(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 November 2005 (24.11.2005)

PCT

(10) International Publication Number
WO 2005/111018 A1

(51) International Patent Classification[7]: C07D 401/14, 403/04, A61K 31/501, 31/5377, A61P 3/00, 25/00, C07D 403/14, 409/14, 413/14, 471/04, A61K 31/553, 31/55

(21) International Application Number: PCT/EP2005/005346

(22) International Filing Date: 17 May 2005 (17.05.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
04011734.3 18 May 2004 (18.05.2004) EP

(71) Applicant *(for all designated States except US)*: **AVENTIS PHARMA DEUTSCHLAND GMBH** [DE/DE]; Brüningstrasse 50, D-95929 Frankfurt am Main (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOELDER, Swen** [DE/DE]; Schulstrasse 54, D-60594 Frankfurt (DE). **MUELLER, Guenter** [DE/DE]; Im Haindell 1b, D-65843 Sulzbach (DE). **SCHOENAFINGER, Karl** [DE/DE]; Holunderweg 8, D-63755 Alzenau (DE). **WILL, David, William** [DE/DE]; Kirchstrasse 21, D-65830 Kriftel (DE). **MATTER, Hans** [DE/DE]; Feldbergring 37, D-63505 Langenselbold (DE). **BOSSART, Martin** [GB/DE]; Hoherodskopfstrasse 2, 63505 Langenselbold (DE).

(74) Agent: **ISENBRUCK, Günter**; Isenbruck, Bösl, Höschler, Wichmann, Huhn, Theodor-Heuss-Anlage 12, D-68165 Mannheim (DE).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

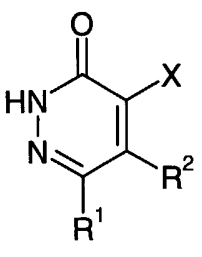
(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2005/111018 A1

(54) Title: PYRIDAZINONE DERIVATIVES, METHODS FOR PRODUCING THEM AND THEIR USE AS PHARMACEUTICALS

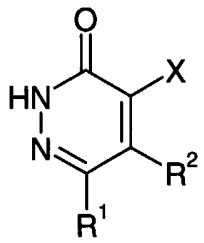


(I)

(57) Abstract: The present invention relates to compounds according to the general formula (I), with the definitions of the substituents X, R^1 and R^2 given below in the text, as well as their physiologically acceptable salts, methods for producing these compounds and their use as pharmaceuticals. Formula (I) These compounds are kinase inhibitors, in particular inhibitors of the kinase GSK15 30 (glycogen synthase kinase-3ß).

Pyridazinone derivatives, methods for producing them and their use as pharmaceuticals

The present invention relates to compounds according to the general formula (I), with the definitions of the substituents X, R^1 and R^2 given below in the text, as well as their physiologically acceptable salts, methods for producing these compounds and their use as pharmaceuticals.



(I)

These compounds are kinase inhibitors, in particular inhibitors of the kinase GSK-3β (glycogen synthase kinase-3β).

It is known from literature that in the case of metabolic diseases such as diabetes or neurodegenerative diseases such as Alzheimer's disease, there is a connection between the therapy of said diseases and the inhibition of GSK-3β or the phosphorylation of the tau-protein (S.E. Nikoulina. Diabetes 51, 2190-2198, 2002; Henrikson. Am. J. Physiol. 284, E892-900, 2003). Many compounds or pharmaceuticals, respectively, are already known to be employed for the treatment of said diseases, which compounds interfere at different places of the biochemical processes causing the respective disease. However, there is only a very limited number of compounds known until now, which effect inhibition of GSK-3β.
WO 04/046117 discloses pyridazinone derivatives, which can be employed for the inhibition of GSK-3β. They differ from the compounds of the present invention in the substitution of the pyridazinone cycle, since at position 4 of the cycle there is an amido group defined as substituent instead of a heteroaryl substituent such as pyrrole or indole.

The International Application PCT-EP 05/002179 also discloses pyridazinone derivatives, which can be employed for the inhibition of GSK-3β. In contrast to the compounds of the present invention, those compounds are substituted at position 4 of the pyridazinone cycle by a benzimidazole group. US-A 2002/0119963 discloses imidazole derivatives having activity for inhibiting CDK5, CDK2 and GSK-3. The imidazole derivatives are substituted via the first nitrogen atom, among others, with a 3-8-membered hydrocyclylalkyl or a 5-14-membered hydroaryl group, but a pyridazinone group is not explicitly disclosed therein. Additionally, the imidazole derivative is substituted with an amino group, which is further substituted with a carboxyl group. Therefore, it is evident, that the pyridazinone derivatives of the present invention are not disclosed by US-A 2002/0119963. Compounds as such explicitly disclosed by US 2002/0119963 are no subject of the present invention.

Furthermore, there are many pyridazinone derivatives described in literature, which differ from those of the present invention due to a different substitution pattern and (partially) different indications.

WO 03/059891 discloses pyridazinone derivatives that are useful for treating diseases and conditions caused or exacerbated by unregulated p38 MAP Kinase activity and/or TNF activity. The compounds described therein can be used, for example, for the treatment of inflammatory conditions, diabetes, Alzheimer's disease or cancer. They differ from the compounds of the present invention in the substitution of the pyridazinone cycle, since the nitrogen at position 2 of the cycle is mostly substituted with alky, aryl or heteroaryl and at position 4 of the cycle there is no heteroaryl group (such as pyrrole or indole) defined as substituent.

JP-A 09 216883 discloses pyridazinone derivatives which can be used to treat heart failure or high blood pressure. The pyridazinone derivatives described therein obligatorily have a pyrazolo[1,5-a]pyridine substituent in position 6, which is in turn substituted in position 2 by aryl, preferably phenyl. The pyridazinone ring itself is additionally substituted in position 2 by substituents such as hydrogen, lower alkyl or a heterocycle, while position 4 has substituents such as hydrogen, acyl, cyano, Heterocyclyl such as tetrazolyl, amino or a protected amino group. Where the substituent in position 4 is a heterocycle, it preferably has 3 to 8 ring members and is saturated. However, a heterocyclic group is not included in the

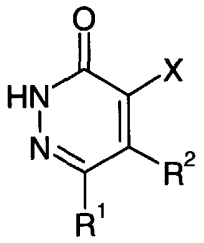
preferred substituents in position 4 of the pyridazinone ring of the compounds disclosed in this document. Compounds as such explicitly disclosed in JP-A 09 215883 are no subject of the present invention.

Bicyclic heterocycles, having an inhibiting effect on aggregation, are described in EP-A 0 639 575. Therein, it is a general formula (I) disclosed having a bicyclus containing the substituent A, from which an indole-derivative can be derived having at least one additional nitrogen atom in the cycle which contains the substituent A. Furthermore, a pyridazinone derivative can theoretically be derived from the substituent B having in turn a multimembered substituent, which mandatorily contains a 1,4-cyclohexylen or 1,4-cyclohex-3-enylen group and a carbonyl group. Therefore, it is evident, that the compounds of the present invention are not disclosed by EP-A 0 639 575. Compounds such as explicitly disclosed by EP-A 0 639 575 are no subject of the present invention.

The documents EP-A 075 436, US 4,734,415 and US 4,353,905 describe pyridazinone derivatives as antihypertensive agents and as agents which increase cardiac contractibility. These pyridazinone derivatives have a phenyl residue at position 6 of the pyridazinone cycle, said phenyl residue is additionally substituted with a heterocycle containing at least one nitrogen atom. Whereas the pyridazinone derivatives described in the documents EP-A 075 436 and US 4,353,905 do not have a substituent at position 4 of the pyridazinone cycle, those disclosed in US 4,734,415 may have an amido group substituted with lower alkyl at this position. Compounds as such, explicitly disclosed by US 4,743,415, are not a subject of the present invention.

Thus, there exists a strong need for compounds having an inhibitory effect for GSK-3β and/or the phosphorylation of the tau-protein. The object of the present invention is to provide compounds showing this ability.

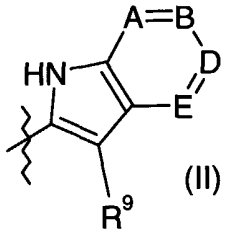
This object is attained by pyridazinone derivatives according to the below-mentioned formula (I)



(I)

wherein:

X is a residue selected from the group consisting of:



(II)

, tetrazolyl and unsubstituted and at least monosubstituted triazolyl, imidazolyl, pyrrolyl and pyrazolyl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where not more than three of the substituents A, B, D and E may be N;

R^1 is halogen;

unsubstituted or at least monosubstituted C_1-C_{10}-alkyl,

where the substituents are selected from the group consisting of: halogen, CN, NO_2, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-O-C(O)R^7$, $-NR^7R^8$, $-NR^8C(O)R^7$, $-C(O)NR^7R^8$, $-NR^8C(S)R^7$, $-C(S)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-NR^8SO_2R^7$, $-SO_2NR^7R^8$, $-O-SO_2R^7$, $-SO_2-O-R^7$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

or unsubstituted or at least monosubstituted heterocyclyl, aryl oder heteroaryl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-O-C(O)R^7$, $-NR^7R^8$, $-NR^8C(O)R^7$, $-C(O)NR^7R^8$, $-NR^8C(S)R^7$, $-C(S)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-NR^8SO_2R^7$, $-SO_2NR^7R^8$, $-O-SO_2R^7$, $-SO_2-O-R^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^2 is hydrogen or C_1-C_{10}-alkyl;

R^3 is selected from the group consisting of:

hydrogen, halogen, -CN, -NO_2, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -O-$C(O)R^8$, -NR^7R^8, -$NR^7C(O)R^8$, -$C(O)NR^7R^8$, -$NR^7C(S)R^8$, -$C(S)NR^7R^8$, -SR^8, -$S(O)R^8$, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^4 is selected from the group consisting of:

hydrogen, halogen, -CN, -NO_2, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -O-$C(O)R^8$, -NR^7R^8, -$NR^7C(O)R^8$, -$C(O)NR^7R^8$, -$NR^7C(S)R^8$, -$C(S)NR^7R^8$, -SR^8, -$S(O)R^8$, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^5 is selected from the group consisting of:

hydrogen, halogen, -CN, -NO_2, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -O-$C(O)R^8$, -NR^7R^8, -$NR^7C(O)R^8$, -$C(O)NR^7R^8$, -$NR^7C(S)R^8$, -$C(S)NR^7R^8$, -SR^8, -$S(O)R^8$, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^6 is selected from the group consisting of:

hydrogen, halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^7 is H;

or unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkyinyl, aryl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), $-C(O)NH_2$, trifluoromethyl, trifluoromethoxy, -CN, $-NH_2$, $-NH(C_1$-C_{10}-alkyl) and $-N(C_1$-C_{10}-alkyl)$_2$,

and the C_1-C_{10}-alkyl-, aryl, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^8 is H;

or unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkyinyl, aryl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -CN, -NH_2, -NH(C_1-C_{10}-alkyl) and -N(C_1-C_{10}-alkyl)$_2$,

and the C_1-C_{10}-alkyl-, aryl, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is selected from the group consisting of:

hydrogen, halogen, -CN, -NO_2, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -C(O)R^8, -C(O)OR^8, -O-C(O)R^8, -NR^7R^8, -NR^7C(O)R^8, -C(O)NR^7R^8, -NR^7C(S)R^8, -C(S)NR^7R^8, -SR^8, -S(O)R^8, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^{10} is unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, aryl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, C_2-C_{10}-alkenyl or C_2-C_{10}-alkyinyl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -CN, -NH_2, -NH(C_1-C_{10}-alkyl) and -N(C_1-C_{10}-alkyl)$_2$,

and the C_1-C_{10}-alkyl-, aryl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_6-

alkyl, C_1-C_6-alkoxy, -C(O)-(C_1-C_6-alkyl), oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

Heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

Aryl is a 6 to 10-membered, aromatic mono- or bicyclus;

Heterocyclyl is a 4- to 10-membered, non-aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S,

or a physiologically acceptable salt thereof,

with the provisio that R^1 is not unsubstituted or at least monosubstituted pyrazolo[1,5-a]pyridinyl.

