.95 (1H, d, J = 9.0 Hz), 7.69 (1H, d, J = 12.0 Hz), 7.00 (1H, s), 5.15 (1H, d, J = 6.0 Hz), 4.88-4.93 (1H, m), 4.58-4.62 (1H, m), 4.15-4.18 (1H, m), 3.86-3.93 (1H, m), 3.46 (2H, s), 2.42 (6H, br s), 2.23 (3H, s), 1.81-2.11 (3H, m), 1.63-1.68 (1H, m), 1.41 (3H, d, J = 6.0 Hz) , 1.16 (3H, d, J = 6.0 Hz)	463.30	462.29
138	1H-NMR (300MHz DMSO-d6) δ: 9.93 (1H, s), 9.22 (1H, s), 8.18 (1H, s), 7.96 (1H, d, J = 9.0 Hz), 7.67 (1H, d, J = 6.0 Hz), 6.99 (1H, s), 5.16 (1H, d, J = 6.0 Hz), 4.57-4.61 (1H, m), 4.14-4.20 (1H, m), 3.83-3.96 (2H, m), 3.43-3.52 (4H, m), 2.32-2.36 (8H, br m), 2.14 (3H, s), 2.04-2.06 (1H, m), 1.45-1.55 (1H, m), 1.40 (3H, d, J = 9.0 Hz), 1.10 (3H, d, J = 9.0 Hz).	463.30	462.29
139	1H-NMR (DMSO-D6) δ: 9.94 (1H, s), 9.21 (1H, s), 8.18 (1H, s), 7.96 (1H, d, J = 9.0 Hz), 7.67 (1H, d, J = 6.0 Hz), 6.99 (1H, s), 5.17 (1H, s), 4.61 (1H, br s), 4.15-4.22 (1H, m), 3.97 (1H, s), 3.83 (1H, br s), 3.44 (4H, s), 2.36 (9H, br s) 2.21 (3H, s), 2.06-2.16 (1H, m), 1.48-1.58 (1H, m), 1.38 (3H, d, J = 6.0 Hz), 1.10 (3H, d, J = 9.0 Hz).	463.35	462.29

[1155]

[1156] [表83]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
140	1H-NMR (DMSO-D6) δ: 9.78 (1H, s), 9.21 (1H, s), 8.19 (1H, d, J = 2 Hz), 7.64-7.74 (2H, m), 6.98 (1H, s), 5.17 (1H, d, J = 4.5 Hz), 4.98-5.00 (1H, br m), 4.88-4.91 (1H, br m), 3.43 (2H, s), 2.36 (8H, br s), 2.14 (3H, s), 2.03-2.06 (2H, br m), 1.72-1.77 (2H, m), 1.40 (3H, d, J = 6.3 Hz), 1.25-1.21 (6H, m).	477.35	476.30
141	1H-NMR (DMSO-D6) δ: 9.94 (1H, s), 9.21 (1H, s), 8.19 (1H, s), 7.95 (1H, d, J = 9.0 Hz), 7.66 (1H, d, J = 12.0 Hz), 6.98 (1H, s), 5.17 (1H, d, J = 3.0 Hz), 4.58-4.62 (1H, m), 4.00-4.04 (2H, br m), 3.64-3.67 (2H, br m), 3.44 (2H, s), 2.27-2.37 (10H, br m), 2.13 (3H , s) 0.96 (6H, d, J=6.0 Hz).	477.35	476.30
142	1H-NMR (300MHz DMSO-d6) δ: 9.95 (1H, s), 9.22 (1H, s), 8.18 (1H, s), 7.93 (1H, d, J = 6.0 Hz), 7.65-7.68 (1H, m), 6.99 (1H, s), 5.17 (1H, d, J = 3.0 Hz), 4.58-4.62 (1H, m), 3.90-3.95 (2H, m), 3.77 (2H, s), 3.39-3.48 (2H, m), 2.27-2.37 (6H,br m), 2.16 (3H,s), 1.69-1.74 (2H, m), 1.39 (3H, d, J = 6.0 Hz), 1.10 (6H, s).	477.35	476.30
143	1H-NMR (DMSO-D6) δ: 10.17 (1H, s), 9.32 (1H, s), 8.37 (1H, d, J = 9.0 Hz), 8.22 (1H, s), 7.68-7.72 (1H, m), 7.24 (1H, s), 5.27 (1H, d, J = 3.0 Hz), 5.20 (2H, s), 4.63-4.68 (1H, m), 3.45 (2H, s), 2.27-2.43 (8H, br m), 2.15 (3H, s), 1.77 (4H, s), 1.48 (4H, d, J = 9.0 Hz), 1.40 (3H, d, J = 9.0 Hz).	475.35	474.29
144	1H-NMR (300MHz DMSO-d6) δ: 10.20 (1H, s), 9.36 (1H, s), 8.22-8.26 (2H, m), 7.66 (1H, d, J = 9.0 Hz), 7.31 (1H, s), 5.30 (1H, d, J = 6.0 Hz), 4.77-4.87 (2H, m), 4.67-4.70 (1H, m), 3.46 (2H, s), 2.89-2.97 (2H, m) , 2.55-2.60 (1H, m), 2.32-2.37 (8H, br m), 2.14 (3H, s), 1.94 (2H, d, J = 12 Hz), 1.68-1.76 (2H, br m), 1.40 (3H, d, J = 6.0 Hz).	531.30	530.27
145	1H-NMR (DMSO-D6) δ: 10.20 (1H, s), 9.36 (1H, s), 8.19 (2H, d, J = 12 Hz), 7.74 (1H, d, J = 9 Hz), 7.32 (1H, s), 5.29 (1H, d, J = 6 Hz), 4.69 (1H, s), 3.77-3.84 (8H, m), 3.45 (2H, s), 2.33-2.38 (8H, br m), 2.15 (3H, s), 1.40 (3H, d, J = 6 Hz)	465.30	464.26
146	1H-NMR (DMSO-D6) δ: 10.15 (1H, s), 9.34 (1H, s), 8.40 (1H, d, J = 9 Hz), 8.25 (1H, s), 7.74 (1H, d, J = 9 Hz), 7.26 (1H, s), 5.21 (1H, d, J = 3 Hz), 4.44-4.50 (1H, m), 3.69-3.83 (4H, m), 3.53 (2H, s), 2.73-2.90 (11H, br m), 1.56-1.92 (8H, br m), 0.85-0.90 (3H, m)	477.35	476.30

[1157]

[1158] [表84]

[1159]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
147	1H-NMR (DMSO-D6) δ: 10.09 (1H, d, J = 12.6 Hz), 9.32 (1H, s), 8.22-8.35 (1H, m), 7.66 (1H, d, J = 8.4 Hz), 7.26 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.61-4.74 (3H, m), 3.76-3.85 (6H, br m), 3.05 (2H, d, J = 12.9 Hz), 2.09 (2H, br s), 2.68-2.78 (3H, br m), 1.55-1.80 (10H, br m), 1.39 (3H, d, J = 6.6 Hz).	517.40	516.30
148	1H-NMR (DMSO-D6) δ: 10.08 (1H, d, J = 10.2 Hz), 9.32 (1H, s), 8.26-8.33 (1H, m), 7.66 (1H, d, J = 8.7 Hz), 7.26 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.61-4.73 (3H, m), 4.44 (1H, br m), 3.76-3.83 (6H, br m), 3.52 (2H, br s), 2.90 (3H, br s), 2.72-2.78 (2H, br m), 2.40 (2H, br s), 2.13 (2H, br s), 1.55-1.80 (10H, br m), 1.39 (3H, d, J = 6.3 Hz).	561.35	560.32
149	1H-NMR (DMSO-D6) δ: 10.08 (1H, d, J = 8.4 Hz), 9.32 (1H, s), 8.26-8.33 (1H, m), 7.64-7.68 (1H, m), 7.26 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.61-4.73 (3H, m), 3.72-3.78 (6H, br m), 2.66-2.90 (5H, br m), 2.17 (3H, s), 1.95 (2H, br s), 1.55-1.78 (10H, br m), 1.39 (3H, d, J = 6.3 Hz).	531.40	530.31
150		499.3	498.27
151	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.60 (1H, d, J = 8.7 Hz), 8.52 (1H, s), 8.22 (1H, d, J = 2.7 Hz), 7.63 (1H, dd, J = 8.7, 2.7 Hz), 6.93 (1H, s), 4.84 (1H, q, J = 6.6 Hz), 3.89-3.85 (6H, m), 3.67 (2H, t, J = 5.3 Hz), 2.88 (6H, dd, J = 14.2, 8.2 Hz), 2.71 (2H, t, J = 5.5 Hz), 1.86-1.81 (4H, m), 1.76-1.72 (2H, m), 1.52 (3H, d, J = 6.4 Hz).	507.3	506.28
152	1H-NMR (CDCl3) δ: 9.16 (2H, br s), 8.51 (1H, d, J = 8.7 Hz), 8.34 (1H, d, J = 1.8 Hz), 7.69 (1H, dd, J = 8.7, 2.3 Hz), 6.93 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 4.04 (1H, d, J = 13.3 Hz), 3.88-3.83 (4H, m), 3.16 (1H, d, J = 13.3 Hz), 2.72-2.61 (3H, m), 2.53-2.46 (1H, m), 2.24-2.18 (4H, m), 2.15-2.08 (1H, m), 2.01-1.94 (1H, m), 1.88-1.80 (4H, m), 1.77-1.72 (2H, m), 1.52 (3H, d, J = 6.4 Hz), 1.18 (3H, d, J = 6.4 Hz).	477.3	476.30
153			449.25
154			405.19
155		449.3	448.27
156		490.3	489.29

[1160] [表85]

[1161]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
157	1H-NMR (DMSO-D6) δ: 9.99 (1H, s), 9.24 (1H, s), 8.20 (1H, d, J = 1.8 Hz), 7.93 (1H, d, J = 8.4 Hz), 7.67-7.71 (1H, m), 7.04 (1H, s), 5.17 (1H, d, J = 4.8 Hz), 4.582-4.62 (1H, m), 3.70 (2H, d, J = 12 Hz), 3.45 (2H, s), 2.22-2.45 (8H, br m), 2.14 (3H, s), 1.64-1.66 (2H, br m), 1.38 (3H, d, J = 6.3 Hz), 0.68-0.73 (1H, m), 0.20-0.22 (1H, m).	461.30	460.27
158	1H-NMR (DMSO-D6) δ: 9.93 (1H, s), 9.23 (1H, s), 8.19 (1H, s), 7.84 (1H, d, J = 8.7 Hz), 7.65-7.68 (1H, m), 7.03 (1H, s), 5.18 (1H, d, J = 4.5 Hz), 4.58-4.62 (1H, m), 4.09-4.19 (4H, m), 3.43 (2H, s), 2.36 (8H, br s), 2.15 (3H, s), 1.74 (4H, br s), 1.47 (4H, br s), 1.38 (3H, d, J = 6.36 Hz).	477.40	476.30
159	1H-NMR (DMSO-D6) δ: 10.12 (1H, s), 9.33 (1H, s), 8.36 (1H, d, J = 8.7 Hz), 8.21 (1H, d, J = 1.8 Hz), 7.70-7.73 (1H, m), 7.25 (1H, s), 5.21 (1H, d, J = 4.8 Hz), 4.44-4.49 (1H, m), 4.36 (1H, br s), 3.70-3.82 (4H, m), 3.45-3.56 (4H, m), 2.31-2.39 (10H, br m), 1.84-1.92 (1H, m), 1.63-1.72 (7H, m), 0.841-0.91 (3H, m).	507.40	506.31
160	1H-NMR (DMSO-D6) δ: 10.12 (1H, s), 9.33 (1H, s), 8.36 (1H, d, J = 8.1 Hz), 8.21 (1H, d, J = 1.5 Hz), 7.70-7.73 (1H, m), 7.25 (1H, s), 5.19 (1H, d, J = 4.8 Hz), 4.44-4.49 (1H, m), 4.38 (1H, br s), 3.70-3.82 (4H, m), 3.46-3.56 (4H, m), 2.40 (10H, br s), 1.84-1.92 (1H, m), 1.58-1.72 (7H, m), 0.85-0.90 (3H, m).	507.40	506.31
161	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.31 (1H, s), 8.23 (1H, d, J = 8.4 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.26 (1H, s), 5.26 (1H, d, J = 4.5 Hz), 4.61-4.69 (3H, m), 4.526-4.56 (2H, m), 3.71-3.82 (4H, m), 3.62-3.66 (1H, m), 3.46 (2H, s), 2.84-2.88 (2H, m), 2.62-2.65 (2H, m), 1.67-1.73 (6H, br m), 1.39 (3H, d, J = 6.3 Hz).	462.30	461.25
162	1H-NMR (DMSO-D6) δ: 9.99 (1H, s), 9.29 (1H, s), 8.20 (1H, d, J = 8.7 Hz), 7.49 (1H, d, J = 8.7 Hz), 7.24 (1H, s), 5.26 (1H, br s), 4.65 (1H, q, J = 6.3 Hz), 3.83-3.66 (4H, m), 3.64-3.50 (6H, m), 2.85-2.74 (4H, m), 2.67-2.57 (2H, m), 2.54-2.35 (6H, m), 1.77-1.60 (6H, m), 1.38 (3H, d, J = 6.4 Hz).	519.4	518.31
163	1H-NMR (DMSO-D6) δ: 10.12 (1H, s), 9.31 (1H, s), 8.27 (1H, d, J = 8.2 Hz), 7.63 (1H, d, J = 8.7 Hz), 7.25 (1H, s), 5.27 (1H, d, J = 4.1 Hz), 4.70-4.60 (1H, m), 4.46 (2H, s), 3.84-3.68 (4H, m), 3.64 (2H, t, J = 5.9 Hz), 2.99 (2H, d, J = 11.9 Hz), 2.87 (2H, t, J = 5.5 Hz), 2.50-2.39 (2H, m), 1.91-1.81 (2H, m), 1.77-1.60 (6H, m), 1.56-1.42 (2H, m), 1.38 (3H, d, J = 6.9 Hz).	553.3	552.26

[1162] [表86]

[1163]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
164	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.28 (1H, s), 8.25 (1H, d, J = 8.7 Hz), 8.05 (1H, d, J = 3.2 Hz), 7.48 (1H, dd, J = 9.1, 2.7 Hz), 7.23 (1H, s), 5.25 (1H, d, J = 4.6 Hz), 4.69-4.60 (1H, m), 4.45-4.36 (1H, m), 3.83-3.66 (4H, m), 2.99-2.88 (2H, m), 2.60-2.50 (2H, m), 1.95-1.85 (2H, m), 1.76-1.60 (6H, m), 1.50-1.35 (5H, m).	450.3	449.25
165	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.28 (1H, s), 8.26 (1H, d, J = 9.1 Hz), 8.05 (1H, d, J = 2.7 Hz), 7.49 (1H, dd, J = 9.1, 3.2 Hz), 7.23 (1H, s), 5.25 (1H, d, J = 4.6 Hz), 4.69-4.60 (1H, m), 4.43-4.34 (2H, m), 3.83-3.66 (4H, m), 3.52-3.45 (2H, m), 2.78-2.66 (2H, m), 2.39 (2H, t, J = 6.2 Hz), 2.30-2.19 (2H, m), 1.97-1.87 (2H, m), 1.77-1.55 (8H, m), 1.38 (3H, d, J = 6.9 Hz).	494.3	493.28
166	1H-NMR (DMSO-D6) δ: 9.92 (1H, s), 9.23 (1H, s), 8.20 (1H, d, J = 8.7 Hz), 7.45 (1H, d, J = 8.2 Hz), 7.00 (1H, s), 4.57 (1H, t, J = 5.5 Hz), 3.84-3.64 (7H, m), 3.54-3.45 (1H, m), 3.01 (2H, t, J = 5.9 Hz), 2.93-2.82 (1H, m), 2.70 (2H, t, J = 5.7 Hz), 1.77-1.59 (6H, m), 1.21 (3H, d, J = 6.9 Hz).	420.3	419.24
167	1H-NMR (DMSO-D6) δ: 10.13 (1H, s), 9.26 (1H, s), 8.36 (1H, d, J = 8.2 Hz), 8.20 (1H, d, J = 2.3 Hz), 7.70 (1H, dd, J = 8.7, 2.3 Hz), 7.02 (1H, s), 4.57 (1H, t, J = 5.5 Hz), 4.35 (1H, t, J = 5.3 Hz), 3.84-3.65 (5H, m), 3.55-3.39 (5H, m), 2.94-2.82 (1H, m), 2.35-2.34 (10H, m), 1.79-1.61 (6H, m), 1.22 (3H, d, J = 6.9 Hz).	507.4	506.31
168	1H-NMR (CDCl3) , J = 6.9 Hz).), 8.53 (1H, d, J = 8.2 Hz), 8.33 (1H, s), 8.27 (1H, d, J = 1.8 Hz), 7.73 (1H, dd, J = 8.2, 2.3 Hz), 6.84 (1H, s), 4.27-4.16 (1H, m), 3.88-3.73 (4H, m), 3.65 (2H, t, J = 5.3 Hz), 3.53 (2H, s), 2.92-2.74 (2H, m), 2.74-2.38 (10H, m), 1.96-1.64 (6H, m), 1.30 (3H, d, J = 5.9 Hz).	507.4	506.31
169		463.3	462.25
170	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.22 (1H, s), 8.21 (1H, d, J = 8.7 Hz), 7.49 (1H, d, J = 8.7 Hz), 6.99 (1H, s), 4.68 (1H, d, J = 4.6 Hz), 4.50 (1H, br s), 4.13-4.00 (1H, m), 3.81-3.68 (4H, m), 3.64-3.54 (4H, m), 2.87-2.72 (5H, m), 2.70-2.54 (3H, m), 1.80-1.59 (6H, m), 1.09 (3H, d, J = 5.9 Hz).	464.3	463.27
171		464.3	463.27

[1164] [表87]

[1165]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
172	1H-NMR (DMSO-D6) δ: 9.96 (1H, s), 9.25 (1H, s), 8.18 (1H, d, J = 1.5 Hz), 8.07 (1H, d, J = 8.4 Hz), 7.74 (1H, d, J = 8.4 Hz), 7.05 (1H, s), 5.20 (1H, d, J = 4.5 Hz), 4.59 (2H, t, J = 5.7 Hz), 4.38 (4H, br m), 3.43 (1H, s), 2.38-2.27 (9H, br m), 2.15 (1H, s), 1.39 (3H, d, J = 6.3 Hz).	435.30	434.25
173	1H-NMR (DMSO-D6) δ: 9.87 (1H, s), 9.19 (1H, s), 8.18 (1H, d, J = 1.8 Hz), 7.91 (2H, d, J = 10.2 Hz), 7.68 (1H, dd, J1 = 8.7 Hz, J2 = 2.1 Hz), 7.0 (1H, s), 5.20 (1H, d, J = 4.5 Hz), 4.62-4.65 (1H, br m), 4.29 (2H, t, J = 6.3 Hz), 3.46 (2H, br s), 2.50 (5H, br m), 2.270 (4H, br s), 1.81-1.90 (4H, br m), 1.61 (6H, s), 1.40 (3H, d, J = 6.3 Hz).	477.35	476.30
174	1H-NMR (DMSO-D6) δ: 10.08 (1H, s), 9.27 (1H, s), 8.20 (1H, s), 8.05 (1H, d, J = 8.4 Hz), 7.67 (1H, d, J = 7.8 Hz), 7.10 (1H, s), 5.42 (2H, d, J = 16.5 Hz), 5.21 (1H, s), 4.625 (1H, br s), 3.43 (2H, s), 2.36-2.74 (8H, br m), 2.14 (3H, s), 1.63-1.97 (7H, br m), 1.24-1.48 (6H, br m).	489.40	488.30
175	1H-NMR (DMSO-D6) δ: 9.98 (1H, s), 9.31 (1H, s), 8.22 (1H, d, J = 8.7 Hz), 7.52 (2H, d, J = 8.7 Hz), 7.25 (1H, s), 5.27 (1H, d, J = 4.2 Hz), 4.65-4.68 (1H, br m), 3.76-3.82 (5H, br m), 3.42-3.53 (6H, br m), 2.83 (1H, s), 2.66 (2H, br s), 1.72 (6H, br m), 1.39 (3H, d, J = 6.3 Hz).	461.35	460.27
176	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.27 (1H, s), 8.18 (1H, d, J = 8.4 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.22 (1H, s), 5.24 (1H, d, J = 4.8 Hz), 4.63 (1H, br s), 4.33-4.36 (2H, m), 3.71 (4H, br s), 3.42-3.49 (8H, br m), 3.03 (1H, br s), 2.79-2.87 (4H, br m), 2.54-2.58 (2H, m), 1.69 (6H, br s), 1.36 (4H, d, J = 6.6 Hz), 1.20 (1H, s).	505.35	504.30
177	1H-NMR (DMSO-D6) δ: 10.04 (1H, s), 9.27 (1H, s), 8.19 (1H, d, J = 1.8 Hz), 7.85 (1H, d, J = 8.4 Hz), 7.69 (1H, dd, J1 = 2.1 Hz, J2 = 8.7 Hz), 7.10 (1H, s), 5.22 (1H, d, J = 4.8 Hz), 4.59-4.63 (1H, m), 4.30-4.39 (2H, m), 4.15-4.19 (2H, m), 3.71-3.75 (2H, m), 3.61-3.63 (2H, m), 3.59 (1H, s), 2.37-2.49 (10H, br m), 2.14 (3H, s), 1.88-1.95 (2H, m), 1.39 (3H, d, J = 6.6 Hz).	479.35	478.28

[1166] [表88]

[1167]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
178	1H-NMR (DMSO-D6) δ: 10.04 (1H, s), 9.27 (1H, s), 8.19 (1H, d, J = 2.1 Hz), 7.85 (1H, d, J = 8.4 Hz), 7.69 (1H, dd, J1 = 2.1 Hz, J2 = 8.4 Hz), 7.10 (1H, s), 5.22 (1H, d, J = 4.8 Hz), 4.59-4.63 (1H, m), 4.30-4.39 (3H, m), 4.15-4.19 (2H, m), 3.71-3.75 (2H, m), 3.61-3.63 (2H, m), 3.48-3.59 (4H, m), 2.34-2.50 (10H, br m), 1.90-1.95 (2H, m), 1.39 (3H, d, J = 6.6 Hz).	509.40	508.29
179	1H-NMR (DMSO-D6) δ: 10.17 (1H, s), 9.35 (1H, s), 8.30 (1H, d, J = 8.4 Hz), 8.22 (1H, s), 7.72 (1H, d, J = 9 Hz), 7.30 (1H, s), 5.30 (1H, d, J = 4.5 Hz), 4.90 (1H, d, J = 48 Hz), 4.68-4.73 (1H, m), 4.07-4.14 (1H, br m), 3.96-4.02 (1H, br m), 3.86-3.92 (1H, br m), 3.73-3.77 (1H, br m), 3.45 (2H, s), 2.33-2.37 (8H, br m), 2.14 (3H, s), 1.85-2.04 (2H, br m), 1.68 (2H, br s), 1.39 (3H, d, J = 6.6 Hz).	481.35	480.28
180	1H-NMR (DMSO-D6) δ: 10.17 (1H, s), 9.35 (1H, s), 8.32 (1H, d, J = 8.4 Hz), 8.22 (1H, s), 7.23 (1H, d, J = 8.4 Hz), 7.29 (1H, s), 5.31 (1H, d, J = 4.8 Hz), 4.82-4.98 (1H, br d), 4.67-4.71 (1H, m), 4.37 (1H, br s), 3.77-4.10 (4H, m), 3.45-3.48 (4H, m), 2.39 (10H, br s), 1.97-2.03 (2H, m), 1.85 (1H, br s), 1.68 (1H, br s), 1.40 (3H, d, J = 6.3 Hz).	511.40	510.29
181	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.27 (1H, s), 8.19 (1H, s), 7.97 (1H, d, J = 8.4 Hz), 7.71 (1H, d, J = 8.7 Hz), 7.07 (1H, s), 5.34-5.52 (1H, br d), 5.21 (1H, d, J = 4.5 Hz), 4.62-4.64 (1H, m), 4.92-3.36 (5H, m), 3.39-3.49 (4H, m), 2.05-2.50 (12H, m), 1.42 (3H, d, J = 6.3 Hz).	497.40	496.27
182	1H-NMR (DMSO-D6) δ: 10.02 (1H, s), 9.27 (1H, s), 8.19 (1H, s), 7.95 (1H, d, J = 9 Hz), 7.70 (1H, d, J = 9 Hz), 7.07 (1H, s), 5.45 (1H, d, J = 60 Hz), 5.21 (1H, d, J = 6.0 Hz), 4.60-4.68 (1H, m), 3.88-4.37 (5H, m), 3.44-3.50 (4H, m), 2.09-2.54 (12H, br m), 1.40 (3H, d, J = 6.0 Hz)	497.35	496.27
183		507.4	506.31
184	1H-NMR (CDCl3) δ: 9.10 (1H, d, J = 5.5 Hz), 8.54-8.49 (2H, m), 8.26 (1H, d, J = 2.3 Hz), 7.72 (1H, dd, J = 8.7, 2.3 Hz), 6.93 (1H, s), 4.84 (1H, q, J = 6.4 Hz), 3.87-3.80 (6H, m), 3.50 (2H, s), 2.70 (2H, br s), 2.54-2.40 (6H, m), 2.34-2.22 (3H, m), 1.88-1.72 (6H, m), 1.52 (3H, d, J = 6.4 Hz), 1.11 (3H, d, J = 5.9 Hz).	507.4	506.31
185		475.3	474.29
186		477.4	476.30

[1168] [表89]