The above mentioned meanings of the substituents R^1 to R^{10}, A, B, D, E, X, aryl, heteroaryl and heterocyclyl are the basic meanings (definitions) of the respective substituents.

If in the compounds of formula (I) groups, fragments, residues or substituents such as, for example, aryl, heteroaryl, alkyl etc., are present several times, they all independently from each other have the meanings indicated and may hence, in each individual case, be identical with or different from each other. The following comments apply to (for example) aryl as well as to any other residue independently from its classification as aryl group, -substituent, -fragment or –residue. Another example is the -N(C_1-C_3-alkyl)$_2$ group in which the alkyl substitutents may be identical or different (for instance 2 x ethyl or 1 x propyl and 1 x methyl).

If in the above-mentioned definitions of compounds according to formula (I) a substituent, for example aryl, is unsubstituted or at least mono-substituted with a group of further substituents, for example, C_1-C_3-alkyl, C_1-C_3-alkoxy, halogen etc.,

it applies in such cases, where there is a poly-substitution of aryl, that the selection from the group of further substituents is independently from each other. Thus, all combinations of further substituents are comprised in the case of, for example, a double-substitution of aryl. Therefore, aryl may be substituted twice with ethyl, aryl may be mono-substituted with methyl or ethoxy, respectively, aryl may be mono-substituted with ethyl or fluoro, respectively, aryl may be substituted twice with methoxy, etc..

Alkyl, alkenyl and alkynyl residues may be linear or branched, acyclic or cyclic. This also applies when they are part of other groups, for example in alkoxy groups (C_1-C_{10}-alkyl-O-), alkoxycarbonyl groups or amino groups, or when they are substituted.

Examples for alkyl groups are: methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl. This comprises both the n-isomers of these residues and isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl etc.. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example one, two, three or four, identical or different residues, for example aryl, heteroaryl, alkoxy or halogen. The substituents may be present in any desired position of the alkyl group. The term alkyl here also expressly includes cycloalkyl residues and cycloalkyl-alkyl-residues (alkyl substituted by cycloalkyl), where cycloalkyl contains at least three carbon atoms. Examples for such cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. All cycloalkyl groups may be unsubstituted or optionally substituted by one or more further residues, as exemplified above in the case of the alkyl groups.

Examples for alkenyl and alkynyl groups are the vinyl residue, the 1-propenyl residue, the 2-propenyl residue (allyl residue), the 2-butenyl residue, the 2-methyl-2-propenyl residue, the 3-methyl-2-butenyl residue, the ethynyl residue, the 2-propynyl residue (propargyl residue), the 2-butynyl residue or the 3-butynyl residue. The term alkenyl here also expressly includes cycloalkenyl residues and cycloalkenyl-alkyl-residues (alkyl substituted by cycloalkenyl) containing at least three carbon atoms. Examples for cycloalkenyl residues are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl.

The alkenyl residues may have 1 to 3 conjugated or unconjugated double bonds (thus also alk-dienyl- as well as alk-trienyl-residues), preferably one double bond in a straight or branched chain; the same applies to alkynyl residues in respect of triple bonds. The alkenyl and alkinyl residues may be unsubstituted or optionally substituted by one or more further residues, as exemplified above in the case of the alkyl groups.

Unless stated otherwise, the above-mentioned aryl, heteroaryl and heterocyclic residues may be unsubstituted or may carry one or more, for example one, two, three or four of the substituents indicated in the above definition, which substituents may be in any desired position. In monosubstituted phenyl residues, for example, the substituent may be in the 2-position, the 3-position or the 4-position, in disubstituted phenyl residues the substituents may be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents may be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-position. In fourfold substituted phenyl residues, the substituents may be in the 2,3,4,5-position, the 2,3,4,6-position, or the 2,3,5,6-position.

The above definitions as well as the following definitions relating to monovalent residues equally apply to the divalent residues phenylene, naphthylene and heteroarylene. Those divalent residues (fragments) may be attached to the adjacent groups by any ring carbon atom. In the case of a phenylene residue, these may be in 1,2-position (ortho-phenylene), 1,3-position (meta-phenylene) or 1,4-position (para-phenylene). In the case of 5-membered ring aromatics containing one heteroatom such as, for example, thiophene or furan, the two free bonds may be in 2,3-position, 2,4-position, 2,5-position or 3,4-position. A divalent residue derived from pyridine may be a 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-pyridinediyl residue. In the case of unsymmetrical divalent residues the present invention includes all positional isomers, i.e., in the case of a 2,3-pyridinediyl residue, for example, it includes the compound in which the one adjacent group is present in the 2-position and the other adjacent group is present in the 3-position as well as the compound in which the one adjacent group is present in the 3-position and the other adjacent group is present in the 2-position.

Unless stated otherwise, heteroaryl residues, heteroarylene residues, heterocyclyl residues, heterocyclylen residues and rings which are formed by two groups bonded to a nitrogen are preferably derived from completely saturated, partially unsaturated or completely unsaturated heterocycles (i.e. heterocycloalkanes, heterocycloalkenes, heteroaromatics), which contain one, two, three or four heteroatoms, which may be identical or different; more preferably they are derived from heterocycles which contain one, two, or three, in particular one or two, heteroatoms, which may be identical or different. Unless stated otherwise, the heterocycles may be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic. The rings preferably are 5-membered rings, 6-membered rings or 7-membered rings. In the case of polycyclic heterocycles containing two or more heteroatoms, they may all be within the same cycle or within different cycles.

According to the present invention, heteroaryl is a residue derived from mono- or bicyclic aromatic heterocycles. Examples of heteroaryl are: pyrrolyl, furanyl (=furyl), thiophenyl (=thienyl), imidazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,3-oxazolyl (=oxazolyl), 1,2-oxazolyl (=isoxazolyl), oxadiazolyl, 1,3-thiazolyl (= thiazolyl), 1,2-thiazolyl (=isothiazolyl), tetrazolyl, pyridinyl (=pyridyl), pyridazinyl, pyrimidinyl, pyrazinyl, 1,2,3-triazinyl, 1,2,4-triazinyl, 1,3,5-triazinyl, 1,2,4,5-tetrazinyl, indazolyl, indolyl, benzothiophenyl, benzofuranyl, benzothiazolyl, benzimidazolyl, quinolinyl (=quinolyl), isoquinolinyl (=isoquinolyl), quinazolinyl, cinnolinyl, quinoxalinyl, phthalazinyl, thienothiophenyl, 1,8-naphthyridinyl, other naphthyridinyle, purinyl pteridinyl or thiazolo[3,2-b][1,2,4]-tiazolyl. In case it is not a monocycle, each of the above heteroaryls includes for its second cycle also its saturated form (perhydro form) or its partially unsaturated form (for example in the dihydro form or the tetrahydro form) in case the respective forms are known and stable. The term "heteroaryl" as used herein comprises therefore, for example, bicyclic residues in which both cycles are aromatic as well as bicyclic residues in which only one cycle is aromatic. Such examples for heteroaryl are: 3H-indolinyl, 2(1H)-quinolinonyl, 4-oxo-1,4-dihydroquinolinyl, 2H-1-oxoisoquinolyl, 1,2-dihydroquinolinyl, 3,4-dihydroquinolinyl, 1,2-dihydroisoquinolinyl, 3,4-dihydro-isoquinolinyl, chromonyl, chromanyl, 1,3-benzodioxolyl, oxindolyl, 1,2,3,4-tetrahydroisoquinolinyl, 1,2,3,4- tetrahydroquinolinyl, 5,6-dihydroquinolyl, 5,6-dihydroisoquinolyl, 5,6,7,8-tetrahydroquinolinyl or 5,6,7,8-tetrahydroisoquinolyl,

According to the present invention, heterocyclyl is a residue derived from mono- or bicyclic non-aromatic heterocycles. Non-aromatic heterocycles comprise in the following especially heterocycloalkanes (completely saturated heterocycles) as well as heterocycloalkenes (partially unsaturated heterocycles). In the case of heterocycloalkenes there are also included compounds having two or more double bonds, which may optionally be conjugated. Examples of heterocyclyl are: pyrrolidinyl, piperidinyl, piperazinyl, imidazolidinyl, pyrazolidinyl, isothiazolidinyl, thiazolidinyl, isoxazolidinyl, oxazolidinyl, tetrahydrofuranyl, tetrahydrothiophenyl 1,3-dioxolanyl, 1,4-dioxinyl, pyranyl, thiopyranyl, tetrahydro-1,2-oxazinyl, tetrahydro-1,3-oxazinyl, morpholinyl, thiomorpholinyl, 1,2-thiazinyl, 1,3-thiazinyl, 1,4-thiazinyl, azepinyl, 1,2-diazepinyl, 1,3-diazepinyl, 1,4-diazepinyl, 1,3-oxazepinyl, 1,3-thiazepinyl, azepanyl, 2-oxo-azepanyl, 1,4-oxazepanyl, azetidinyl, azocanyl, 1,2,3,4-tetrahydropyridinyl, 1,2-dihydropyridinyl, 1,4-dihydropyridinyl, dihydropyridinonyl such as 6-oxo-1,6-dihydro-pyridinyl (= 1,6 dihydropyrdonyl) or 2-oxo-1,2-dihydro-pyridinyl (= 1,2-dihydropyridonyl), pyrimidine-2,4-dionyl, 1,2,3,6-tetrahydropyridinyl, 4(3H)-pyrimidonyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, 3-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.2.1]octyl, dihydrothiophenyl or dihydrothiopyranyl. The degree of saturation of heterocyclic groups is indicated in their individual definitions.

Substituents which may be derived from these heterocycles may be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles may carry a hydrogen atom or a substituent on a ring nitrogen atom, and examples include pyrrole, imidazole, pyrrolidine, morpholine, piperazine residues, etc. Those nitrogen heterocyclic residues may also be attached via a ring nitrogen atom, in particular if the respective heterocyclic residue is bonded to a carbon atom. For example, a thienyl residue may be present as 2-thienyl or 3-thienyl, a piperidinyl residue as 1-piperidinyl (= piperidino), 2-piperidinyl, 3-piperidinyl or 4-piperidinyl. Suitable nitrogen heterocycles may also be present as N-oxides or as quarternary salts containing a counterion which is derived from a physiologically acceptable acid. Pyridyl residues, for example, may be present as pyridine-N-oxides. Suitable sulfur-containing heterocycles may be present as S-oxid or S-S-dioxid.

According to the present invention, aryl is a residue derived from mono- or bicyclic aromatics, where the cycle does not contain any heteroatoms. In case it is not a

monocycle, the term aryl includes for its second cycle also its saturated form (perhydro form) or its partially unsaturated form (for example in the dihydro form or the tetrahydro form) in case the respective forms are known and stable. The term aryl as used herein comprises therefore, for example, bicyclic residues in which both cycles are aromatic as well as bicyclic residues in which only one cycle is aromatic. Such examples for heteroaryl are: phenyl, naphthyl, indanyl, 1,2-dihydronaphthenyl, 1,4-dihydronaphthenyl, indenyl or 1,2,3,4-tetrahydronaphth yl.

Arylalkyl (such as aryl-(C_1-C_6-alkyl)-) means an alkyl residue (such as C_1-C_6-alkyl), which in turn is substituted by an aryl residue. Heteroarylalkyl (such as heteroaryl-(C_1-C_6-alkyl)-) means an alkyl residue (such as C_1-C_6-alkyl), which in turn is substituted by a heteroaryl residue. Heterocyclylalkyl (such as heterocyclyl-(C_1-C_6-alkyl)-) means an alkyl residue (such as C_1-C_6-alkyl), which in turn is substituted by a heterocyclyl residue. Such arylalkyl, heteroarylalkyl or heterocyclylalkyl residues may themselves be a substituent of another substituent or fragment (such as heterocyclyl-(C_1-C_6-alkyl)-NH-), which means that a substituent or fragment (such as -NH-) in turn is substituted by a heterocyclylalkyl residue (such as heterocyclyl-(C_1-C_6-alkyl)-). Further possible substitutions of an alkyl residue include examples such as H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)- or (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)- , which means an alkyl residue (such as C_1-C_6-alkyl), which in turn is substituted by $-NH_2$, -NH(C_1-C_6-alkyl) or -N(C_1-C_6-alkyl)$_2$, respectively. Additionally, a residue such as (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)- may itself be a substituent of another substituent or fragment (such as (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-), which means that a substituent or fragment (such as -O-) in turn is substituted by a substituted alkyl residue (such as (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-). For the definitions and possible substitutions of alkyl, heteroaryl, heterocyclyl and aryl it is referred to the above-mentioned definitions.

Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, most preferably fluorine or chlorine.

The present invention includes all stereoisomeric forms of the compounds of the formula (I). Centers of asymmetry that are present in the compounds of formula (I) all independently of one another have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds according to the present invention

which may exist as enantiomers may be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both: the cis form and the trans form as well as mixtures of these forms in all ratios. All these forms are an object of the present invention. The preparation of individual stereoisomers may be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally, a derivatization may be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers may be carried out at the stage of the compounds of the formula (I) or at the stage of an intermediate during the synthesis. The present invention also includes all tautomeric forms of the compounds of formula (I), in particular keto-enol tautomerism, i.e. the respective compounds may be present either in their keto form or in their enol form or in mixtures thereof in all ratios.

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding physiologically or toxicologically acceptable salts.

Physiologically acceptable salts are particularly suitable for medical applications, due to their greater solubility in water compared with the starting or base compounds. Said salts must have a physiologically acceptable anion or cation. Suitable physiologically acceptable acid addition salts of the compounds of the invention are salts of inorganic acids such as hydrochloric acid, hydrobromic acid, phosphoric acid, metaphosphoric acid, nitric acid, sulfonic acid and sulfuric acid and also of organic acids such as, for example, acetic acid, theophyllinacetic acid, methylene-bis-b-oxynaphthoic acid, benzenesulfonic acid, benzoic acid, citric acid, ethanesulfonic acid, salicylic acid, fumaric acid, gluconic acid, glycolic acid, isethionic acid, lactic acid, lactobionic acid, maleic acid, malic acid, methane-sulfonic acid, succinic acid, p-toluenesulfonic acid, tartaric acid and trifluoroacetic acid. Suitable pharmaceutically acceptable basic salts are ammonium salts, alkali metal salts (such as sodium salts and potassium salts) and alkaline earth metal salts (such as magnesium salts and calcium salts).

Salts having a pharmaceutically unacceptable anion are likewise included within the scope of the present invention as useful intermediates for preparing or purifying pharmaceutically acceptable salts and/or for use in nontherapeutic applications, for example in-vitro applications.

If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions).

The respective salts according to the formula (I) may be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts.

The present invention furthermore includes all solvates of compounds of the formula (I), for example hydrates or adducts with alcohols, active metabolites of the compounds of the formula (I), and also derivatives, which contain physiologically tolerable and cleavable groups, for example esters or amides.

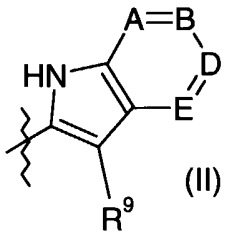
The term "physiologically functional derivative" used herein relates to any physiologically acceptable derivative of an inventive compound of the formula I, for example an ester which on administration to a mammal, for example humans, is capable of forming (directly or indirectly) a compound of the formula I or an active metabolite thereof.

The physiologically functional derivatives also include prodrugs of the compounds of the invention. Such prodrugs may be metabolized in vivo to a compound of the invention. These prodrugs may or may not be active themselves and are also object of the present invention.

The compounds of the invention may also be present in various polymorphous forms, for example as amorphous and crystalline polymorphous forms. All polymorphous forms of the compounds of the invention are included within the scope of the invention and are another aspect of the invention.

Preferred compounds of the formula (I) are those compounds in which one or more, including all, of the above-mentioned substituents R^1 to R^{10}, A, B, D, E, X, aryl, heteroaryl and heterocyclyl of the formula (I) independently from each other have the following meanings (definitions), with all possible (if defined) combinations of the preferred meanings, the more preferred meanings, the much more preferred meanings, the particularly preferred meanings or the exceptionally preferred meanings, also in combination with substituents having their basic meanings, being a subject of the present invention.

X is preferably a residue selected from the group consisting of:



(II)

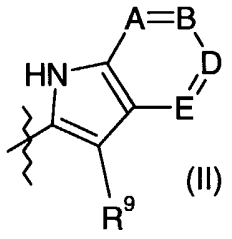
, and unsubstituted and at least monosubstituted pyrrolyl and triazolyl

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

X is more preferably a residue selected from the group consisting of:



(II)

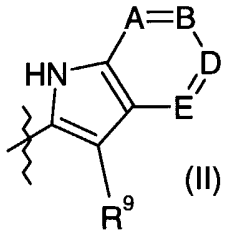
, and unsubstituted and at least monosubstituted pyrrolyl and triazolyl

where the substituents are selected from the group consisting of: halogen, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)NR^8H$, phenyl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, phenyl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

X is particularly preferred



(II)

,

which residue is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is preferably CR^3;

B is preferably CR^4;

D is preferably CR^5;

E is preferably CR^6;

Unless each of the substituents A, B, D and E has its preferred meaning, preferably only two of the substituents A, B, D and E are N; more preferably only one of the substituents A, B, D and E is N;

R^1 is preferably:

unsubstituted or at least monosubstituted C_1-C_6-alkyl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkoxy, $-NH_2$, $-NH(C_1$-C_6-alkyl), $-N(C_1$-C_6-alkyl)$_2$, heterocyclyl-(C_1-C_6-alkyl)-NH-, aryl-(C_1-C_6-alkyl)-NH-, heterocyclyl, aryl and heteroaryl,

and the aryl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_4-alkyl, C_1-C_4-alkoxy, fluor, chloro, trifluoromethyl, trifluoromethoxy or -OH;

or unsubstituted or at least monosubstituted heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: halogen, R^{10}, $-(CH_2)_n$-NR^7R^8 where n is 1 to 3, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^7H$, $-NR^7(C_1$-C_6-alkyl), $-C(O)NR^7H$, $-SR^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^1 is more preferably:

unsubstituted or at least monosubstituted phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, dihydropyridinonyl, imidazolyl, 1H-pyrrolo[2,3-b]pyridinyl, benzo[b]thiophenyl, benzodioxolyl or thiazolo[3,2-b][1,2,4]-triazolyl,

where the substituents are selected from the group consisting of: halogen, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^7H$, $-NR^7(C_1-C_6\text{-alkyl})$, $-C(O)NR^7H$, $-SR^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^1 is much more prefarably:

unsubstituted or at least monosubstituted phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, dihydropyridinonyl, imidazolyl, 1H-pyrrolo[2,3-b]pyridinyl benzo[b]thiophenyl, benzodioxolyl or thiazolo[3,2-b][1,2,4]-triazolyl,

where the substituents are selected from the group consisting of: halogen, C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, $H_2N-(C_1-C_6\text{-alkyl})$-, ($C_1-C_6$-alkyl)HN-($C_1-C_6$-alkyl)-, ($C_1-C_6$-alkyl)$_2$N-($C_1-C_6$-alkyl)-, -OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)thio-, -O-phenyl, $-NH_2$, $-N(C_1-C_6\text{-alkyl})_2$, $-NH(C_1-C_6\text{-alkyl})$, $H_2N-(C_1-C_6\text{-alkyl})-NH-$, ($C_1-C_6$-alkyl)HN-($C_1-C_6$-alkyl)-NH-, ($C_1-C_6$-alkyl)$_2$N-($C_1-C_6$-alkyl)-NH-, heterocyclyl-(C_1-C_6-alkyl)-NH-, heteroaryl-(C_1-C_6-alkyl)-NH-, phenyl-(C_1-C_6-alkyl)-NH-, trifluoromethyl, trifluoromethoxy, phenyl and heteroaryl,

and the phenyl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^1 is particularly preferred:

unsubstituted or at least monosubstituted phenyl, thiophenyl, pyrazolyl, pyridinyl or pyrimidinyl,

where the substituents are selected from the group consisting of: C_1-C_4-alkyl, -OH, C_1-C_4-alkoxy, (C_1-C_4-alkyl)thio-, (C_1-C_4-alkyl)HN-(C_1-C_4-alkyl)-, $H_2N-(C_1-C_4\text{-alkyl})$-, trifluoromethyl, trifluoromethoxy and $-NH(C_1-C_4\text{-alkyl})$,

and -NH(C_1-C_4-alkyl) may in turn be at least monosubstituted with phenyl, piperazinyl, piperidinyl or morpholinyl.

R^1 is exceptionally preferred:

pyridin-4-yl, 2-ethylamino-pyrimidin-4-yl, 3,5-dimethyl-4-hydroxyphenyl, 2-(1-phenylethylamino)-pyrimidin-4-yl, 2-(2-morpholin-4-ylethylamino)-pyrimidin-4-yl, 2-methylamino-pyrimidin-4-yl, 6-methyl-2-(2-morpholin-4-ylethylamino)-pyrimidin-4-yl, 3-methoxy-4-hydroxy-phenyl, 2-methylsulfanyl-pyrimidin-4-yl, 4-butylamino-pyrimidin-4-yl, 3-hydroxy-phenyl, thiophen-3-yl, 1H-pyrazol-4-yl, 4-hydroxy-3-methoxy-5-methylaminomethyl-phenyl, 4-hydroxy-phenyl or 2,6-dimethyl-pyrimidin-4-yl;

R^2 is preferably hydrogen or C_1-C_6-alkyl; R^2 is particularly preferred hydrogen.