[1169]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
187		489.3	488.30
188		477.4	476.30
189		489.3	488.30
190		486.3	485.25
191		442.2	441.19
192		463.3	462.25
193		464.3	463.27
194		463.3	462.25
195		507.4	506.31
196	1H-NMR (DMSO-D6) δ: 10.03 (1H, s), 9.31 (1H, s), 8.23 (1H, d, J = 8.4 Hz), 7.57 (1H, d, J = 8.4 Hz), 7.26 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.65-4.69 (1H, m), 3.95 (2H, s), 3.72-3.83 (4H, br m), 3.68 (1H, s), 2.88 (4H, br s), 1.73 (6H, br s), 1.40 (3H, d, J = 6.6 Hz).	445.25	444.24
197	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.30 (1H, s), 8.22 (1H, d, J = 9.0 Hz), 7.50 (1H, d, J = 9.0 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 6.0 Hz), 4.65-4.71 (3H, m), 4.30-4.34 (2H, m), 3.71-3.82 (4H, m), 3.51 (2H, s), 2.82 (4H, d, J = 6.0 Hz), 2.74 (2H, d, J = 6.0 Hz), 1.72-1.73 (6H, br m), 1.39 (3H, d, J = 6.0 Hz).	476.30	475.27
198	1H-NMR (DMSO-D6) δ: 10.18 (1H, s), 9.35 (1H, s), 8.22-8.32 (2H, m), 7.70-7.73 (1H, m), 7.30(1H, s), 5.31 (1H, d, J = 3.0 Hz), 4.89 (1H, d, J = 45.0 Hz), 4.65-4.71 (1H, m), 4.01-4.13 (2H, m), 3.82 (2H, s), 3.43 (2H, d, J = 12.0 Hz), 2.37 (8H, br s), 2.15 (3H, s), 1.98-2.08 (2H, m), 1.75-1.84 (1H, m), 1.69 (1H, br m), 1.42 (3H, d).	481.30	480.28
199	1H-NMR (DMSO-D6) δ: 10.18 (1H, s), 9.36 (1H, s), 8.23-8.32 (2H, m), 7.72-7.73 (1H, br m), 7.31 (1H, s), 5.30 (1H, s), 4.89 (1H, d, J = 48.0 Hz), 4.58 (2H, s), 4.02-4.11 (2H, m), 3.82 (2H, s), 3.49 (4H, s), 1.99-2.50 (10H, br m), 1.69-1.84 (4H, br m), 1.42 (3H, d, J = 8.0 Hz).	511.35	510.29
200	1H-NMR (DMSO-D6) δ: 9.98 (1H, s), 9.30 (1H, s), 8.22 (1H, d, J = 8.7 Hz), 7.52 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 6.0 Hz), 4.65-4.69 (1H, m), 3.71-3.82 (4H, m), 3.34-3.48 (4H, m), 3.01-3.06 (1H, m), 2.80-2.86 (4H, m), 2.57-2.61 (2H, m), 2.24 (3H, s), 1.72 (6H, br, s), 1.39 (3H, d, J = 6.3 Hz)	475.30	474.29

[1170] [表90]

[1171]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
201	1H-NMR (DMSO-D6) δ: 10.09 (1H, s), 9.32 (1H, s), 8.26 (1H, d, J = 8.4 Hz), 7.68 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 4.5 Hz), 4.65-4.69 (1H, m), 4.54 (1H, t, 5.4 Hz), 3.87 (2H, s), 3.83 (2H, s), 3.74-3.78 (4H, m), 3.55-3.61 (2H, m), 2.78-2.82 (2H, m), 1.69-1.73 (6H, br, m), 1.41 (3H, d, J = 6.3 Hz).	436.25	435.24
202	1H-NMR (CDCl3) δ: 9.08 (1H, s), 8.58-8.47 (2H, m), 8.29 (1H, d, J = 2.0 Hz), 7.74 (1H, dd, J = 8.5, 2.2 Hz), 6.84 (1H, s), 5.93 (1H, br s), 4.28-4.16 (1H, m), 3.89-3.72 (4H, m), 3.61 (2H, t, J = 5.4 Hz), 3.52 (2H, s), 2.94-2.29 (12H, m), 1.96-1.62 (6H, m), 1.30 (3H, d, J = 5.9 Hz).	507.4	506.31
203	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.72-8.61 (2H, m), 8.36 (1H, d, J = 2.4 Hz), 7.76 (1H, dd, J = 9.0, 2.7 Hz), 6.85 (1H, s), 5.90 (1H, br s), 4.28-4.16 (1H, m), 3.88-3.71 (8H, m), 3.27 (2H, t, J = 5.4 Hz), 2.94-2.73 (2H, m), 1.98-1.59 (6H, m), 1.30 (3H, d, J = 6.3 Hz).	463.3	462.25
204	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.36 (1H, d, J = 8.3 Hz), 8.21 (1H, s), 7.42 (1H, d, J = 8.3 Hz), 6.82 (1H, s), 5.94 (1H, br s), 4.26-4.16 (1H, m), 3.87-3.66 (8H, m), 3.03-2.72 (8H, m), 1.93-1.62 (6H, m), 1.29 (3H, d, J = 5.9 Hz).	464.3	463.27
205	1H-NMR (CDCl3) δ: 9.06 (1H, s), 8.60 (1H, d, J = 8.7 Hz), 8.49 (1H, br s), 8.29 (1H, d, J = 1.4 Hz), 7.72 (1H, dd, J = 8.7, 1.8 Hz), 6.87 (1H, s), 5.22 (2H, br s), 4.20 (1H, t, J = 8.0 Hz), 4.12-4.04 (1H, m), 4.03-3.95 (1H, m), 3.90 (1H, t, J = 8.0 Hz), 3.57-3.45 (3H, m), 2.99-2.83 (4H, m), 2.56-2.35 (4H, m), 2.28 (2H, q, J = 7.3 Hz), 2.02-1.86 (4H, m), 1.61-1.47 (4H, m).	487.3	486.29
206	1H-NMR (CDCl3) δ: 9.07 (1H, s), 8.62-8.45 (2H, m), 8.29 (1H, s), 7.73 (1H, d, J = 8.2 Hz), 6.88 (1H, s), 4.20 (1H, t, J = 8.0 Hz), 4.12-4.04 (1H, m), 4.03-3.76 (6H, m), 3.59-3.44 (3H, m), 2.98-2.84 (4H, m), 2.54-2.37 (4H, m), 2.29 (2H, q, J = 7.3 Hz), 1.93-1.65 (6H, m).	475.3	474.29
207	1H-NMR (CDCl3) δ: 9.04 (1H, s), 8.65 (1H, d, J = 9.6 Hz), 8.36 (1H, s), 7.04 (1H, d, J = 10.1 Hz), 6.87 (1H, s), 5.15 (2H, br s), 4.19 (1H, t, J = 8.0 Hz), 4.12-4.04 (1H, m), 4.03-3.95 (1H, m), 3.89 (1H, t, J = 7.8 Hz), 3.62-3.46 (5H, m), 3.08-3.01 (4H, m), 2.28 (2H, q, J = 7.3 Hz), 1.99-1.82 (4H, m), 1.59-1.45 (4H, m).	474.3	473.27

[1172] [表91]

[1173]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
208	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.62 (1H, d, J = 10.1 Hz), 8.40 (1H, s), 7.07 (1H, d, J = 9.6 Hz), 6.89 (1H, s), 4.19 (1H, t, J = 7.8 Hz), 4.12-4.04 (1H, m), 4.03-3.88 (2H, m), 3.86-3.74 (4H, m), 3.63-3.48 (5H, m), 3.10-3.01 (4H, m), 2.34-2.24 (2H, m), 1.88-1.62 (6H, m).	462.3	461.27
209	1H-NMR (CDCl3) δ: 9.13-9.07 (1H, m), 8.49-8.40 (1H, m), 8.32-8.17 (1H, m), 7.57-7.47 (1H, m), 6.97-6.92 (1H, m), 4.91-4.57 (3H, m), 4.06-3.76 (7H, m), 3.28-3.15 (1H, m), 3.07-2.80 (3H, m), 2.26-2.06 (1H, m), 1.95-1.61 (9H, m), 1.54 (3H, d, J = 6.4 Hz).	503.4	502.28
210	1H-NMR (CDCl3) δ: 9.14-9.06 (1H, m), 8.49-8.40 (1H, m), 8.30-8.14 (1H, m), 7.58-7.47 (1H, m), 6.99-6.90 (1H, m), 4.91-4.81 (1H, m), 4.80-4.65 (2H, m), 4.03-3.79 (6H, m), 3.34-2.79 (7H, m), 2.15-1.66 (8H, m), 1.54 (3H, d, J = 6.3 Hz).	503.3	502.28
211	1H-NMR (DMSO-D6) δ: 10.17-10.05 (1H, m), 9.31 (1H, s), 8.36-8.22 (1H, m), 7.65 (1H, d, J = 8.8 Hz), 7.25 (1H, s), 5.28 (1H, d, J = 4.4 Hz), 4.89-4.52 (3H, m), 3.93-3.59 (7H, m), 3.04-2.71 (3H, m), 2.60-2.44 (1H, m), 1.87-1.13 (15H, m).	517.4	516.30
212	1H-NMR (DMSO-D6) δ: 10.16-10.07 (1H, m), 9.31 (1H, s), 8.36-8.23 (1H, m), 7.66 (1H, d, J = 8.3 Hz), 7.28-7.22 (1H, m), 5.28 (1H, d, J = 4.4 Hz), 4.83-4.54 (4H, m), 4.25-4.04 (2H, m), 3.92-3.64 (6H, m), 3.09-2.73 (3H, m), 2.59-2.49 (1H, m), 1.92-1.59 (8H, m), 1.38 (3H, d, J = 6.8 Hz).	519.3	518.28
213	1H-NMR (CDCl3) δ: 9.13-9.07 (1H, m), 8.51-8.41 (1H, m), 8.34-8.18 (1H, m), 7.58-7.46 (1H, m), 6.99-6.90 (1H, m), 4.92-4.63 (3H, m), 4.39-4.29 (1H, m), 4.25-4.15 (1H, m), 4.06-3.79 (6H, m), 3.27-3.15 (1H, m), 3.11-2.87 (3H, m), 2.31-2.17 (1H, m), 2.08-1.66 (7H, m), 1.54 (3H, d, J = 6.8 Hz).	519.3	518.28
214	1H-NMR (CDCl3) δ: 9.13-9.07 (1H, m), 8.49-8.39 (1H, m), 8.32-8.15 (1H, m), 7.57-7.47 (1H, m), 6.97-6.92 (1H, m), 4.86 (1H, q, J = 6.4 Hz), 4.81-4.64 (2H, m), 4.01-3.76 (6H, m), 3.16-2.62 (7H, m), 1.98-1.46 (13H, m).	517.4	516.30
215	1H-NMR (CDCl3) δ: 9.13-9.07 (1.0H, m), 8.45 (1.0H, d, J = 8.7 Hz), 8.32-8.17 (1.0H, m), 7.59-7.43 (1.0H, m), 6.97-6.92 (1.0H, m), 4.91-4.73 (2.3H, m), 4.51-4.31 (1.7H, m), 4.09-3.42 (8.0H, m), 3.05-2.84 (3.0H, m), 2.38-2.17 (1.0H, m), 1.94-1.70 (6.0H, m), 1.54 (3.0H, d, J = 6.4 Hz).	489.3	488.26

[1174] [表92]