R^3 is preferably selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -NR^8H, -NR^8(C_1-C_6-alkyl), -$C(O)NR^8H$, -SR^8, -SO_2NR^8H, -SO_2R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^3 is more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), -$C(O)NR^8H$, difluoromethyl, trifluoromethyl and trifluoromethoxy,

R^3 is much more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, phenyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, heteroaryl-(C_1-C_6-alkyl)-O-, phenyl-(C_1-C_6-alkyl)-O-, H_2N-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-O-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), heterocyclyl-HN-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (heterocyclyl)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, -C(O)NH_2, -C(O)N(C_1-C_6-alkyl)$_2$, -C(O)NH(C_1-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NHC(O)-, HO-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, heteroaryl-(C_1-C_6-alkyl)-NHC(O)-, phenyl-(C_1-C_6-alkyl)-NHC(O)-, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the heteroaryl-, heterocyclyl- and phenyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^3 is particularly preferred selected from the group consisting of:

hydrogen, fluoro, chloro, -C(O)OH, 2-dimethylamino-ethoxy, 2-diethylamino-ethoxy, methoxy, ethoxy, 2-piperidin-1-yl-ethoxy, piperidin-1-ylmethyl, 2-piperidin-1-yl-ethoxy, 2-(4-methyl-piperazin-1-yl)-ethoxy, 4-methyl-piperazin-1-ylmethyl, 2-morpholin-4-yl-ethoxy, 4-cyclopropyl-piperazin-1-ylmethyl, (1-cyclopropyl-piperidin-4-ylamino)-methyl, 2-carboxy-pyrrolidin-1-ylmethyl, [(1-cyclopropyl-piperidin-4-yl)methylamino]-methyl, morpholin-4-ylmethyl, 1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl, methyl, ethyl, trifluoromethyl and trifluoromethoxy;

R^3 is exceptionally preferred selected from the group consisting of:

hydrogen;

R^4 is preferably selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-NR^8H$, $-NR^8(C_1-C_6\text{-alkyl})$, $-C(O)NR^8H$, $-SR^8$, $-SO_2NR^8H$, $-SO_2R^8$, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^4 is more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)OH$, $-C(O)O-(C_1-C_6\text{-alkyl})$, $-C(O)NR^8H$, difluoromethyl, trifluoromethyl and trifluoromethoxy,

R^4 is much more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, phenyl-(C_1-C_6-alkyl)-, $H_2N-(C_1-C_6\text{-alkyl})$-, ($C_1-C_6$-alkyl)HN-($C_1-C_6$-alkyl)-, ($C_1-C_6$-alkyl)$_2$N-($C_1-C_6$-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, heteroaryl-(C_1-C_6-alkyl)-O-, phenyl-(C_1-C_6-alkyl)-O-, $H_2N-(C_1-C_6\text{-alkyl})-O$-, ($C_1-C_6$-alkyl)HN-($C_1-C_6$-alkyl)-O-, ($C_1-C_6$-alkyl)$_2$N-($C_1-C_6$-alkyl)-O-, -C(O)OH, $-C(O)O-(C_1-C_6\text{-alkyl})$, heterocyclyl-HN-($C_1-C_3$-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (heterocyclyl)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, $-C(O)NH_2$, $-C(O)N(C_1-C_6\text{-alkyl})_2$, $-C(O)NH(C_1-C_6\text{-alkyl})$, $H_2N-(C_1-C_6\text{-alkyl})-NHC(O)$-, HO-($C_1-C_6$-alkyl)-NHC(O)-, ($C_1-C_6$-alkyl)HN-($C_1-C_6$-alkyl)-NHC(O)-, ($C_1-C_6$-alkyl)$_2$N-($C_1-C_6$-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, heteroaryl-(C_1-C_6-alkyl)-NHC(O)-, phenyl-(C_1-C_6-alkyl)-NHC(O)-, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the heteroaryl-, heterocyclyl- and phenyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^4 is particularly preferred selected from the group consisting of:

hydrogen, fluoro, chloro, -C(O)OH, 2-dimethylamino-ethoxy, 2-diethylamino-ethoxy, methoxy, ethoxy, 2-piperidin-1-yl-ethoxy, piperidin-1-ylmethyl, 2-piperidin-1-yl-ethoxy, 2-(4-methyl-piperazin-1-yl)-ethoxy, 4-methyl-piperazin-1-ylmethyl, 2-morpholin-4-yl-ethoxy, 4-cyclopropyl-piperazin-1-ylmethyl, (1-cyclopropyl-piperidin-4-ylamino)-methyl, 2-carboxy-pyrrolidin-1-ylmethyl, [(1-cyclopropyl-piperidin-4-yl)methylamino]-methyl, morpholin-4-ylmethyl, 1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl, methyl, ethyl, trifluoromethyl and trifluoromethoxy;

R^5 is preferably selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-NR^8H$, $-NR^8(C_1-C_6\text{-alkyl})$, $-C(O)NR^8H$, $-SR^8$, $-SO_2NR^8H$, $-SO_2R^8$, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluormethyl, trifluoromethoxy or -OH;

R^5 is more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, -C(O)OH, $-C(O)O-(C_1-C_6\text{-alkyl})$, $-C(O)NR^8H$, difluoromethyl, trifluoromethyl and trifluoromethoxy,

R^5 is much more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, phenyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-

alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, heteroaryl-(C_1-C_6-alkyl)-O-, phenyl-(C_1-C_6-alkyl)-O-, H_2N-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-O-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), heterocyclyl-HN-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (heterocyclyl)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, -C(O)NH_2, -C(O)N(C_1-C_6-alkyl)$_2$, -C(O)NH(C_1-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NHC(O)-, HO-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, heteroaryl-(C_1-C_6-alkyl)-NHC(O)-, phenyl-(C_1-C_6-alkyl)-NHC(O)-, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the heteroaryl-, heterocyclyl- and phenyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^5 is particularly preferred selected from the group consisting of:

hydrogen, fluoro, chloro, -C(O)OH, 2-dimethylamino-ethoxy, 2-diethylamino-ethoxy, methoxy, ethoxy, 2-piperidin-1-yl-ethoxy, piperidin-1-ylmethyl, 2-piperidin-1-yl-ethoxy, 2-(4-methyl-piperazin-1-yl)-ethoxy, 4-methyl-piperazin-1-ylmethyl, 2-morpholin-4-yl-ethoxy, 4-cyclopropyl-piperazin-1-ylmethyl, (1-cyclopropyl-piperidin-4-ylamino)-methyl, 2-carboxy-pyrrolidin-1-ylmethyl, [(1-cyclopropyl-piperidin-4-yl)methylamino]-methyl, morpholin-4-ylmethyl, 1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl, methyl, ethyl, trifluoromethyl and trifluoromethoxy;

R^6 is preferably selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, -(CH_2)$_n$-NR^7R^8 where n is 1 to 3, -OR^8, -C(O)R^8, -C(O)OR^8, -NR^8H, -NR^8(C_1-C_6-alkyl), -C(O)NR^8H, -SR^8, -SO_2NR^8H, -SO_2R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^6 is more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), $-C(O)NR^8H$, difluoromethyl, trifluoromethyl and trifluoromethoxy,

R^6 is much more preferably selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, phenyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, heteroaryl-(C_1-C_6-alkyl)-O-, phenyl-(C_1-C_6-alkyl)-O-, H_2N-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-O-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), heterocyclyl-HN-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (heterocyclyl)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, $-C(O)NH_2$, -C(O)N(C_1-C_6-alkyl)$_2$, -C(O)NH(C_1-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NHC(O)-, HO-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, heteroaryl-(C_1-C_6-alkyl)-NHC(O)-, phenyl-(C_1-C_6-alkyl)-NHC(O)-, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the heteroaryl-, heterocyclyl- and phenyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^6 is particularly preferred selected from the group consisting of:

hydrogen, fluoro, chloro, -C(O)OH, 2-dimethylamino-ethoxy, 2-diethylamino-ethoxy, methoxy, ethoxy, 2-piperidin-1-yl-ethoxy, piperidin-1-ylmethyl, 2-piperidin-1-yl-ethoxy, 2-(4-methyl-piperazin-1-yl)-ethoxy, 4-methyl-piperazin-1-ylmethyl, 2-morpholin-4-yl-ethoxy, 4-cyclopropyl-piperazin-1-ylmethyl, (1-cyclopropyl-piperidin-4-ylamino)-methyl, 2-carboxy-pyrrolidin-1-ylmethyl, [(1-cyclopropyl-piperidin-4-yl)methylamino]-methyl, morpholin-4-ylmethyl, 1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl, methyl, ethyl, trifluoromethyl and trifluoromethoxy;

R^6 is exceptionally preferred hydrogen;

R^7 is preferably:

H;

or unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, phenyl or heteroaryl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, -C(O)OH, -C(O)O-(C_1-C_3-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, oxo, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^7 is more preferably:

unsubstituted or at least monosubstituted C_1-C_6-alkyl, heterocyclyl or heterocyclyl-(C_1-C_6-alkyl)-,

where the substituents are selected from the group consisting of: -OH, -C(O)OH, C_1-C_6-alkoxy, C_1-C_6-alkyl, $-NH_2$, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^7 is particularly preferred:

unsubstituted or at least monosubstituted C_1-C_4-alkyl,

where the substituents are selected from the group consisting of: morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, -C(O)OH, $-NH_2$, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, -C(O)OH, fluoro, chloro or -OH;

or morpholinyl, piperazinyl, piperidinyl, imidazolyl or pyrrolidinyl, which may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, -C(O)OH, fluoro, chloro or -OH;

R^8 is preferably:

H;

or unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, phenyl or heteroaryl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, -C(O)OH, -C(O)O-(C_1-C_3-alkyl), -

$C(O)NH_2$, trifluoromethyl, trifluoromethoxy, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, oxo, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^8 is more preferably:

unsubstituted or at least monosubstituted C_1-C_6-alkyl, heterocyclyl or heterocyclyl-$(C_1-C_6\text{-alkyl})$-,

where the substituents are selected from the group consisting of: -OH, $-C(O)OH$, C_1-C_6-alkoxy, C_1-C_6-alkyl, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, $-C(O)OH$, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^8 is particularly preferred:

unsubstituted or at least monosubstituted C_1-C_4-alkyl,

where the substituents are selected from the group consisting of: morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, $-C(O)OH$, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, $-C(O)OH$, fluoro, chloro or -OH;

or morpholinyl, piperazinyl, piperidinyl, imidazolyl or pyrrolidinyl, which may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, $-C(O)OH$, fluoro, chloro or -OH;