[1175]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
216	1H-NMR (CDCl3) δ: 9.13-9.06 (1H, m), 8.49-8.38 (1H, m), 8.29-8.14 (1H, m), 7.58-7.46 (1H, m), 6.99-6.90 (1H, m), 4.93-4.78 (2H, m), 4.74-4.59 (1H, m), 4.37-4.26 (1H, m), 4.12-3.76 (7H, m), 3.76-3.63 (1H, m), 3.25-3.23 (6H, m), 1.94-1.68 (6H, m), 1.54 (3H, d, J = 6.3 Hz).	519.3	518.28
217	1H-NMR (DMSO-D6) δ: 9.99 (1H, s), 9.31 (1H, s), 8.26 (1H, d, J = 8.4 Hz), 7.52 (1H, d, J = 8.7 Hz), 7.26 (1H, s), 6.00 (2H, br s), 5.26 (1H, br s), 4.66-4.67 (1H, br m), 3.60-3.66 (4H, m), 3.82 (2H, s), 2.72-2.93 (5H, m), 2.56-2.60 (2H, m), 1.72-1.73 (6H, br m), 1.69-1.73 (6H, br, m), 1.39 (3H, d, J = 6.3 Hz).	449.1	448.27
218	1H-NMR (DMSO-D6): δ: 10.04 (1H, s), 9.28 (1H, s), 8.29 (1H ,d, J = 9.0 Hz), 8.08 (1H, d, J = 2.9 Hz), 7.51 (1H,d, J = 12 Hz), 7.21 (1H, s), 5.23 (3H, d, J = 18 Hz), 4.63-4.67 (1H, m), 4.43 (2H, br s), 3.54 (2H, s), 2.79-2.82 (2H, s), 2.26-2.28 (4H, s), 1.96(2H, br s), 1.76 (6H, s), 1.46 (4H, d, J = 9 Hz), 1.39 (3H, d, J = 6 Hz)	506.30	505.28
219	1H-NMR (DMSO-D6) δ: 9.85 (1H, s), 9.23 (1H, s), 8.05 (1H, s), 7.86 (1H, d, J = 9 Hz), 7.04 (1H, s), 5.34-5.52 (1H, br s), 5.19 (1H, d, J = 3 Hz), 4.61-4.64 (1H, m), 3.89-4.38 (6H, m), 3.49 (2H, d, J = 9 Hz), 2.73 (2H, s), 2.19 (4H, d, J = 6 Hz) 2.04 (2H, s), 1.64 (2H, d, J = 9 Hz), 1.39 (3H, d, J = 6 Hz)	498.30	497.26
220	1H-NMR (DMSO-D6) δ: 9.99 (1H, s), 9.27 (1H, s), 8.27 (1H, d, J = 9 Hz), 8.05-8.06 (1H, s), 7.49 (1H, d, J = 12 Hz), 5.19-5.25 (3H, m), 4.61-4.68 (1H, m), 4.40-4.45 (1H, m), 2.96 (2H, d, J = 12 Hz), 2.62 (2H, d, J = 3 Hz), 1.93 (2H, d, J = 9 Hz), 1.94 (4H, s), 1.37-1.52 (9H, m)	462.25	461.25
221	1H-NMR (DMSO-D6) δ: 9.81 (1H, s), 9.22 (1H, s), 8.03 (1H, s), 7.85 (1H, d, J = 9 Hz), 7.49 (1H, d, J = 9 Hz), 7.04 (1H, s), 5.34-5.52 (1H, br s), 5.18 (1H, d, J = 6 Hz), 4.61-4.64 (1H, m), 4.42 (1H, s), 4.36-4.41 (4H, m), 2.95 (2H, d, J = 18 Hz), 2.60 (2H, d, J = 3 Hz), 2.24-2.25 (3H, m), 2.10 (2H, d, J = 15 Hz), 1.38-1.50 (5H, m)	454.25	453.23
222	1H-NMR (DMSO-d6) δ: 9.30 (1H, s), 8.21(1H, d, J = 9.0 Hz), 8.06 (1H, d, J = 3.0 Hz), 7.48-7.52 (1H, m), 7.27 (1H, s), 4.72-4.96 (1H, m), 4.65-4.69 (1H, m), 4.39-4.40 (1H, m), 4.01-4.07 (2H, m), 3.87-3.93 (1H, m), 3.65-3.73 (1H, br m), 3.49-3.53 (2H, m), 2.75 (2H, br s), 2.32-2.45 (2H, m), 2.29-2.32 (2H, m) , 1.84-2.07 (5H, br m) , 1.64-1.67 (3H, m) , 1.39 (3H, d, J = 3.0 Hz)	512.25	511.27

[1176] [表93]

[1177]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
223	1H-NMR (CDCl3) δ: 9.12-9.05 (1H, m), 8.52-8.42 (1H, m), 8.29-8.12 (1H, m), 7.55-7.44 (1H, m), 6.96-6.88 (1H, m), 5.41-5.14 (2H, br m), 4.90-4.68 (3H, m), 4.11-3.83 (3H, m), 3.29-3.13 (2H, m), 3.04-2.91 (2H, m), 2.45-2.11 (5H, m), 2.07-1.45 (13H, m).	529.3	528.30
224	1H-NMR (CDCl3) δ: 9.12-9.05 (1H, m), 8.51-8.42 (1H, m), 8.28-8.12 (1H, m), 7.54-7.43 (1H, m), 6.95-6.88 (1H, m), 5.36-5.18 (2H, br m), 4.89-4.69 (3H, m), 4.11-3.83 (3H, m), 3.27-3.12 (2H, m), 3.03-2.91 (2H, m), 2.45-2.10 (5H, m), 2.06-1.45 (13H, m).	529.4	528.30
225	1H-NMR (DMSO-D6) δ: 10.22-10.14 (1H, m), 9.29 (1H, s), 8.30-8.18 (1H, m), 7.64 (1H, d, J = 8.7 Hz), 7.22 (1H, s), 5.32-5.13 (3H, m), 4.71-4.57 (3H, m), 3.87-3.74 (2H, m), 3.37 (2H, t, J = 13.5 Hz), 2.92-2.73 (3H, m), 2.66-2.29 (2H, m), 2.26-2.19 (3H, m), 2.08-1.86 (2H, m), 1.86-1.67 (4H, m), 1.55-1.34 (7H, m).	529.3	528.30
226	1H-NMR (CDCl3) δ: 9.10-9.04 (1H, m), 8.51-8.43 (1H, m), 8.22-8.08 (1H, m), 7.54-7.43 (1H, m), 6.95-6.89 (1H, m), 5.37-5.16 (2H, br m), 4.89-4.62 (3H, m), 4.05-3.79 (3H, m), 3.41-3.28 (1H, m), 3.03-2.90 (3H, m), 2.86-2.76 (1H, m), 2.72-2.59 (1H, m), 2.53-2.43 (1H, m), 2.42-2.36 (3H, m), 2.23-2.07 (2H, m), 2.02-1.85 (4H, m), 1.61-1.48 (7H, m).	529.4	528.30
227		545.3	544.29
228	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.50-8.41 (1H, m), 8.23-8.08 (1H, m), 7.53-7.44 (1H, m), 6.94-6.89 (1H, m), 5.37-5.17 (2H, br m), 4.88-4.70 (3H, m), 4.03-3.88 (3H, m), 3.47-3.40 (2H, m), 3.02-2.91 (2H, m), 2.66-2.54 (4H, m), 2.00-1.88 (4H, m), 1.85-1.60 (5H, m), 1.60-1.49 (6H, m).	529.3	528.30
229	1H-NMR (DMSO-D6) δ: 10.24-10.10 (1H, m), 9.31-9.25 (1H, m), 8.30-8.15 (1H, m), 7.71-7.36 (2H, m), 7.25-7.16 (1H, m), 5.63-5.02 (4H, m), 4.71-4.48 (3H, m), 4.33-4.18 (1H, m), 3.88-3.57 (5H, m), 3.22-2.70 (3H, m), 1.87-1.66 (4H, m), 1.56-1.25 (8H, m).	531.3	530.28
230		515.3	514.28
231	1H-NMR (CDCl3) δ: 9.11-9.05 (1H, m), 8.51-8.42 (1H, m), 8.23-8.11 (1H, m), 7.53-7.45 (1H, m), 6.95-6.89 (1H, m), 5.38-5.06 (3H, m), 4.89-4.68 (3H, m), 4.06-3.83 (3H, m), 3.57-3.42 (2H, m), 3.06-2.83 (5H, m), 2.67-2.56 (1H, m), 2.29-1.84 (6H, m), 1.79-1.47 (7H, m).	547.4	546.29

[1178] [表94]

[1179]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
232	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.43 (1H, m), 8.23-8.11 (1H, m), 7.53-7.45 (1H, m), 6.95-6.90 (1H, m), 5.37-5.16 (2H, br m), 4.88-4.66 (3H, m), 4.39-4.28 (1H, m), 4.05-3.81 (3H, m), 3.62-3.51 (2H, m), 3.10-2.85 (4H, m), 2.84-2.76 (1H, m), 2.66-2.56 (1H, m), 2.20-1.45 (13H, m).	545.3	544.29
233	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.43 (1H, m), 8.23-8.10 (1H, m), 7.54-7.45 (1H, m), 6.95-6.90 (1H, m), 5.37-5.16 (2H, br m), 4.88-4.66 (3H, m), 4.39-4.28 (1H, m), 4.05-3.81 (3H, m), 3.62-3.51 (2H, m), 3.09-2.86 (4H, m), 2.84-2.76 (1H, m), 2.66-2.56 (1H, m), 2.21-1.47 (13H, m).	545.4	544.29
234	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.53-8.45 (1H, m), 8.24-8.10 (1H, m), 7.54-7.45 (1H, m), 6.95-6.89 (1H, m), 5.36-5.16 (2H, br m), 4.88-4.73 (4H, m), 4.59-4.51 (3H, m), 4.10-3.93 (2H, m), 3.74 (1H, t, J = 5.9 Hz), 3.58-3.52 (2H, m), 3.04-2.91 (2H, m), 2.03-1.84 (4H, m), 1.61-1.48 (7H, m).	531.3	530.28
235	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.43 (1H, m), 8.20-8.06 (1H, m), 7.52-7.44 (1H, m), 6.95-6.89 (1H, m), 5.36-5.05 (3H, m), 4.88-4.79 (1H, m), 4.75-4.61 (2H, m), 4.03-3.75 (5H, m), 3.53-3.46 (2H, m), 3.38-3.24 (2H, m), 3.03-2.89 (2H, m), 2.02-1.85 (4H, m), 1.60-1.49 (7H, m).	533.3	532.27
236	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.51-8.43 (1H, m), 8.20-8.06 (1H, m), 7.52-7.43 (1H, m), 6.95-6.89 (1H, m), 5.36-5.16 (2H, br m), 4.88-4.58 (7H, m), 4.06-3.72 (3H, m), 3.56-3.50 (4H, m), 3.40-3.34 (2H, m), 3.02-2.88 (2H, m), 2.01-1.87 (4H, m), 1.60-1.49 (7H, m).	557.3	556.29
237	1H-NMR (CDCl3) δ: 9.11-9.05 (1H, m), 8.52-8.42 (1H, m), 8.27-8.12 (1H, m), 7.50 (1H, d, J = 8.7 Hz), 6.95-6.89 (1H, m), 5.38-4.67 (5H, m), 4.34-3.82 (3H, m), 3.12-2.90 (4H, m), 2.31-1.49 (20H, m), 1.42-1.22 (1H, m).	543.4	542.31
238	1H-NMR (CDCl3) δ: 9.11-9.05 (1H, m), 8.52-8.42 (1H, m), 8.25-8.10 (1H, m), 7.50 (1H, d, J = 8.7 Hz), 6.95-6.89 (1H, m), 5.42-4.68 (5H, m), 4.34-3.85 (3H, m), 3.07-2.89 (4H, m), 2.28-1.49 (20H, m), 1.39-1.21 (1H, m).	543.4	542.31
239	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.43 (1H, m), 8.23-8.08 (1H, m), 7.54-7.42 (1H, m), 6.95-6.90 (1H, m), 5.36-5.16 (2H, br m), 4.89-4.43 (3H, m), 4.14-3.79 (2H, m), 3.73-3.48 (4H, m), 3.38-3.27 (2H, m), 2.93 (2H, t, J = 5.7 Hz), 2.37-2.31 (3H, m), 2.04-1.48 (11H, m).	515.4	514.28

[1180] [表95]

[1181]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
240	1H-NMR (CDCl3) δ: 9.12 (1H, br s), 8.58-7.92 (2H, m), 7.42-7.28 (1H, br m), 6.92 (1H, s), 5.38-5.12 (2H, br m), 4.84 (1H, q, J = 6.4 Hz), 3.67 (2H, t, J = 6.4 Hz), 3.54-3.39 (2H, m), 3.23-3.12 (1H, m), 3.09-2.91 (4H, m), 2.81-2.59 (2H, m), 2.41 (3H, s), 2.02-1.72 (4H, m), 1.61-1.46 (7H, m).	487.3	486.29
241	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.29 (1H, s), 8.27 (1H, d, J = 9 Hz), 8.26 (1H, d, J = 3 Hz), 7.48 -7.52 (1H, m), 7.24 (1H, s), 5.25 (1H, d, J = 4.2 Hz), 4.64-4.68 (1H, m), 4.28-4.32 (4H, m), 3.08-3.12 (1H, br m), 2.73-2.80 (1H, m), 2.54-2.61 (2H, m), 2.00 (1H, br s), 1.69-1.71 (7H, br m), 1.43-1.60 (2H, m), 1.39 (3H, d, J = 6.6 Hz).	450.20	449.25
242	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.28 (1H, s), 8.28 (1H, d, J = 9 Hz), 8.06 (1H, d, J = 3 Hz), 7.48 -7.52 (1H, m), 7.21 (1H, s), 5.24 (1H, d, J = 4.5 Hz), 5.19 (1H, br s), 4.63-4.66 (1H, m), 4.25-4.30 (1H, m), 3.09 (1H, d, J = 12.3 Hz), 2.73-2.80 (1H, m), 2.54 (2H, br s), 2.02-2.05 (1H, br m), 1.59 -1.76 (5H, m), 1.40 -1.55 (9H, m).	462.20	461.25
243	1H-NMR (DMSO-D6) δ: 9.98 (1H, s), 9.31 (1H, s), 8.19 (1H, d, J = 9 Hz), 8.06 (1H, d, J = 2.7 Hz), 7.46-7.50 (1H, m), 7.27 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.73-4.92 (1H, br m), 4.66-4.70 (1H, m), 4.38-4.42 (1H, m), 3.78-4.11 (4H, m), 2.92-2.99 (2H, br m), 2.56-2.60 (2H, m), 1.83-2.20 (6H, m), 1.66 (1H, br s), 1.38-1.51 (5H, m).	468.25	467.24
244		449.15	448.23
245	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.24 (1H, s), 8.28 (1H, d, J = 2.4 Hz), 8.01 (1H, d, J = 8.7 Hz), 7.76 (1H, dd, J1 = 12.0 Hz, J2 = 2.7 Hz), 6.98 (1H, s), 5.05 (1H, d, J = 5.1 Hz), 4.87-4.89 (1H, m), 4.38-4.40 (1H, m), 4.16-4.18 (1H, m), 3.88-3.92 (1H, m), 3.61-3.65 (2H, m), 3.41 (2H, s), 3.01-3.05 (2H, m), 2.85 (1H, br s), 1.83-2.09 (4H, m), 1.62-1.69 (2H, m), 1.674 (3H, d, J = 6.3 Hz), 0.86-0.91 (3H, m)	463.20	462.25
246	1H-NMR (DMSO-D6) δ: 10.01 (1H, s), 9.24 (1H, s), 8.28 (1H, d, J = 2.4 Hz), 8.01 (1H, d, J = 8.7 Hz), 7.76 (1H, dd, J1 = 12.0 Hz, J2 = 2.7 Hz), 6.98 (1H, s), 5.05 (1H, d, J = 5.1 Hz), 4.87-4.89 (1H, m), 4.38-4.40 (1H, m), 4.16-4.18 (1H, m), 3.88-3.92 (1H, m), 3.61-3.65 (2H, m), 3.41 (2H, s), 3.01-3.05 (2H, m), 2.85 (1H, br s), 1.83-2.09 (4H, m), 1.62-1.69 (2H, m), 1.674 (3H, d, J = 6.3 Hz), 0.86-0.91 (3H, m)	463.20	462.25