R^9 is preferably selected from the group consisting of:

hydrogen, halogen, -CN, R^{10},, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)O-(C_1-C_6\text{-alkyl})$, $-C(O)-(C_1-C_6\text{-alkyl})$, $-SR^8$, $-C(O)NR^8H$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is more preferably selected from the group consisting of:

hydrogen; halogen; $-C(O)-(C_1-C_3\text{-alkyl})$; $(C_1-C_6\text{-alkyl})$thio-; trifluoromethyl; trifluoromethoxy;

unsubstituted and at least monosubstituted C_1-C_6-alkyl and C_2-C_6-alkenyl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, phenyl, -OH, C_1-C_6-alkoxy, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and phenyl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, $-CO-(C_1-C_3\text{-alkyl})$, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

and heteroaryl and phenyl, which in turn may be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluormethyl, trifluoromethoxy or -OH

R^9 is much more preferably selected from the group consisting of:

hydrogen; bromo; chloro; $-C(O)-(C_1-C_3\text{-alkyl})$;

unsubstituted and at least monosubstituted C_1-C_4-alkyl and C_2-C_4-alkenyl,

where the substituents are selected from the group consisting of: phenyl azetidinyl, pyridinyl, pyrazolyl, pyrimidinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and phenyl, azetidinyl, pyridinyl, pyrazolyl, pyrimidinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

and phenyl, pyrazolyl, imidazolyl and pyridinyl, which may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is particularly preferred:

hydrogen, chloro, acetyl, methyl, ethyl, isobutyl, 1-methyl-1H-pyrazol-4-yl, morpholin-4-ylmethyl and phenyl;

R^{10} is preferably:

unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)- or C_2-C_6-alkenyl,

where the substituents are selected from the group consisting of: halogen, -C_1-C_6-alkyl, C_1-C_6-alkoxy, -OH, -C(O)-C_1-C_3-alkyl, -C(O)OH, -C(O)O-(C_1-C_3-alkyl), $-C(O)NH_2$, $-NH_2$, $-NH(C_1-C_6\text{-alkyl})$ and $-N(C_1-C_6\text{-alkyl})_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^{10} is particularly preferred:

unsubstituted or at least monosubstituted C_1-C_4-alkyl or C_2-C_4-alkenyl,

where the substituents are selected from the group consisting of: phenyl, azetidinyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, -C(O)OH, C_1-C_3-alkoxy, $-NH_2$, -NH(C_1-C_3-alkyl) and -N(C_1-C_3-alkyl)$_2$,

and phenyl, azetidinyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, -C(O)OH, fluoro, chloro or -OH;

Heteroaryl is preferably imidazolyl, thiophenyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzo[b]thiophenyl, thiazolo[3,2-b][1,2,4]-triazolyl, pyrrolyl, chinolinyl, isochinolinyl, 1,2,3,4-tetrahydrochinolinyl, benzimidazolyl, indolyl or 1,3-benzodioxolyl; heteroaryl is particularly preferred pyridinyl, pyrazolyl, thiophenyl or pyrimidinyl;

Aryl is preferably naphthyl, indanyl or phenyl; aryl is particularly preferred phenyl.

Heterocyclyl is preferably acetidinyl, azepanyl, thiomorpholinyl, 1,4-oxazepanyl, azocanyl, 3-azabicyclo[3.2.2]nonyl, 6-azybicyclo[3.2.1]octyl, dihydropyridinonyl, pyrimidindionyl, 4-oxo-azepanyl, 1,4-diazepanyl, tetrahydrofuranyl, 1,3-dioxolanyl, morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl; heterocyclyl is particularly preferred piperidinyl, morpholinyl or piperazinyl;

Examples for embodiments of preferred compounds of the formula (I) in reference to the above described definitions are:

i) R^1 to R^{10}, A, B, D, E, X heteroaryl, heterocyclyl and aryl have each its preferred meaning; or

ii) R^1 has its preferred meaning and all other substituents have their basic meaning; or

iii) R^2 has its particularly preferred meaning and all other substituents have their basic meaning; or

iv) R^3 to R^6 have each its preferred meaning and all other substituents have their basic meaning; or

v) R^7 and R^8 have each its preferred meaning and all other substituents have their basic meaning; or

vi) R^9 has its preferred meaning and all other substituents have their basic meaning; or

vii) R^{10} has its preferred meaning and all other substituents have their basic meaning; or

viii) A has its preferred meaning and all other substituents have their basic meaning; or

ix) B has its preferred meaning and all other substituents have their basic meaning; or

x) D has its preferred meaning and all other substituents have their basic meaning; or

xi) E has its preferred meaning and all other substituents have their basic meaning; or

xii) X has its preferred meaning and all other substituents have their basic meaning; or

xiii) A, B, D and E have each its preferred meaning and all other substituents have their basic meaning; or

xiv) A, B, D and E have each its preferred meaning, X has its particularly preferred meaning, and all other substituents have their basic meaning; or

xv) Heteroaryl has its preferred meaning and all other substituents have their basic meaning; or

xvi) Heterocyclyl has its preferred meaning and all other substituents have their basic meaning; or

xvii) Aryl has its preferred meaning and all other substituents have their basic meaning; or

xviii) R^1 to R^{10}, X heteroaryl, heterocyclyl and aryl have each its preferred meaning and A, B, D and E have their basic meaning, where only two of them may be N; or

xix) R^1, R^3, R^4, R^5, R^6 and R^9 have each its more preferred meaning, R^7, R^8, R^{10}, heteroaryl, heterocyclyl and aryl have each its preferred meaning, R^2 and X have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xx) R^1, R^3, R^4, R^5, R^6 and R^9 have each its much more preferred meaning, heterocyclyl and heteroaryl have each its preferred meaning, R^2 and X have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xxi) R^2, R^3, R^4, R^5, R^6, R^9 and X have each its particularly preferred meaning, R^1 has its exceptionally preferred meaning; B, D and E have each its preferred meaning and A has its basic meaning; or

xxii) R^2, R^4, R^5, R^9 and X have each its particularly preferred meaning, R^1, R^3 and R^6 have each its exceptionally preferred meaning, B, D and E have each its preferred meaning and A has its basic meaning; or

xxiii) R^2, R^3, R^4, R^5, R^6, R^9 and X have each its particularly preferred meaning, R^1 has its exceptionally preferred meaning and A, B, D and E have their basic meaning, where only two of them may be N; or

xxiv) R^2, R^3, R^4, R^5, R^6, R^9 and X have each its particularly preferred meaning, R^1 has its much more preferred meaning, B, D, E, heteroaryl and heterocyclyl have each its preferred meaning and A has its basic meaning; or

xxv) R^2, R^9 and X have each its particularly preferred meaning, R^3, R^4, R^5 and R^6 have each its much more preferred meaning, R^1 has its exceptionally preferred meaning, B, D, E, heteroaryl and heterocyclyl have each its preferred meaning and A has its basic meaning; or

xxvi) R^2, R^3, R^4, R^5, R^6 and X have each its particularly preferred meaning, R^9 has its much more preferred meaning, R^1 has its exceptionally preferred meaning, B, D, E, heteroaryl and heterocyclyl have each its preferred meaning and A has its basic meaning; or

xxvii) R^2, R^3, R^4, R^5, R^6, R^8 and R^{10} have each its particularly preferred meaning, R^9 has its much more preferred meaning, X has its more preferred meaning, R^1 has its exceptionally preferred meaning, B, D, E, heteroaryl and heterocyclyl have each its preferred meaning and A has its basic meaning; or

xxviii) R^1 and R^9 have each its much more preferred meaning, R^3 and R^6 have each its exceptionally preferred meaning, R^2, R^4, R^5 and X have each its particularly preferred meaning and A, B, D, E, heterocyclyl and heteroaryl have each its preferred meaning; or

xxix) R^1 and R^9 have each its much more preferred meaning, X has its more preferred meaning, R^3, R^4, R^5, R^6, aryl, heterocyclyl and heteroaryl have each its preferred meaning, R^2, R^8 and R^{10} have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only two of them may be N; or

xxx) R^3, R^4, R^5, R^6 and R^9 have each its much more preferred meaning, heteroaryl and heterocyclyl have each its preferred meaning, R^1, R^2 and X have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xxxi) R^1, R^3, R^4, R^5, R^6 and R^9 have each its much more preferred meaning, aryl, heterocyclyl and heteroaryl have each its preferred meaning, R^2, R^7, R^{10} and X have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xxxii) R^1, R^3, R^4, R^5, R^6, R^7, R^8 and R^9 have each its more preferred meaning, X has its particularly preferred meaning, R^2, R^{10}, heteroaryl, heterocyclyl and aryl have each its preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xxxiii) R^1 has its more preferred meaning, R^9 has its much more preferred meaning, R^7, R^8, R^{10}, heteroaryl, heterocyclyl and aryl have each its preferred meaning, R^3 and R^6 have each its exceptionally preferred meaning, R^2, R^4, R^5 and X have each its particularly preferred meaning and A, B, D and E have their basic meaning, where only one of them may be N; or

xxxiv) R^2 to R^{10}, X heteroaryl, heterocyclyl and aryl have each its preferred meaning and R^1, A, B, D and E have their basic meaning, where only two of them may be N; or

xxxv) R^1, R^2, R^7 to R^{10}, X heteroaryl, heterocyclyl and aryl have each its preferred meaning and R^3 to R^6, A, B, D and E have their basic meaning, where only two of them may be N; or

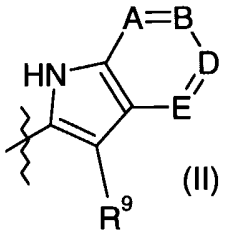
As indicated before, the preferred compounds according to formula (I) are not limited to the above examples. Furthermore, all combinations of each substituent in its basic meaning with the preferred meanings, the more preferred meanings, the much more preferred meanings, the particularly preferred meanings or the exceptionally preferred meanings of the other substituents or all combinations of the preferred meanings, the more preferred meanings, the much more preferred meanings, the particularly preferred meanings or the exceptionally preferred meanings of the respective substituents, which are not exemplified above, are also a subject of the present invention. It is self-evident, that this is only the case, if the definitions of the respective substituents allow such a combination.

Most preferred compounds according to the general formula (I) are selected from the group consisting of:

4-(5-chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(5-trifluoromethyl-1H-indol-2-yl)-2H-pyridazin-3- one; 4-(3-phenyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-ethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-acetyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[5-(2-piperidin-1-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-{6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[5-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(2-morpholin-4-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(4-cyclopropyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-{6-[(1-cyclopropyl-piperidin-4-ylamino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, (S)-1-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid, 4-(6-{[(1-cyclopropyl-piperidin-4-yl)-methyl-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(6-morpholin-4-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one, 2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid, 4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[3-isobutyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one, 6-(3-hydroxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one, 4-{6-[1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(1H-pyrrolo[3,2-b]pyridin-2-yl)-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-thiophen-3-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3-methoxy-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3- one and 4-(3-chloro-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one.