[1182] [表96]

[1183]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
247	1H-NMR (DMSO-D6) δ: 9.92 (1H, s), 9.23 (1H, s), 8.19 (1H, s), 7.95 (1H, d, J = 9.0 Hz), 7.70 (1H, d, J = 9.0 Hz), 6.98 (1H, s), 5.06 (1H, d, J = 6 Hz), 4.89 (1H, m), 4.4 (2H, m), 4.18-4.14 (1H, m), 3.91-3.88 (1H, m), 3.44 (4H, br s), 2.51 (10H, br s), 2.11-1.83 (4H, m) , 1.69-1.62 (2H, m), 1.16 (3H, d, J = 6 Hz), 0.91-0.86 (3H, m).	507.30	506.31
248	1H-NMR (DMSO-D6) δ: 9.92 (1H, s), 9.23 (1H, s), 8.20 (1H, s), 7.98 (1H, d, J = 9.0 Hz), 7.70 (1H, d, J = 6.0 Hz), 7.02 (1H, s), 5.12 (1H, d, J = 6 Hz), 4.85-4.83 (1H, m), 4.45-4.43 (1H, m), 4.20-4.16 (1H, m), 3.91-3.87 (1H, m), 3.48 (4H, br s), 2.50 (10H, br s), 2.12-1.83 (4H, m) , 1.67-1.60 (2H, m), 1.16 (3H, d, J = 6 Hz), 0.89-0.84 (3H, m).	507.30	506.31
249	1H-NMR (DMSO-D6) δ: 10.19 (1H, s), 9.34 (1H, s), 8.40 (1H, d, J = 9 Hz), 8.25 (1H, s), 7.74-7.78 (1H, m), 7.27 (1H, s), 5.27 (1H, d, J = 3 Hz), 4.64-4.72 (2H, m), 3.70-3.88 (4H, m), 3.47-3.49 (4H, m), 3.32-3.38 (2H, m), 3.01 (2H, s), 2.72-2.73 (2H, s), 1.68-1.74 (6H, m), 1.40 (3H, d, J = 6 Hz)	507.25	506.28
250	1H-NMR (DMSO-D6) δ: 9.85 (1H, s), 9.28 (1H, s), 8.04 (1H, d, J = 3 Hz), 7.85 (1H, d, J = 9.3 Hz), 7.47 -7.51 (1H, m), 7.04 (1H, s), 5.34 -5.52 (1H, br m), 5.19 (1H, d, J = 4.8 Hz), 4.61-4.64 (1H, m), 3.89-4.32 (5H, m), 3.05-3.15 (1H, br m), 2.75-2.79 (2H, m), 2.54 (2H, br s), 2.03-2.24 (3H, br m), 1.68 -1.71 (1H, m), 1.45-1.53 (2H, m), 1.39 (3H, d, J = 6.6 Hz).	454.15	453.23
251	1H-NMR (DMSO-d6) δ: 10.00 (1H, s), 9.31 (1H, s), 8.20(1H, d, J = 9.3 Hz), 8.06 (1H, d, J = 3.0 Hz), 7.46-7.50 (1H, m), 7.27 (1H, s), 5.27 (1H, d, J = 4.5 Hz), 4.75-5.01 (1H, m), 4.66-4.70 (1H, m), 4.23-4.26 (1H, m), 3.78-4.19 (4H, m), 3.07-3.12 (1H, m), 2.72-2.78 (1H, m), 2.50-2.55 (2H, m), 1.97-2.03 (4H, m), 1.64-1.83 (2H, m), 1.49-1.59 (2H, m), 1.38-1.47 (3H, m).	468.20	467.24
252	1H-NMR (DMSO-d6) δ: 9.97 (1H, s), 9.29 (1H, s), 8.27 (1H, d, J = 9.0 Hz), 8.06 (1H, d, J = 2.7 Hz), 7.49-7.53 (1H, m), 7.24 (1H, s), 5.25 (1H, d, J = 4.8 Hz), 4.64-4.68 (1H, m), 4.35-4.39 (2H, m), 3.71-3.77 (4H, m), 3.46-3.52 (2H, m), 3.01 (1H, d, J = 11.4 Hz), 2.65-2.69 (1H, m), 2.40-2.45 (2H, m), 2.12-2.18 (2H, m), 1.97-2.08 (1H, m), 1.62-1.78 (7H, br s), 1.48-1.60 (1H, m), 1.30-1.45 (4H, m).	494.20	493.28

[1184] [表97]

[1185]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
253	1H-NMR (DMSO-d6) δ: 10.02 (1H, s), 9.28 (1H, s), 8.28 (1H, d, J = 9.0 Hz), 8.07 (1H, d, J = 2.4 Hz), 7.49-7.53 (1H, m), 7.22 (1H, s), 5.19-5.26 (3H, m), 4.61-4.69 (1H, m), 4.39 (2H, br s), 3.49 (2H, d, J = 3.9 Hz), 3.01 (2H, d, J = 8.7 Hz), 2.67-2.73 (1H, m), 2.35-2.45 (2H, s), 1.98-2.27 (3H, m), 1.77 (5H, br m), 1.38-1.56 (9H, m).	506.30	505.28
254	1H-NMR (DMSO-d6) δ: 9.83 (1H, s), 9.19 (1H, s), 8.00 (1H, d, J = 3.0 Hz), 7.82 (1H, d, J = 9.0 Hz), 7.45-7.49 (1H, m), 7.01 (1H, s), 5.31-5.49 (1H, m), 5.15 (1H, d, J = 4.8 Hz), 4.57-4.61 (1H, m), 3.87-4.36 (6H, m), 3.42-3.48 (2H, m), 2.97 (1H, d, J = 7.2 Hz), 2.62-2.67 (1H, m), 2.37-2.47 (2H, m), 1.99-2.23 (5H, m), 1.47-1.59 (1H, m), 1.34-1.36 (3H, m).	498.20	497.26
255	1H-NMR (DMSO-D6) δ: 10.03 (1H, s), 9.31 (1H, s), 8.20 (1H, d, J = 9 Hz), 8.06 (1H, d, J = 2.7 Hz), 7.48-7.52 (1H, m), 7.27 (1H, s), 5.28 (1H, d, J = 4.5 Hz), 4.80-4.96 (1H, br m), 4.66-4.70 (1H, m), 4.37 (2H, br s), 3.78-4.10 (4H, m), 3.49 (2H, d, J = 6.4 Hz), 3.02-3.00 (1H, br m), 2.66-2.73 (1H, m), 2.49 (2H, br s), 1.97-2.27 (5H, m), 1.53-1.97 (4H, m), 1.38-1.42 (4H, m).	512.25	511.27
256		461.3	460.23
257		449.3	448.23
258		463.3	462.25
259		569.3	568.26
260		463.3	462.25
261		463.21	462.25
262	1H-NMR (CDCl3) δ: 9.09 (1H, s), 8.51-8.43 (1H, m), 8.27-8.18 (1H, m), 7.53-7.44 (1H, m), 6.95-6.90 (1H, m), 5.36-5.18 (2H, br m), 4.89-4.71 (3H, m), 4.01-3.89 (3H, m), 3.79-3.64 (1H, m), 3.33-3.26 (2H, m), 3.07-2.91 (2H, m), 2.86-2.73 (2H, m), 2.34-2.22 (2H, m), 2.02-1.81 (6H, m), 1.74-1.41 (9H, m).	559.4	558.31
263	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.42 (1H, m), 8.23-8.07 (1H, m), 7.53-7.44 (1H, m), 6.95-6.90 (1H, m), 5.37-5.17 (2H, br m), 4.88-4.70 (3H, m), 4.02-3.86 (3H, m), 3.65-3.55 (2H, m), 3.34-3.28 (2H, m), 3.06-2.90 (2H, m), 2.82-2.32 (10H, m), 2.02-1.86 (4H, m), 1.62-1.49 (7H, m).	588.4	587.33

[1186] [表98]

[1187]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
264	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.52-8.42 (1H, m), 8.20-8.05 (1H, m), 7.53-7.44 (1H, m), 6.95-6.89 (1H, m), 5.36-5.18 (2H, br m), 4.88-4.71 (3H, m), 4.02-3.88 (3H, m), 3.34-3.27 (2H, m), 3.08-2.89 (2H, m), 2.78-2.20 (11H, m), 2.02-1.87 (4H, m), 1.61-1.50 (7H, m).	558.4	557.32
265	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.51-8.42 (1H, m), 8.22-8.09 (1H, m), 7.52-7.43 (1H, m), 6.95-6.89 (1H, m), 5.37-5.17 (2H, br m), 4.84 (1H, q, J = 6.4 Hz), 4.73-4.61 (2H, m), 3.95-3.74 (2H, m), 3.45-3.26 (10H, m), 3.02-2.88 (2H, m), 2.31-2.24 (3H, m), 2.01-1.86 (4H, m), 1.60-1.50 (7H, m).	570.4	569.32
266	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.48-8.39 (1H, m), 8.17-8.03 (1H, m), 7.55-7.45 (1H, m), 6.97-6.91 (1H, m), 4.91-4.81 (1H, m), 4.80-4.58 (6H, m), 4.03 (1H, br s), 3.95-3.73 (6H, m), 3.56-3.50 (4H, m), 3.40-3.34 (2H, m), 3.01-2.88 (2H, m), 1.92-1.70 (6H, m), 1.53 (3H, d, J = 6.4 Hz).	545.3	544.29
267	1H-NMR (CDCl3) δ: 9.10-9.05 (1H, m), 8.51-8.42 (1H, m), 8.23-8.10 (1H, m), 7.52-7.44 (1H, m), 6.95-6.89 (1H, m), 5.34-5.19 (2H, br m), 4.84 (1H, q, J = 6.4 Hz), 4.73-4.62 (2H, m), 4.24-4.12 (1H, m), 4.04-3.76 (3H, m), 3.41-3.28 (6H, m), 3.03-2.87 (2H, m), 2.59-2.46 (2H, m), 2.09-1.86 (6H, m), 1.67-1.52 (7H, m).	571.4	570.31
268	1H-NMR (CDCl3) δ: 9.11-9.05 (1H, m), 8.48-8.38 (1H, m), 8.21-8.08 (1H, m), 7.54-7.46 (1H, m), 6.97-6.90 (1H, m), 4.86 (1H, q, J = 6.4 Hz), 4.74-4.62 (2H, m), 4.23-3.98 (2H, m), 3.94-3.76 (6H, m), 3.41-3.28 (6H, m), 3.03-2.86 (2H, m), 2.58-2.46 (2H, m), 2.09-1.97 (2H, m), 1.92-1.58 (6H, m), 1.54 (3H, d, J = 6.4 Hz).	559.4	558.31
269	1H-NMR (CDCl3) δ: 9.12-9.06 (1H, m), 8.49-8.39 (1H, m), 8.24-8.08 (1H, m), 7.55-7.46 (1H, m), 6.97-6.91 (1H, m), 5.29-5.05 (1H, m), 4.91-4.80 (1H, m), 4.76-4.60 (2H, m), 4.05 (1H, br s), 3.96-3.75 (8H, m), 3.53-3.46 (2H, m), 3.38-3.23 (2H, m), 3.03-2.89 (2H, m), 1.91-1.71 (6H, m), 1.54 (3H, d, J = 6.4 Hz).	521.3	520.27
270	1H-NMR (CDCl3) δ: 9.11-9.05 (1H, m), 8.48-8.38 (1H, m), 8.24-8.09 (1H, m), 7.54-7.47 (1H, m), 6.96-6.91 (1H, m), 4.86 (1H, q, J = 6.3 Hz), 4.74-4.66 (2H, m), 4.06 (1H, br s), 3.96-3.78 (6H, m), 3.41-3.29 (6H, m), 3.03-2.88 (2H, m), 2.17-2.06 (2H, m), 1.91-1.71 (6H, m), 1.54 (3H, d, J = 6.4 Hz).	503.4	502.28

[1188] [表99]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
271	1H-NMR (CDCl3) δ: 9.16 (1H, s), 8.57 (1H, s), 8.43 (1H, d, J = 8.7 Hz), 8.31 (1H, d, J = 2.3 Hz), 7.75 (1H, dd, J = 8.7, 2.3 Hz), 7.07 (1H, s), 4.88 (1H, q, J = 6.4 Hz), 4.31-4.19 (2H, m), 3.83-3.70 (2H, m), 3.61 (2H, t, J = 5.5 Hz), 3.53 (2H, s), 3.02-2.92 (1H, m), 2.78-2.32 (10H, m), 2.27-2.07 (4H, m), 1.55 (3H, d, J = 6.4 Hz).	518.3	517.29
272	1H-NMR (DMSO-D6) δ: 10.36 (1H, s), 9.37 (1H, s), 8.35-8.29 (2H, m), 7.80 (1H, dd, J = 8.7, 2.7 Hz), 7.32 (1H, d, J = 0.9 Hz), 5.32 (1H, d, J = 4.6 Hz), 4.73-4.63 (1H, m), 4.14-3.97 (2H, m), 3.73-3.55 (4H, m), 3.40 (2H, s), 3.21-3.11 (1H, m), 3.03 (2H, t, J = 5.3 Hz), 2.83 (1H, br s), 2.15-2.01 (2H, m), 1.99-1.85 (2H, m), 1.39 (3H, d, J = 6.4 Hz).	474.3	473.23
273	1H-NMR (CDCl3) δ: 9.16 (1H, s), 8.53 (1H, s), 8.47 (1H, d, J = 10.1 Hz), 7.11-7.04 (2H, m), 4.87 (1H, q, J = 6.4 Hz), 4.29-4.16 (2H, m), 3.80-3.67 (2H, m), 3.64-3.55 (4H, m), 3.11-3.02 (4H, m), 2.99-2.89 (1H, m), 2.23-2.01 (4H, m), 1.55 (3H, d, J = 6.4 Hz).	461.3	460.24
274	1H-NMR (DMSO-D6) δ: 10.04 (1H, s), 9.33 (1H, s), 8.10 (1H, d, J = 8.2 Hz), 7.47 (1H, d, J = 8.2 Hz), 7.30 (1H, s), 5.31 (1H, d, J = 4.6 Hz), 4.73-4.62 (1H, m), 4.17-3.99 (2H, m), 3.83 (2H, s), 3.71-3.52 (2H, m), 3.22-3.12 (1H, m), 3.02 (2H, t, J = 5.9 Hz), 2.71 (2H, t, J = 5.7 Hz), 2.14-2.01 (2H, m), 1.99-1.84 (2H, m), 1.40 (3H, d, J = 6.4 Hz).	431.3	430.22
275	1H-NMR (CDCl3) δ: 9.06 (1H, s), 8.55 (1H, d, J = 8.7 Hz), 8.39 (1H, s), 8.27 (1H, d, J = 2.3 Hz), 7.74 (1H, dd, J = 8.2, 2.3 Hz), 6.87 (1H, s), 5.11-4.96 (4H, m), 4.43-4.32 (1H, m), 3.98-3.87 (4H, m), 3.61 (2H, t, J = 5.3 Hz), 3.52 (2H, s), 3.02-2.23 (10H, m), 1.95-1.70 (6H, m).	505.4	504.30
276	1H-NMR (CDCl3) δ: 9.09 (1H, s), 8.67-8.57 (2H, m), 8.25 (1H, d, J = 2.3 Hz), 7.65 (1H, dd, J = 8.9, 2.5 Hz), 6.87 (1H, s), 5.10-5.04 (2H, m), 5.03-4.97 (2H, m), 4.42-4.33 (1H, m), 3.96-3.83 (6H, m), 3.21-3.11 (4H, m), 2.93-2.85 (2H, m), 1.92-1.70 (6H, m).	475.3	474.25
277	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.62 (1H, d, J = 10.1 Hz), 8.39 (1H, br s), 7.08 (1H, d, J = 10.1 Hz), 6.86 (1H, s), 5.10-4.95 (4H, m), 4.42-4.31 (1H, m), 3.95-3.83 (4H, m), 3.65-3.55 (4H, m), 3.12-3.02 (4H, m), 2.02-1.70 (6H, m).	448.3	447.25

[1189]

[1190] [表100]

[1191]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
278	1H-NMR (DMSO-D6) δ: 10.06 (1H, s), 9.33 (1H, s), 8.11 (1H, d, J = 8.2 Hz), 7.51 (1H, d, J = 8.7 Hz), 7.30 (1H, d, J = 0.9 Hz), 5.30 (1H, d, J = 4.6 Hz), 4.73-4.63 (1H, m), 4.49 (1H, t, J = 5.3 Hz), 4.18-4.01 (2H, m), 3.71-3.52 (6H, m), 3.22-3.11 (1H, m), 2.89-2.74 (4H, m), 2.59 (2H, t, J = 6.2 Hz), 2.15-2.01 (2H, m), 1.99-1.84 (2H, m), 1.40 (3H, d, J = 6.4 Hz).	475.3	474.25
279	1H-NMR (DMSO-D6) δ: 10.08 (1H, s), 9.33 (1H, s), 8.11 (1H, d, J = 8.2 Hz), 7.52 (1H, d, J = 8.2 Hz), 7.30 (1H, d, J = 0.9 Hz), 5.30 (1H, d, J = 4.6 Hz), 4.73-4.62 (1H, m), 4.18-4.00 (2H, m), 3.68-3.52 (2H, m), 3.51-3.38 (4H, m), 3.21-3.11 (1H, m), 3.08-2.99 (1H, m), 2.89-2.77 (4H, m), 2.64-2.55 (2H, m), 2.24 (3H, s), 2.14-2.01 (2H, m), 1.99-1.84 (2H, m), 1.40 (3H, d, J = 6.4 Hz).	500.3	499.28
280	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.30 (1H, s), 8.18 (1H, d, J = 6 Hz), 7.46 (1H, d, J = 9 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 6 Hz), 4.65-4.69 (1H, m), 4.37-4.41 (1H, m), 4.00 (1H, d, J = 3 Hz), 3.70-3.82 (4H, br s), 3.48-3.58 (3H, m), 3.08-3.10 (1H, m), 2.51-2.58 (1H, m), 2.40-2.46 (2H, m), 2.08-2.13 (2H, br s), 1.63-1.73 (8H, m), 1.39 (3H, d, J = 6 Hz)	476.20	475.27
281	1H-NMR (DMSO-d6) δ: 10.21 (1H, s), 9.29 (1H, s), 8.14 (1H, d, J = 9.0 Hz), 7.75 (1H, dd, J1 = 3.0 Hz, J2 = 3.0 Hz), 7.11 (1H, s), 5.40-5.45 (2H, m), 5.21 (1H, d, J = 3.0 Hz), 4.61-4.65 (1H, m), 3.62-3.65 (2H, m), 3.32 (2H,s), 3.03 (2H, s), 2.73-2.76 (1H, m), 1.79-1.98 (7H, m), 1.45-1.47 (3H, m), 1.39-1.41 (3H, m)	475.15	474.25
282	1H-NMR (DMSO-D6) δ: 9.95 (1H, s), 9.30 (1H, s), 8.22 (1H, d, J = 9.0 Hz), 7.52 (1H, d, J = 9.0 Hz), 7.25 (1H, s), 5.27-5.25 (1H, d, J = 6.0 Hz), 4.68-4.65 (1H, m), 3.94-3.91 (2H, m), 3.82-3.69 (6H, m), 3.36-3.32 (2H, m), 2.85-2.81 (4H, m), 2.66-2.62 (1H, m), 1.82-1.72 (8H, m), 1.59-1.47 (2H, m), 1.39 (3H, d, J = 6.0 Hz).	490.15	489.29
283	1H-NMR (DMSO-d6) δ: 9.94 (1H, s), 9.30 (1H, s), 8.19 (1H,d, J = 9.0 Hz), 7.49 (1H, d, J = 9.0 Hz), 7.25 (1H, s), 5.25 (1H, d, J = 3.0 Hz), 4.65-4.68 (1H, m), 4.51 (1H, d, J = 3.0 Hz), 3.76-3.82 (4H, m), 3.67-3.71 (2H, m), 3.36-3.41 (1H, m), 2.72-2.81 (4H, m), 2.40-2.43 (1H, m), 1.80-1.89 (4H, m), 1.71-1.73 (6H, m), 1.38-1.40 (3H, m), 1.08-1.33 (4H, m)	504.25	503.30

[1192] [表101]

[1193]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
284	1H-NMR (DMSO-d6) δ: 9.95 (1H, s), 9.30 (1H, s), 8.20 (1H, d, J = 9.0 Hz), 7.52 (1H, d, J = 9.0 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 3.0 Hz), 4.65-4.68 (1H, m), 4.30 (1H, d, J = 3.0 Hz), 3.76-3.78 (4H, m), 3.68-3.74 (2H, s), 2.72-2.81 (4H, m), 2.40-2.43 (1H, m), 1.72-1.80 (10H, m), 1.38-1.47 (7H, m)	504.25	503.30
285	1H-NMR (DMSO-D6) δ: 10.10(1H, d, J = 15.0 Hz), 9.32 (1H, s), 8.51-8.46 (2H, m), 8.32-8.26 (1H, m), 7.69-7.60 (1H, m), 7.30-7.26 (3H, m), 5.27 (1H, d, J = 3.0 Hz), 4.75-4.65 (3H, m), 3.91-3.76 (8H, m), 2.84-2.80 (2H, m), 1.73 (6H, br s), 1.40 (3H, d, J = 6.0 Hz).	525.15	524.26
286	1H-NMR (DMSO-D6) δ: 10.13 (1H, d, J = 12.0 Hz), 9.32 (1H, s), 8.36-8.27 (1H, m), 7.70-7.66 (1H, m), 7.55 (1H, s), 7.26 (1H, s), 7.08 (1H, s), 6.87 (1H, s), 5.27 (1H, d, J = 6.0 Hz), 5.14 (2H, d, J = 9.0 Hz), 4.73-4.65 (3H, m), 3.84-3.77 (6H, m), 2.99-2.83 (2H, m), 1.74 (6H, s), 1.40 (3H, d, J = 6.0 Hz).	514.20	513.26
287	1H-NMR (DMSO-D6) δ: 9.97 (1H, s), 9.30 (1H, s), 8.21 (1H, d, J = 8.4 Hz), 7.49 (1H, d, J = 8.4 Hz), 7.25 (1H, s), 5.26 (1H, d, J = 4.5 Hz), 4.65-4.69 (1H, m), 3.76-3.78 (4H, m), 3.49 (2H, s), 2.82-2.86 (2H, m), 2.67-2.69 (2H, m), 2.37 (3H, s), 1.73 (6H, br), 1.39 (3H, d, J = 6.3 Hz)	420.15	419.24
288		451.3	450.25
289		451.3	450.25
290		479.3	478.28
291	1H-NMR (CDCl3) δ: 9.17 (1H, s), 9.03 (1H, s), 8.35 (1H, d, J = 8.7 Hz), 8.33 (1H, d, J = 2.3 Hz), 7.71 (1H, dd, J = 8.7, 2.3 Hz), 7.00 (1H, s), 5.19-5.13 (1H, m), 4.86 (1H, q, J = 6.4 Hz), 4.25 (1H, d, J = 13.3 Hz), 4.07-4.01 (2H, m), 3.89 (1H, td, J = 11.4, 2.7 Hz), 3.78 (1H, d, J = 11.0 Hz), 3.68-3.59 (1H, m), 3.50 (2H, s), 2.49 (8H, br s), 2.29 (3H, s), 1.53 (3H, d, J = 6.9 Hz), 1.30 (3H, d, J = 6.9 Hz).	479.4	478.28
292	1H-NMR (CDCl3) δ: 9.21 (1H, s), 9.16 (1H, s), 8.35-8.32 (2H, m), 7.69 (1H, dd, J = 8.7, 2.3 Hz), 6.94 (1H, s), 5.26 (2H, s), 4.82 (1H, q, J = 6.4 Hz), 4.03 (2H, dd, J = 10.5, 2.3 Hz), 3.69 (2H, dd, J = 10.5, 1.4 Hz), 3.50 (2H, s), 2.48 (8H, br s), 2.28 (3H, s), 2.14-2.00 (5H, m), 1.52 (3H, d, J = 6.4 Hz).	491.4	490.28
293		509.4	508.29
294		509.4	508.29
295		521.3	520.29

[1194] [表102]