In a further embodiment of the present invention the compounds according to general formula (I) are defined as follows:

X is a residue selected from the group consisting of:



(II)

, tetrazolyl and unsubstituted and at least monosubstituted triazolyl, imidazolyl, pyrrolyl and pyrazolyl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where not more than three of the substituents A, B, D and E may be N;

R^1 is halogen;

unsubstituted or at least monosubstituted C_1-C_{10}-alkyl,

where the substituents are selected from the group consisting of: halogen, -CN, -NO_2, -OR^7, -$C(O)R^7$, -$C(O)OR^7$, -O-$C(O)R^7$, -NR^7R^8, -$NR^8C(O)R^7$, -$C(O)NR^7R^8$, -$NR^8C(S)R^7$, -$C(S)NR^7R^8$, -SR^7, -$S(O)R^7$, -SO_2R^7, -$NR^8SO_2R^7$, -$SO_2NR^7R^8$, -O-SO_2R^7, -SO_2-O-R^7, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or OH;

or unsubstituted or at least monosubstituted aryl oder heteroaryl,

where the substituents are selected from the group consisting of: halogen, -CN, -NO_2, R^{10}, -OR^7, -$C(O)R^7$, -$C(O)OR^7$, -O-$C(O)R^7$, -NR^7R^8, -$NR^8C(O)R^7$, -$C(O)NR^7R^8$, -$NR^8C(S)R^7$, -$C(S)NR^7R^8$, -SR^7, -$S(O)R^7$, -SO_2R^7, -$NR^8SO_2R^7$, -$SO_2NR^7R^8$, -O-SO_2R^7, -SO_2-O-R^7, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or OH;

R^2 is hydrogen or C_1-C_{10}-alkyl;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, halogen, -CN, NO_2, R^{10}, -OR^8, -$C(O)R^8$, -$C(O)OR^8$, -O-$C(O)R^8$, -NR^7R^8, -$NR^7C(O)R^8$, -$C(O)NR^7R^8$, -$NR^7C(S)R^8$, -$C(S)NR^7R^8$, -SR^8, -$S(O)R^8$, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^7 and R^8 are independently from each other:

H;

or unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkyinyl, heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, oxo, halogen, -OH, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, C(O)OH, -C(O)O-(C_1-C_6-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -CN, -NH_2, -NH(C_1-C_{10}-alkyl) and -N(C_1-C_{10}-alkyl)$_2$,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is selected from the group consisting of:

hydrogen, halogen, -CN, -NO_2, R^{10}, -OR^8, -C(O)R^8, -C(O)OR^8, -O-C(O)R^8, -NR^7R^8, -NR^7C(O)R^8, -C(O)NR^7R^8, -NR^7C(S)R^8, -C(S)NR^7R^8, -SR^8, -S(O)R^8, -SO_2R^8, -$NR^7SO_2R^8$, -$SO_2NR^7R^8$, -O-SO_2R^8, -SO_2-O-R^8, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^{10} is unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkyinyl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), -C(O)NH_2,

trifluoromethyl, trifluoromethoxy; -CN, $-NH_2$, $-NH(C_1-C_{10}\text{-alkyl})$ and $-N(C_1-C_{10}\text{-alkyl})_2$,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, $-C(O)-(C_1-C_6\text{-alkyl})$, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

Heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

Aryl is a 6 to 10-membered, aromatic mono- or bicyclus;

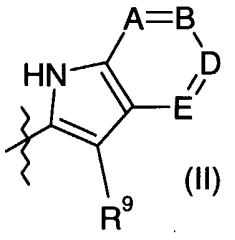
Heterocyclyl is a 4- to 10-membered, non-aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

or a physiologically acceptable salt thereof.

Preferably, in this further embodiment the substituent R^1 is not unsubstituted or at least monosubstituted pyrazolo[1,5-a]pyridinyl.

More preferred compounds of this further embodiment are defined as follows:

X is a residue selected from the group consisting of:



(II)

, and unsubstituted and at least monosubstituted pyrrolyl,

where the substituents are selected from the group consisting of: fluoro; chloro; bromo; trifluoromethyl; trifluoromethoxy;

unsubstituted and at least monosubstituted phenoxy, phenyl and pyridinyl,

where the substituents are selected from the group consisting of: C_1-C_6-alkyl, C_1-C_6-alkoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy and -OH;

and unsubstituted and at least monosubstituted C_1-C_6-alkyl and C_1-C_6-alkoxy,

where the substituents are selected from the group consisting of: phenyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, $-NH_2$, $-NH(C_1$-C_6-alkyl) and $-N(C_1$-C_6-alkyl$)_2$,

and phenyl, azetidinyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where only one of the substituents A, B, D and E may be N;

R^1 is: unsubstituted or at least monosubstituted phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, 1H-pyrrolo[2,3-

b]pyridinyl, benzo[b]thiophenyl, benzodioxolyl or thiazolo[3,2-b][1,2,4]-triazolyl,

where the substituents are selected from the group consisting of: halogen, C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)thio-, -O-phenyl, $-NH_2$, $-N(C_1$-C_6-alkyl$)_2$, $-NH(C_1$-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NH-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NH-, (C_1-C_6-alkyl$)_2$N-(C_1-C_6-alkyl-NH-, heterocyclyl-(C_1-C_6-alkyl)-NH-, heteroaryl-(C_1-C_6-alkyl)-NH-, phenyl-(C_1-C_6-alkyl)-NH-, trifluoromethyl, trifluoromethoxy, phenyl and heteroaryl,

and the phenyl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^2 is hydrogen;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, fluoro, chloro, bromo, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl$)_2$N-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, H_2N-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl$)_2$N-(C_1-C_6-alkyl)-O-, $-C(O)N(C_1$-C_6-alkyl$)_2$, $-C(O)NH(C_1$-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NHC(O)-, HO-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl$)_2$N-(C_1-C_6-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, trifluoromethyl and trifluoromethoxy,

and the heterocyclyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is selected from the group consisting of:

hydrogen; chloro; iodo; bromo; -C(O)-(C_1-C_3-alkyl);

unsubstituted and at least monosubstituted C_1-C_4-alkyl and C_2-C_4-alkenyl,

where the substituents are selected from the group consisting of: phenyl azetidinyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, $-NH_2$, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and phenyl, azetidinyl, pyridinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

and phenyl, imidazolyl and pyridinyl, which may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH

Heteroaryl is imidazolyl, thiophenyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzo[b]thiophenyl, thiazolo[3,2-b][1,2,4]-triazolyl, pyrrolyl, chinolinyl, isochinolinyl, 1,2,3,4-tetrahydrochinolinyl, benzoimidazolyl, indolyl or 1,3-benzodioxolyl;

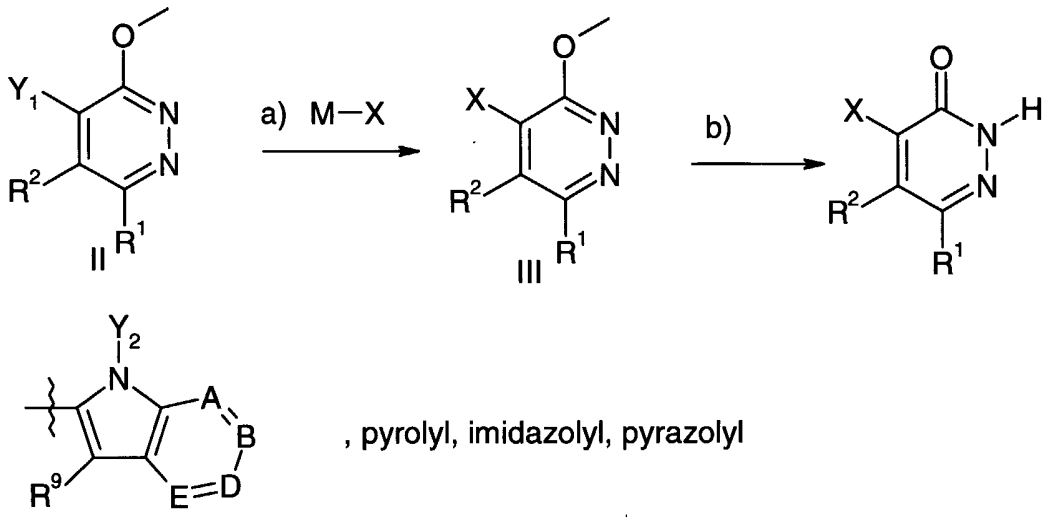
Heterocyclyl is acetidinyl, azepanyl, 4-oxo-azepanyl, 1,4-diazepanyl, tetrahydrofuranyl, 1,3-dioxolanyl, morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

or a physiologically acceptable salt thereof.

Compounds of this invention may be prepared by known methods or in accordance with the reaction sequences described below. The starting materials used in the preparation of compounds of the invention are known or commercially available, or can be prepared by known methods or by specific reaction schemes described herein.

The below schemes illustrate some important routes for preparing compounds according to formula (I)

Scheme 1:



Y_1 = Cl, Br or I

Y_2 = H or a suitable protecting group, preferably tert-butoxycarbonyl (Boc)

Thus, for example a compound of the formula I is obtained from intermediates II by metal catalysed coupling and elimination of the methylgroup.

M may be for example $B(OH)_2$, $B(OC_1\text{-}C_{10}\text{-alkyl})_2$, $Sn(C_1\text{-}C_{10}\text{-alkyl})_3$, $Zn(C_1\text{-}C_{10}\text{-alkyl})$. Intermediates II and M-X are either commercially available or are prepared by procedures known to a person skilled in the art.

In case Y_2 is a protecting group, said group is removed using methods known by a person skilled in the art.

Elimination of the methylgroup in step b) from compounds of the formula III can be carried out using any suitable reagent known by a person skilled in the art.

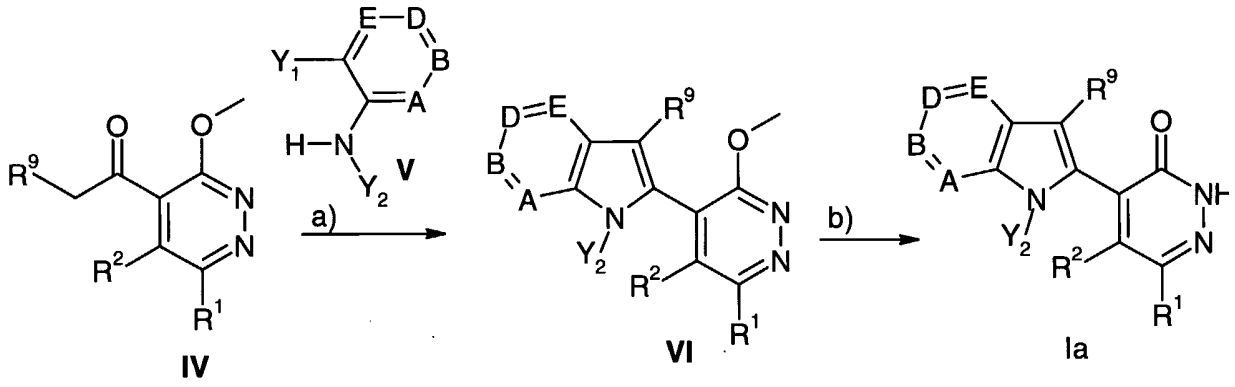
Optionally A, B, D, E, R1 and R^9 can be modified after the metal catalysed coupling. For example, if R^1 = Cl, Br, I, it can be exchanged by palladium Suzuki or Stille coupling. (I. Parrot et al., Synthesis; 7, 1999; 1163-1168)

If R^9 =H, it can be converted to Cl, Br or I by procedures know to a person skilled in the art. Furthermore, Cl, Br and I may in turn be exchanged with other

substituents being defined for R^9 by standard metal catalysed procedures known to a person skilled in the art.