[1195]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
296		465.3	464.26
297		465.3	464.26
298		477.3	476.26
299		465.3	464.23
300		465.3	464.23
301		477.3	476.23
302		449.3	448.23
303		463.3	462.25
304		491.4	490.28
305		477.3	476.26
306		491.4	490.28
307		477.3	476.26
308		507.4	506.28
309		477.3	476.26
310		464.3	463.23
311		478.3	477.25
312		491.4	490.28
313		491.4	490.28
314		512.3	511.20
315		505.4	504.30
316		479.3	478.28
317		491.3	490.28
318		463.3	462.25
319		491.4	490.28
320		495.4	494.26
321		491.4	490.28
322		493.4	492.30
323	1H-NMR (CDCl3) δ: 9.09 (1H, s), 8.64 (1H, d, J = 9.1 Hz), 8.57 (1H, s), 8.27 (1H, d, J = 2.7 Hz), 7.67 (1H, dd, J = 8.7, 2.7 Hz), 6.87 (1H, s), 5.10-5.04 (2H, m), 5.03-4.97 (2H, m), 4.43-4.32 (1H, m), 3.96-3.85 (6H, m), 3.78 (2H, s), 3.25-3.14 (2H, m), 1.99-1.62 (8H, m).	475.3	474.25
324	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.59 (1H, d, J = 9.6 Hz), 8.45 (1H, s), 6.94 (1H, s), 6.71 (1H, d, J = 9.6 Hz), 4.85 (1H, q, J = 6.4 Hz), 4.71 (2H, t, J = 6.6 Hz), 4.55-4.48 (2H, m), 4.24 (4H, s), 4.04 (1H, br s), 3.87-3.80 (4H, m), 3.80-3.72 (1H, m), 3.51 (4H, s), 1.88-1.58 (6H, m), 1.53 (3H, d, J = 6.4 Hz).	504.3	503.28

[1196] [表103]

[1197]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
325	1H-NMR (CDCl3) δ: 9.10 (1H, s), 8.53 (1H, d, J = 8.2 Hz), 8.35 (1H, s), 8.24 (1H, d, J = 1.8 Hz), 7.72 (1H, dd, J = 8.7, 2.3 Hz), 6.95 (1H, d, J = 0.9 Hz), 4.86 (1H, q, J = 6.4 Hz), 4.41 (4H, s), 4.04 (1H, br s), 3.93-3.82 (4H, m), 3.46 (2H, s), 2.52-2.20 (4H, br m), 1.99-1.67 (10H, m), 1.54 (3H, d, J = 6.4 Hz).	490.4	489.29
326	1H-NMR (CDCl3) δ: 9.12 (1H, s), 8.55 (1H, d, J = 8.7 Hz), 8.49 (1H, s), 8.27 (1H, d, J = 1.8 Hz), 7.72 (1H, d, J = 7.8 Hz), 6.95 (1H, s), 4.86 (1H, q, J = 6.1 Hz), 4.05 (1H, s), 3.94-3.82 (4H, m), 3.51 (2H, s), 2.82-2.58 (3H, br m), 2.51-2.24 (2H, br m), 2.04-1.72 (10H, m), 1.54 (3H, d, J = 6.4 Hz).	473.3	472.27
327	1H-NMR (CDCl3) δ: 9.03 (1H, s), 8.22 (1H, d, J = 8.7 Hz), 7.96 (1H, s), 6.92-6.85 (2H, m), 4.89-4.79 (1H, m), 4.75-4.67 (2H, m), 4.55-4.48 (2H, m), 4.12 (1H, d, J = 5.0 Hz), 4.00 (4H, s), 3.92-3.81 (4H, m), 3.80-3.71 (1H, m), 3.48 (4H, s), 2.40 (3H, s), 1.90-1.70 (6H, m), 1.53 (3H, d, J = 6.4 Hz).	517.4	516.30
328	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.30 (1H, d, J = 8.7 Hz), 8.07 (1H, s), 7.46 (1H, d, J = 9.1 Hz), 6.92 (1H, s), 4.85 (1H, q, J = 6.4 Hz), 3.92-3.79 (4H, m), 3.64-3.51 (4H, m), 3.16-2.90 (7H, m), 2.71-2.65 (2H, m), 2.62-2.39 (7H, m), 1.91-1.70 (6H, m), 1.53 (3H, d, J = 6.4 Hz).	548.4	547.34
329	1H-NMR (DMSO-d6) δ: 10.17 (1H, s), 9.28 (1H, s), 8.12-8.19 (2H, m), 7.63 (1H, dd, J1 = 3.0 Hz, J2 = 3.0 Hz), 7.11 (1H, s), 5.40-5.46 (2H, m), 5.21 (1H, d, J = 3.0 Hz), 4.59-4.67 (1H, m), 3.79-3.82 (2H, m), 3.53 (2H, s), 2.96 (2H, m), 2.66-2.82 (1H, m), 2.09 (1H, m), 1.77-1.86 (7H, m), 1.47-1.53 (3H, m) , 1.41-1.44 (3H, m)	489.25	488.26
330	1H-NMR (DMSO-d6) δ: 10.11 (1H, s), 9.32 (1H, s), 8.41-8.47 (2H,m), 8.26-8.30 (1H, m), 7.63-7.68 (2H, m), 7.26-7.36 (2H, m), 5.26 (1H, d, J = 3.0 Hz), 4.79 (1H, s), 4.65-4.69 (2H, m), 3.83-3.90 (3H, m), 3.70-3.78 (5H, m), 2.82-2.87 (2H, m), 1.74-1.81 (6H, m), 1.39 (3H, d, J = 3.0 Hz)	525.20	524.26
331	1H-NMR (DMSO-D6) δ: 10.11 (1H, d, J = 12.0 Hz), 9.32 (1H, s), 8.29-8.27 (1H, m), 7.69-7.68 (2H, m), 7.43 (1H, s), 7.26 (1H, s), 6.27 (1H, d, J = 3.0 Hz), 5.27-5.25 (3H, m), 4.76-4.64 (3H, m), 3.88-3.77 (6H, m), 2.93-2.89 (2H, m), 1.74 (6H, m), 1.40 (3H, d, J = 6.0 Hz).	514.25	513.26

[1198] [表104]

[1199]

实施例编号	NMR 数据	$(M+H)^+$	精确质量
332	1H-NMR (DMSO-d6) δ: 10.14 (1H, s), 9.32 (1H, s), 8.46 (1H, s), 8.27-8.37 (1H, m), 7.97 (1H, s), 7.64-7.70 (1H, m), 7.26 (1H, d, J = 3.0 Hz), 5.38-5.42 (2H, m), 5.26 (1H, d, J = 3.0 Hz), 4.65-4.76 (6H, m), 2.83-3.00 (2H, m), 1.74-1.89 (6H, m), 1.39 (3H, d, J = 3.0 Hz)	515.25	514.26
333	1H-NMR (DMSO-D6) δ: 10.16 (1H, d, J = 12.6 Hz), 8.33 (1H, d, J = 1.5 Hz), 8.24-8.40 (2H, m), 7.70 (1H, d, J = 8.4 H), 7.27 (1H, d, J = 2.4 H), 5.24-5.32 (3H, m), 4.66-4.73 (3H, m), 3.76-3.85 (6H, m), 2.99-3.02 (1H, m), 2.84-2.86 (1H, m), 1.74 (6H, br s), 1.39 (3H, d, J = 8.4 H).	515.25	514.26
334	1H-NMR (CDCl3) δ: 9.05 (1H, s), 8.30 (1H, d, J = 8.7 Hz), 8.04 (1H, s), 7.45 (1H, d, J = 8.7 Hz), 6.92 (1H, s), 4.85 (1H, q, J = 6.4 Hz), 4.12 (1H, br s), 3.93-3.80 (4H, m), 3.62-3.53 (2H, m), 3.11-3.01 (1H, m), 3.00-2.90 (6H, m), 2.64-2.42 (7H, m), 2.39 (3H, s), 1.91-1.70 (6H, m), 1.53 (3H, d, J = 6.4 Hz).	518.4	517.33
335	1H-NMR (DMSO-d6) δ: 9.79 (1H, s), 9.28 (1H, s), 8.43 (2H, d, J = 15 Hz), 8.18-8.27 (1H, m), 7.58-7.67 (2H, m), 7.23-7.34 (2H, m), 5.08 (1H, d, J = 4.5 Hz), 4.65-4.81 (3H, m), 3.80-3.88 (8H, m), 2.76-2.93 (2H, m), 1.72 (6H, s), 1.40 (3H, d, J = 6.3 Hz).	525.20	524.26
336	1H-NMR (DMSO-d6) δ: 10.14 (1H, s), 9.33 (1H, s), 8.27-8.34 (1H, m), 8.04 (1H, s), 7.67-7.74 (2H, m), 7.27 (1H, d, J = 3.0 Hz), 5.60-5.64 (2H, m), 4.79 (1H, s), 4.66-4.70 (2H, m), 3.64-3.91 (7H, m), 2.99-3.03 (1H, m), 2.84-2.99 (1H, m), 1.74-1.89 (6H, m), 1.39 (3H, d, J = 3.0 Hz)	515.25	514.26
337	1H-NMR (DMSO-d6) δ: 10.14 (1H, s), 9.33 (1H, s), 8.27-8.34 (1H, m), 8.04 (1H, s), 7.67-7.74 (2H, m), 7.27 (1H, d, J = 3.0 Hz), 5.60-5.64 (2H, m), 5.26 (1H, d, J = 3.0 Hz), 4.66-4.79 (3H, m), 3.77-3.91 (6H, m), 2.86-3.02 (2H, m), 1.74-1.89 (6H, m), 1.39 (3H, d, J = 3.0 Hz)	515.25	514.26

[1200] [实施例20]

[1201] 人CDK4/细胞周期蛋白D3抑制活性

[1202] 使用从Carna Biosciences株式会社购入的检测试剂盒(QS S Assist CDK4/Cyclin D3_FP试剂盒),测定了化合物的CDK4/细胞周期蛋白D3抑制活性。该检测试剂盒是基于Molecular Devices公司的IMAP技术,通过定量由激酶磷酸化的荧光底物与IMAP结合试剂结合而引起的荧光偏振的变化,来测定激酶活性。

[1203] 将试剂盒附带的10×检测缓冲液、或与试剂盒附带相同组成的自调制检测缓冲液用于各溶液调制。将试剂盒附带的10×检测缓冲液用纯化水进行10倍稀释,调制了检测缓冲液。检测缓冲液由20mM HEPES(pH7.4)、0.01%Tween20、和2mM二硫苏糖醇构成。试验化合物溶液如下调制:将试验化合物用二甲亚砜(DMSO)调制成终浓度的100倍,然后用检测缓冲液进行25倍稀释,调制成终浓度的4倍。将试剂盒附带的5×ATP/底物/Metal溶液用检测缓冲液进行5倍稀释来调制ATP/底物/Metal溶液。将试剂盒附带的CDK4/细胞周期蛋白D3以达

到终浓度的2倍的方式用检测缓冲液进行稀释来调制酶溶液(CDK4/细胞周期蛋白D3终浓度为12.5～25ng/孔)。将5×IMAP结合缓冲液A和5×IMAP结合缓冲液B分别用纯化水进行5倍稀释,然后以达到IMAP结合缓冲液A:IMAP结合缓冲液B＝85:15的形式进行混合,向其中添加IMAP结合试剂使达到400倍稀释来调制检测试剂。

[1204] 向384孔板中添加5μL的试验化合物溶液、5μL的ATP/底物/Metal溶液,进一步添加10μL的酶溶液或检测缓冲液,进行混合而引发酶反应。总反应液量为20μL/孔,反应液组成为20mM HEPES(pH7.4)、0.01％Tween20、2mM二硫苏糖醇、100nM FITC标记肽底物(自Carna Biosciences没有公开关于底物肽序列的信息)、100μM ATP、1mM氯化镁、1％DMSO、12.5～25ng/孔CDK4/细胞周期蛋白D3。在室温下反应45分钟后,向各孔中添加60μL的检测试剂,在室温、遮光条件下进一步反应30分钟。接着,使用酶标仪,测定了在激发波长:485nm、测定波长:535nm下的荧光偏振。

[1205] 将添加酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为100％,将添加检测缓冲液来代替酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为0％,以此方式计算试验化合物的酶活性抑制率,并且通过拟合用量反应曲线来计算针对CDK4/细胞周期蛋白D3的50％抑制浓度。

[1206] 将各化合物针对CDK4/细胞周期蛋白D3活性的抑制活性示于以下的表中。

[1207] 表中的活性强度显示出:+++为IC_{50}值＜10nM,++为10nM≤IC_{50}值＜100nM,+为100nM≤IC_{50}值。

[1208] [实施例21]人CDK2/细胞周期蛋白A2抑制活性

[1209] 使用从Carna Biosciences株式会社购入检测试剂盒(QS S Assist CDK2/Cyclin A2_FP试剂盒),测定了化合物的CDK2/细胞周期蛋白A2抑制活性。本检测试剂盒基于Molecular Devices公司的IMAP技术,通过定量由激酶磷酸化的荧光底物与IMAP结合试剂结合而引起的荧光偏振的变化,来测定激酶活性。