Through a different process according to scheme II, compounds of the formula I are obtained from intermediates IV and V by palladium catalysed indol synthesis and elimination of the methylgroup in step b). (C. Chen, D. Lieberman, R. D. Larsen, T. R. Verhoeven, P. J. Reider, *J. Org. Chem.* **1997**, *62*, 2676-2677)

Scheme 2:



Y_1= Cl, Br or I

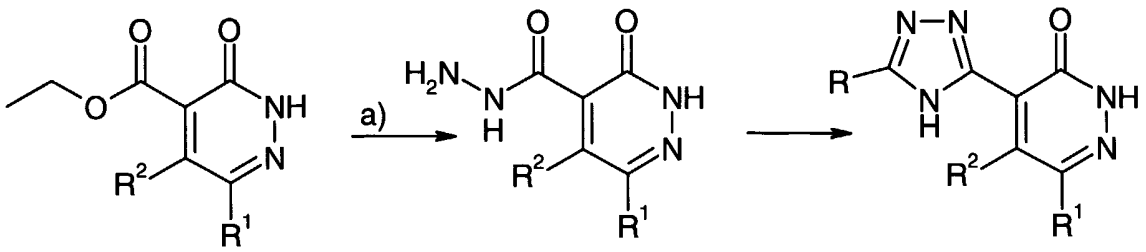
Y_2= H or a suitable protecting groups, preferably tert-butoxycarbonyl (Boc)

Optionally, A, B, D, E, R^1 and R^9 can be modified after the metal catalysed coupling. For example, if R^1= Cl, Br, I it can be exchanged by palladium Suzuki or Stille coupling.

If R^9=H, it can be converted to Cl, Br or I by procedures know to a person skilled in the art. Cl, Br and I may in turn be exchanged with other substituents being defined for R^9 by standard metal catalysed procedures known to a person skilled in the art.

Yet another process to compounds of the formula 1, where X is a substituted triazolyl and R has the same definition as R^3, is outlined in the following scheme 3.

Scheme 3:



VII VIII

Compounds of the formula VIII can be obtained as outlined in the scheme from intermediates VII by procedures known to a person skilled in the art. In step a) compound VII is reacted with a suitable hydrazine, followed by conversion with a suitable acetimidic acid ester in steb b) to obtain a compound of formula (VIII).

Intermediates VII are either commercially available or synthesized by procedures known to a person skilled in the art.

All reactions for the synthesis of the compounds of the formula (I) are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in Houben-Weyl, Methoden der Organischen Chemie (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or Organic Reactions, John Wiley & Sons, New York. Depending on the circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of the formula (I), it can be necessary or advantageous to temporarily block functional groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later reaction step are converted into the desired functional groups. Such synthesis strategies and protective groups and precursor groups which are suitable in an individual case are known to the skilled person. If desired, the compounds of the formula (I) can be purified by customary purification procedures, for example by recrystallization or chromatography. The starting compounds for the preparation of the compounds of the formula (I) are commercially available or can be prepared according to or analogously to literature procedures. The compounds obtained with the above-mentioned synthesis methods are a further object of the present invention.

Subject of the present invention is also the use of compounds according to the general formula (I) as pharmaceuticals or medicaments, respectively. With respect to the definition of the substituents X, R^1 and R^2 (as well as all further substituents defined by the before-mentioned substituents) the same explanations as laid out above in the context with the compounds as such apply.

Compounds of the formula (I) for use as pharmaceutical, in which one or more, including all, of the above-mentioned substituents have the preferred meanings, the more preferred meanings, the much more preferred meanings, the particularly preferred meanings or the exceptionally preferred meanings defined above, including all possible combinations, are also a subject of the present invention.

The compounds of general formula (I) are kinase inhibitors and can therefore be employed for the treatment of diseases, which may result from an abnormal activity of kinases. As abnormal kinase activity, there may be mentioned, for example, that of PI3K, AkT, GSK-3β and the like.

In particular, compounds according to the present invention can be used for the inhibition of the kinase GSK-3β. This effect is particularly relevant for the treatment of metabolic diseases such as type II diabetes or neurodegenerative diseases such as Alzheimer's disease.

Furthermore, compounds according to the general formula (I) have an inhibitory effect in respect of the phosphorylation of the tau-protein. This effect is particularly relevant for the treatment of neurodegenerative diseases such as Alzheimer's disease.

Examples of diseases, which can be treated with the compounds according to the present invention, include: neurodegenerative diseases, strokes, cranial and spinal traumas and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X or immunodeficiency. Neurodegenerative diseases are preferably: Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration and Pick's disease.

Compounds according to the present invention are preferably employed for the treatment of metabolic diseases, in particular of type II diabetes.

In another embodiment of the present invention, the compounds according to the general formula (I) are preferably employed for the treatment of neurodegenerative diseases, in particular of Alzheimer's disease.

In the above-mentioned explanation the item treatment also includes prophylaxis, therapy or curing of the above-mentioned diseases.

All references to "compound(s) according to formula (I)" refer hereinbelow to a compound/compounds of the formula (I) as described above and also to their salts, solvates and physiologically functional derivatives as described herein.

The compounds of the formula (I) can be administered to animals, preferably to mammals, and in particular to humans. The compounds of the formula (I) can be administered as pharmaceuticals by themselves, in mixtures with one another or in mixtures with other pharmaceuticals or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the use of the compounds of the formula (I) for preparing one or more medicaments for prophylaxis and/or treatment of the before-mentioned diseases, pharmaceutical preparations (or pharmaceutical compositions) comprising an effective dose of at least one compound of the formula (I) as well as pharmaceutical preparations comprising an effective dose of at least one compound of the formula (I) for prophylaxis and/or treatment of the before-mentioned diseases

The amount of a compound according to formula (I) which is required in order to attain the desired biological effect depends on a number of factors, for example the specific compound selected, the intended use, the type of administration and the clinical state of the patient. In general, the daily dose is in the range from 0.3 mg to 100 mg (typically from 3 mg to 50 mg) per day per kilogram of body weight, for example 3-10 mg/kg/day. An intravenous dose can be, for example, in the range from 0.3 mg to 1.0 mg/kg and can be administered in a suitable manner as an infusion of 10 ng to 100 ng per kilogram per minute. Suitable infusion solutions for these purposes may contain, for example, from 0.1 ng to 10 mg, typically from 1 ng to 10 mg per milliliter. Individual doses may contain, for

example, from 1 mg to 10 g of the active compound. Thus, ampoules for injections can contain, for example, from 1 mg to 100 mg, and orally administerable individual dose formulations such as, for example, tablets or capsules can contain, for example, from 1.0 to 1000 mg, typically from 10 to 600 mg. In the case of pharmaceutically acceptable salts, the abovementioned masses relate to the mass of the free compound on which the salt is based. The compound used for the prophylaxis or therapy of the abovementioned conditions may be the compounds according to formula (I) themselves, but they are preferably present in the form of a pharmaceutical composition together with an acceptable carrier. The carrier must be naturally acceptable, in the sense that it is compatible with the other ingredients of said composition and is not harmful to the patient's health. The carrier may be a solid or a liquid or both and is preferably formulated with the compound as an individual dose, for example as a tablet which may contain from 0.05% to 95% by weight of the active compound. Further pharmaceutically active substances may also be present, including further compounds according to formula (I). The pharmaceutical compositions of the invention may be prepared according to any of the known pharmaceutical methods which essentially comprise mixing the ingredients with pharmacologically acceptable carriers and/or excipients.

Besides at least one compound according to formula (I) as well as one or more carriers, the pharmaceutical preparations can also contain additives. As additives can be employed, for example: fillers, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents, buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The pharmaceutical compositions of the invention may be in form of a pill, tablet, lozenge, coated tablet, granule, capsule, hard or soft gelatin capsule, aqueous solution, alcoholic solution, oily solution, syrup, emulsion suspension pastille suppository, solution for injection or infusion, ointment, tincture, cream, lotion, powder, spray, transdermal therapeutic systems, nasal spray, aerosol mixture, microcapsule, implant, rod or plaster.

Pharmaceutical compositions of the invention are those which are suitable for oral, rectal, topical, peroral (e.g. sublingual) and parenteral (e.g. subcutaneous, intramuscular, intradermal or intravenous) administration, although the most suitable manner of administration depends in each individual case on the nature and severity of the condition to be treated and on the nature of the compound according to formula (I) used in each case. Sugar-coated formulations and sugar-coated delayed-release formulations, too, are included within the scope of the invention. Preference is given to acid-resistant and enteric formulations. Suitable enteric coatings include cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl-methylcellulose phthalate and anionic polymers of methacrylic acid and methyl methacrylate.

Suitable pharmaceutical compounds for oral administration may be present in separate units as, for example, capsules, cachets, lozenges or tablets, which in each case contain a particular amount of the compound according to formula (I); as powders (gelatin capsules or cachets) or granules; as solution or suspension in an aqueous or nonaqueous liquid; or as an oil-in-water or water-in-oil emulsion. As already mentioned, said compositions can be prepared according to any suitable pharmaceutical method which includes a step in which the active compound and the carrier (which may comprise one or more additional components) are contacted. In general, the compositions are prepared by uniform and homogeneous mixing of the active compound with a liquid and/or finely dispersed solid carrier, after which the product is shaped, if necessary. Thus a tablet, for example, may be prepared by pressing or shaping a powder or granules of the compound, where appropriate with one or more additional components. Pressed tablets can be prepared by tableting the compound in free-flowing form, for example a powder or granules, mixed, where appropriate, with a binder, lubricant, inert diluent and/or one or more surface active/dispersing agents in a suitable machine. Shaped tablets can be prepared by shaping the pulverulent compound, moistened with an inert liquid diluent, in a suitable machine. As diluents can be used, for example, starch, cellulose, saccharose, lactose or silica. The pharmaceutical compositions of the invention may also comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talc, a coloring, a coating (sugar-coated tablets) or a varnish.

Pharmaceutical compositions which are suitable for peroral (sublingual) administration include lozenges which contain a compound according to formula (I) with a flavoring, usually sucrose and gum arabic or tragacanth, and pastilles which comprise the compound in an inert base such as gelatin and glycerol or sucrose and gum arabic.

Suitable pharmaceutical compositions for parenteral administration preferably comprise sterile aqueous preparations of a compound according to formula (I) which are preferably isotonic with the blood of the intended recipient. These preparations are preferably administered intravenously, although they may also be administered subcutaneously, intramuscularly or intradermally as an injection. Said preparations may preferably be prepared by mixing the compound with water and rendering the obtained solution sterile and isotonic with the blood. Injectable compositions of the invention generally contain from 0.1 to 5% by weight of the active compound.

These sterile compositions for parenteral administration may be preferably solutions which are aqueous or non aqueous, suspensions or emulsions. As solvent or vehicle, there may be used water, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, organic esters for injection, for example ethyl oleate or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing mediums. The sterilization may be carried out in several ways, for example by an aseptic filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or in any other sterile medium for injection.