[1210] 将试剂盒附带的10×检测缓冲液用纯化水进行10倍稀释来调制检测缓冲液,用于各溶液调制。检测缓冲液由20mM HEPES(pH7.4)、0.01％Tween20、和2mM二硫苏糖醇构成。试验化合物溶液如下调制:将试验化合物用二甲亚砜(DMSO)调制成终浓度的100倍,然后用检测缓冲液进行25倍稀释,调制成终浓度的4倍。将试剂盒附带的5×ATP/底物/Metal溶液用检测缓冲液进行5倍稀释来调制ATP/底物/Metal溶液。将试剂盒附带的CDK2/细胞周期蛋白A2以达到终浓度的2倍的方式用检测缓冲液进行稀释来调制酶溶液(CDK2/细胞周期蛋白A2终浓度为2.5ng/孔)。将5×IMAP结合缓冲液A用纯化水进行5倍稀释,然后添加IMAP结合试剂使达到400倍稀释来调制检测试剂。

[1211] 向384孔板中添加5μL的试验化合物溶液、5μL的ATP/底物/Metal溶液,进一步添加10μL的酶溶液或检测缓冲液,进行混合来引发酶反应。总反应液量为20μL/孔,反应液组成为20mM HEPES(pH7.4)、0.01％Tween20、2mM二硫苏糖醇、100nM FITC标记肽底物(自Carna Biosciences没有公开关于底物肽序列的信息)、30μM ATP、5mM氯化镁、1％DMSO、2.5ng/孔CDK2/细胞周期蛋白A2。在室温下反应60分钟后,向各孔中添加60μL的检测试剂,在室温、遮光条件下进一步反应30分钟。接着,使用酶标仪测定了在激发波长:485nm、测定波长:535nm下的荧光偏振。

[1212] 将添加酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为100％,将添加

检测缓冲液来代替酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为0％，以此方式计算试验化合物的酶活性抑制率，并且通过拟合用量反应曲线来计算针对CDK2/细胞周期蛋白A2的50％抑制浓度。

[1213] 将各化合物针对CDK2/细胞周期蛋白A2活性的抑制活性示于以下的表中。

[1214] 表中的活性强度显示出：+++为IC_{50}值＜10nM，++为10nM≤IC_{50}值＜100nM，+为100nM≤IC_{50}值。

[1215] [表105]

[1216]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
1	+++	+		2	+++	+
3	+	+		4	++	+
5	+++	+		6	+++	+
7	+++	+		8	++	+
9	+++			10	++	
11	+++			12	+++	
13	+++			14	+++	
15	++			16	+++	
17	++			18	+++	
19	+++			20	+++	
21	++			22	+++	
23	+			24	+++	+
25	++	+		26	++	+
27	++	+		28	++	+
29	++	+		30	+++	+
31	++			32	++	+
33	+++	+		34	++	+
35	++	+		36	+	+
37	++	+		38	+	+
39	+++	+		40	+++	+
41	+++	+		42	+	+
43	+++			44	+++	
45	+++			46	+++	
47	++	+		48	+++	+
49	+++	+		50	++	+
51	+++	+		52	+++	+

[1217] [表106]

[1218]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
53	+++	+		54	+++	+
55	+++	+		56	+++	+
57	+++	+		58	++	+
59	+++	+		60	+++	+

61	+++	+		62	+++	+
63	+++	+		64	+++	+
65	+++	+		66	++	+
67	++	+		68	+++	+
69	+++	+		70	++	+
71	++	+		72	+++	+
73	++	+		74	++	+
75	+++	++		76	+++	+
77	++	+		78	+++	+
79	+++	+		80	+++	+
81	+++	+		82	+++	+
83	+++	++		84	+++	+
85	++	+		86	+++	+
87	+++	+		88	+++	+
89	+++	+		90	+++	+
91	+++	+		92	+++	+
93	+++	+		94	+++	+
95	++	+		96	+++	+
97	+++	+		98	++	+
99	+++	+		100	+++	+
101	+++	+		102	+++	+
103	+++	+		104	+++	+

[1219] [表107]

[1220]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
105	+++	+		106	+++	+
107	+++	+		108	+++	+
109	+++	+		110	+++	+
111	+++	+		112	+++	+
113	+++	+		114	+++	+
115	+++	+		116	+++	+
117	+++	+		118	+++	+
119	+++	+		120	+++	+
121	+++	+		122	+++	+
123	+++	+		124	+++	+
125	++	+		126	+++	+
127	+++	+		128	+++	+
129	+++	+		130	+++	+
131	++	+		132	+++	+
133	++	+		134	+++	+
135	+++	+		136	+++	+
137	++	+		138	+++	+

139	+++	+		140	+++	+
141	+++	+		142	+++	+
143	+++	+		144	+++	+
145	++	+		146	+++	+
147	+++	+		148	+++	+
149	+++	+		150	+++	+
151	+++	+		152	+++	+
153	++	+		154	+++	+
155	+++	+		156	+++	+

[1221] [表108]

[1222]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
157	+++	+		158	+++	+
159	++	+		160	+++	+
161	+++	+		162	+++	+
163	+++	+		164	+++	+
165	+++	+		166	++	+
167	+++	+		168	++	+
169	++	+		170	++	+
171	++	+		172	++	+
173	+++	++		174	+++	+
175	+++	+		176	+++	+
177	+++	+		178	+++	+
179	+++	+		180	+++	+
181	++	+		182	+++	+
183	+++	+		184	+++	+
185	+++	+		186	+++	+
187	+++	+		188	+++	+
189	+++	+		190	++	+
191	++	+		192	++	+
193	++	+		194	+++	+
195	++	+		196	++	+
197	++	+		198	+++	+
199	+++	+		200	+++	+
201	+++	+		202	++	+
203	+++	+		204	++	+
205	+++	+		206	+++	+
207	+++	+		208	+++	+

[1223] [表109]

[1224]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
209	+++	+		210	+++	+

211	+++	+		212	+++	+
213	+++	+		214	+++	+
215	+++	+		216	+++	+
218	+++	+		219	+++	+
220	+++	+		221	+++	+
222	+++	+		223	+++	+
224	+++	+		225	+++	+
226	+++	+		227	+++	+
228	+++	+		229	+++	+
230	+++	+		231	+++	+
232	+++	+		233	+++	+
234	++	+		235	+++	+
236	+++	+		237	+++	+
238	+++	+		239	+++	+
240	+++	+		241	+++	+
242	+++	+		243	+++	+
244	+++	+		245	+++	+
246	+++	+		247	+++	+
248	+++	+		249	++	+
250	+++	+		251	+++	+
252	+++	+		253	+++	+
254	+++	+		255	+++	+
256	+++	+		257	+++	+
258	+++	+		259	+++	+
260	+++	+		261	+++	+

[1225] [表110]

[1226]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
262	+++	+		263	+++	+
264	+++	+		265	+++	+
266	+++	+		267	+++	+
268	+++	+		269	+++	+
270	+++	+		271	+++	+
272	+++	+		273	+++	+
274	+++	+		275	+++	+
276	+++	+		277	++	+
278	+++	+		279	+++	+
280	++	+		281	+++	+
282	+++	+		283	++	+
284	++	+		285	++	+
286	+++	+		287	+++	+
288	+++	+		289	+++	+

290	++	+		291	+++	+
292	+++	+		293	++	+
294	+++	+		295	+++	+
296	+++	+		297	+++	+
298	+++	+		299	++	+
300	++	+		301	++	+
302	+++	++		303	+++	+
304	+++	++		305	+++	++
306	+++	++		307	+++	++
308	+++	+		309	+++	+
310	+++	+		311	+++	+
312	+++	+		313	+++	+

[1227] [表111]

[1228]

实施例编号	CDK4抑制活性	CDK2抑制活性		实施例编号	CDK4抑制活性	CDK2抑制活性
314	+++	+		315	+++	+
316	+++	+		317	+++	+
318	+++	+		319	+++	++
320	+++	+		321	+++	+
322	+++	+		323	++	+
324	+++	+		325	+++	+
326	+++	+		327	+++	+
328	+++	+		329	+++	++
330	++	+		331	++	+
332	++	+		333	+++	+
334	+++	+		335	++	+
336	++	+		337	++	+

[1229] [实施例22]

[1230] 人CDK6/细胞周期蛋白D3抑制活性

[1231] CDK6/细胞周期蛋白D3抑制活性的测定通过Off-chipMobility Shift Assay(MSA)法来进行。MSA法是利用电泳时的移动度根据蛋白质的分子量或电荷的差异而不同来进行分离的方法。在激酶活性测定中,用电泳的原理分离由激酶磷酸化的底物电荷向阴性的变化,通过定量磷酸化的程度,来测定激酶活性。

[1232] 将由20mM HEPES(pH7.5)、0.01％Triton X-100、2mM二硫苏糖醇构成的检测缓冲液用于各溶液调制。试验化合物溶液如下调制:将试验化合物用二甲亚砜(DMSO)调制成终浓度的100倍,然后用检测缓冲液进行25倍稀释,调制成终浓度的4倍。将将ATP/底物/Metal溶液调制为终浓度的4倍。将酶溶液调制为终浓度的2倍。基于来自酶活性的信号和阳性对照化合物的抑制活性值,将酶浓度设定为适合的终浓度。

[1233] 向384孔板中添加5μL的试验化合物溶液、5μL的ATP/底物/Metal溶液,进一步添加10μL的酶溶液或检测缓冲液,进行混合来引发酶反应。总反应液量为20μL/孔,反应液组成为20mM HEPES(pH7.5)、0.01％Triton X-100、2mM二硫苏糖醇、1000nM肽底物(DYRKtide-

F)、300μM ATP、5mM氯化镁、1％DMSO、设定的浓度的CDK6/细胞周期蛋白D3。在室温下反应5小时后，向各孔中添加60μL的终止缓冲液(QuickScout Screening Assist MSA;Carna Biosciences公司制)，使反应停止。接着，使用Caliper Lifesciences公司的LabChip3000，分离、定量反应溶液中的底物肽和磷酸化肽。通过由底物肽峰高度(S)和磷酸化肽峰高度(P)计算的产物比(P/(P+S))来评价激酶反应。

[1234] 将添加酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为100％，将添加检测缓冲液来代替酶溶液、并添加DMSO来代替试验化合物溶液时的酶活性设为0％，以此方式计算试验化合物的酶活性抑制率，并且通过拟合用量反应曲线来计算针对CDK6/细胞周期蛋白D3的50％抑制浓度。

[1235] [实施例23]

[1236] 给予本发明化合物的疾病评价

[1237] 在小鼠CAIA(Collagen Antibody-Induced Arthritis，胶原蛋白抗体诱导的关节炎)发病组(vehicle/+，给药组)中，将4.8mg/ml的针对II型胶原蛋白的单克隆抗体Cocktail(Arthritogenic MoAb Cocktail(Chondrex#53100)以250μL/只进行腹腔内给予(该日作为第1天)。在第4天将LPS(0.5mg/ml的LPS Solution(E.coli 0111:B4)(Chondrex#9028))以100μL/只进行腹腔内给予，来引发疾病。根据疾病评分，经日地进行评价直至第9天。从第4天到第8天，将药剂每天一次连日地进行口服给予。

[1238] 对于非发病组(vehicle/-组)，在第1天将PBS pH7.2(Gibco#20012-027)以250μL/只进行腹腔内给予，在第4天同样地给予LPS。

[1239] 对于所有四肢，疾病的评分设为0～4点的评分，以四肢的合计分进行评价。评分的基准如下:0:没有变化，1:仅一个指肿胀，2:手腕和脚踝肿胀、或多个指肿胀，3:手腕和脚踝肿胀和一个指以上肿胀，4:手腕和脚踝肿胀和全指肿胀。

[1240] [实施例24]

[1241] 使用培养细胞的细胞增殖评价

[1242] 为了评价对于胶质母细胞瘤的作用，实施使用培养细胞的细胞增殖评价。通过测定添加了试验化合物的培养细胞的120小时后的ATP量，来评价试验化合物对细胞增殖的影响。

[1243] 作为培养细胞，使用来源于胶质母细胞瘤的T98G细胞和U-87MG细胞，均由ATCC获取。向384孔板中添加悬浮于包含10％FBS的培养液中的45μL细胞溶液，在37℃、5％CO2条件下进行培养。培养24小时后，添加5μL的在20mM HEPES(pH7.4)中调制的试验化合物(DMSO最终浓度0.4％)，在相同条件下再次进行培养。120小时后，向各孔中添加25μL的ATPlite 1step试剂(购自PerkinElmer公司)，并摇动板2分钟。在暗处静置5分钟，使用Envision multimode reader(购自PerkinElmer公司)，记录发光信号。需说明的是，试验化合物在10^{-5}M～10^{-9}M的范围内进行评价。

[1244] 作为试验化合物添加之前的背景值如下:在24小时培养后的孔中添加5μL的包含4％DMSO的20mM HEPES(pH7.4)，添加25μL的ATPlite 1-step试剂，记录作为背景值的发光信号。另外，在相同条件下培养120小时，将所得物记录为最大发光信号(100％)。绘制各试验化合物的添加浓度及其发光信号％，并计算相对于细胞增殖的最大值的50％抑制浓度。