Suitable pharmaceutical compositions for rectal administration are preferably present as individual dose suppositories. These may be prepared by mixing a compound according to formula (I) with one or more conventional solid carriers, for example cocoa butter, and shaping the resulting mixture.

Suitable pharmaceutical compositions for topical application to the skin are preferably present as ointment, cream, lotion, paste, spray, aerosol or oil. Carriers which may be used are petroleum jelly, lanolin, polyethylene glycols, alcohols and

combinations of two or more of these substances. In general, the active compound is present at a concentration of from 0.1 to 15%, for example from 0.5 to 2%, by weight of the composition.

Transdermal administration is also possible. Suitable pharmaceutical compositions for transdermal administration may be present as individual patches which are suitable for long-term close contact with the epidermis of the patient. Such patches suitably contain the active compound in an optionally buffered aqueous solution, dissolved and/or dispersed in an adhesive or dispersed in a polymer. A suitable active compound concentration is from approx. 1% to 35%, preferably approx. 3% to 15%. A particular possibility is the release of the active compound by electro-transport or iontophoresis, as described, for example, in Pharmaceutical Research, 2(6): 318 (1986).

The following examples illustrate compositions according to the invention:

EXAMPLE A

Gelatin capsules containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I)..... 50 mg
- Cellulose..... 18 mg
- Lactose..... 55 mg
- Colloidal silica..... 1 mg
- Sodium carboxymethylstarch..... 10 mg
- Talc..... 10 mg
- Magnesium stearate..... 1 mg

EXAMPLE B

Tablets containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I)..... 50 mg

- Lactose..... 104 mg
- Cellulose..... 40 mg
- Polyvidone..... 10 mg
- Sodium carboxymethylstarch..... 22 mg
- Talc..... 10 mg
- Magnesium stearate..... 2 mg
- Colloidal silica..... 2 mg
- Mixture of hydroxymethylcellulose, glycerin, titanium oxide (72-3.5-24.5) qs 1 finished film-coated tablet of 245 mg

EXAMPLE C

A solution for injection containing 10 mg of active product and having the following composition is prepared:

- Compound of formula (I)..... 10 mg
- Benzoic acid..... 80 mg
- Benzyl alcohol..... 0.06 ml
- Sodium benzoate..... 80 mg
- Ethanol at 95 %..... 0.4 ml
- Sodium hydroxide..... 24 mg
- Propylene glycol..... 1.6 ml
- Water.....qs 4 ml

Another subject of the present invention is the combination of compounds of the formula (I) with other pharmaceutically active substances not covered by formula (I).

The compounds of the formula (I) are distinguished by beneficial actions on the metabolism of lipids, and they are particularly suitable for weight reduction and, after weight reduction, for maintaining a reduced weight in mammals and as anorectic agents. The compounds are distinguished by their low toxicity and their few side effects.

The compounds may be employed alone or in combination with other weight-reducing or anorectic active compounds. Further anorectic active compounds of

this kind are mentioned, for example, in the Rote Liste, Chapter 01 under weight-reducing agents/appetite suppressants, and may also include those active compounds which increase the energy turnover of the organism and thus lead to weight reduction or else those which influence the general metabolism of said organism such that increased calorie intake does not cause an enlargement of the fat depots and a normal calorie intake causes a reduction in the fat depots of said organism. The compounds are suitable for the prophylaxis and, in particular, for the treatment of problems of excess weight or obesity.

The compounds of formula (I) have a beneficial effect on the glucose metabolism, they particularly lower the blood-sugar level and can be used for treatment of type I and type II diabetes. The compounds can therefore be used alone or in combination with other blood-sugar lowering active compounds (antidiabetics). In a further aspect of the invention, the compounds of the formula I may be administered in combination with one or more further pharmacologically active substances which may be selected, for example, from the group consisting of antidiabetics, antiadipose agents, blood-pressure-lowering active compounds, lipid reducers and active compounds for the treatment and/or prevention of complications caused by diabetes or associated with diabetes.

Suitable antidiabetics include insulins, amylin, GLP-1 and GLP-2 derivatives such as, for example, those disclosed by Novo Nordisk A/S in WO 98/08871 and also oral hypoglycemic active compounds.

Said oral hypoglycemic active compounds preferably include sulfonyl ureas, biguanidines, meglitinides, oxadiazolidinediones, thiazolidinediones, glucosidase inhibitors, glucagon receptor antagonists, GLP-1 agonists, potassium channel openers such as, for example, those disclosed by Novo Nordisk A/S in WO 97/26265 and WO 99/03861, insulin sensitizers, activators of insulin receptor kinase, inhibitors of liver enzymes involved in the stimulation of gluconeogenesis and/or glycogenolysis, for example glycogen phosphorase inhibitors, modulators of glucose uptake and glucose elimination, lipid metabolism-modifying compounds such as antihyperlipidemic active compounds and antilipidemic active compounds, for example HMGCoA-reductase inhibitors, inhibitors of cholesterol transport/cholesterol uptake, inhibitors of the reabsorption of bile acid or inhibitors of microsomal triglyceride transfer protein (MTP), compounds which reduce food

intake, PPAR and RXR agonists and active compounds which act on the ATP-dependent potassium channel of beta cells.

In one embodiment of the present invention, the present compounds are administered in combination with insulin.

In another embodiment, the compounds of the invention are administered in combination with a sulfonylurea such as, for example, tolbutamide, glibenclamide, glimepiride, glipizide, gliquidone, glisoxepide, glibornuride or gliclazide. In another embodiment, the compounds of the present invention are administered in combination with a biguanidine such as, for example, metformin. In another embodiment, the compounds of the present invention are administered in combination with a meglitinide such as, for example, repaglinide. In yet another embodiment, the compounds of the present invention are administered in combination with a thiazolidinedione such as, for example, troglitazone, ciglitazone, pioglitazone, rosiglitazone or the compounds disclosed by Dr. Reddy's Research Foundation in WO 97/41097, in particular 5-[[4-[(3,4-dihydro-3-methyl-4-oxo-2-quinazolinylmethoxy]phenyl]methyl]-2,4-thiazolidinedione.

In another embodiment, the compounds of the present invention are administered in combination with an α-glucosidase inhibitor such as, for example, miglitol or acarbose.

In another embodiment, the compounds of the present invention are administered in combination with an active compound which acts on the ATP-dependent potassium channel of the beta cells, such as, for example, tolbutamide, glibenclamide, glimepiride, glipizide, gliclazide or repaglinide. In yet another embodiment, the compounds of the present invention are administered in combination with an antihyperlipidemic active compound or an antilipidemic active compound such as, for example, cholestyramine, colestipol, clofibrate, fenofibrate, gemfibrozil, lovastatin, pravastatin, simvastatin, atorvastatin, cerivastatin, fluvastatin, probucol, ezetimibe or dextrothyroxine.

In another embodiment, the compounds of the present invention are administered in combination with more than one of the aforementioned compounds, for example in combination with a sulfonylurea and metformin, a sulfonylurea and acarbose,

repaglinide and metformin, insulin and a sulfonylurea, insulin and metformin, insulin and troglitazone, insulin and lovastatin, etc.

Furthermore, the compounds of the invention may be administered in combination with one or more antiadipose agents or appetite-controlling active compounds.

Such active compounds may be selected from the group consisting of CART agonists, NPY antagonists, MC4 agonists, orexin antagonists, H3 agonists, TNF agonists, CRF agonists, CRF BP antagonists, urocortin agonists, β3 agonists, MSH (melanocyte-stimulating hormone) agonists, CCK agonists, serotonin re-uptake inhibitors, mixed serotonin and noradrenalin reuptake inhibitors, 5HT modulators, MAO inhibitors, bombesin agonists, galanin antagonists, growth hormone, growth-hormone-releasing compounds, TRH agonists, uncoupling protein 2 or 3 modulators, leptin agonists, dopamine agonists (bromocriptine, doprexin), lipase/amylase inhibitors, cannabinoid receptor 1 antagonists, modulators of acylation-stimulating protein (ASP), PPAR modulators, RXR modulators, hCNTF mimetics or TR-β agonists.

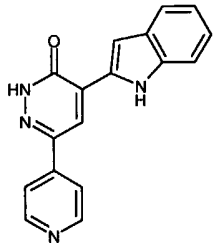
In one embodiment of the invention, the antiadipose agent is leptin or modified leptin. In another embodiment, the antiadipose agent is dexamphetamine or amphetamine. In another embodiment, the antiadipose agent is fenfluramine or dexfenfluramine. In yet another embodiment, the antiadipose agent is sibutramine or the mono- and bis-demethylated active metabolite of sibutramine. In another embodiment, the antiadipose agent is orlistate. In another embodiment, the antiadipose agent is mazindol, diethylpropione or phentermine.

Furthermore, the compounds of the present invention may be administered in combination with one or more antihypertensive active compounds. Examples of antihypertensive active compounds are betablockers such as alprenolol, atenol, timolol, pindolol, propanolol and metoprolol, ACE (angiotensin-converting enzyme) inhibitors such as, for example, benazepril, captopril, enalapril, fosinopril, lisinopril, quinapril and rampril, calcium channel blockers such as nifedipine, felodipine, nicardipine, isradipine, nimodipine, diltiazem and verapamil, and also alphablockers such as doxazosin, urapidil, prazosin and terazosin. Furthermore, reference may be made to Remington: The Science and Practice of Pharmacy, 19th edition, Gennaro, editor, Mack Publishing Co., Easton, PA, 1995.

It is self-evident that every suitable combination of the compounds of the invention with one or more of the aforementioned compounds and optionally one or more other pharmacologically active substances is to be regarded as covered by the scope of protection of the present invention.

The following examples illustrate the invention without limitation.

Example 1
4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 6-Pyridin-4-yl-2H-pyridazin-3-one

99,5g 4-acetylpyridine is added to a cold (10°C) solution of 222,4 potassium carbonate and 76,3 glyoxylic acid monohydrate in 1L of water and the solution stirred at room temperature for 2.5 h. After cooling in to 0°C 325 ml of acetic acid are added followed by 58,8 ml hydrazine hydrate and the resulting solution stirred under reflux for 1,5h. The solution is then cooled to 0°C, the pH adjusted to 7 with solid K2CO3, the precicpitate collected and ished with Water and i-PrOH to give 89.27g (64%) of 6-pyridin-4-yl-2H-pyridazin-3-one.

MS: (M+1) = 174

b) 3-Chloro-6-pyridin-4-yl-pyridazine

75,6 g 6-Pyridin-4-yl-2H-pyridazin-3-one is added in small portions to 234,5 g phosphorus oxychloride and the resulting mixture stirred for 1 h at 100°C. Diluting in to ice cold water, adjusting the pH 7 with aqueous sodium hydroxide and extraction with dichloromethane yielded 54 g 3-chloro-6-pyridin-4-yl-pyridazine which is used without further purification.
MS: (M+1) = 191

c) 3-Methoxy-6-pyridin-4-yl-pyridazine

63 ml of a 32% sodium methoxide solution in methanol are added to a solution of 57 g 3-chloro-6-pyridin-4-yl-pyridazine in methanol and the reaction mixture stirred under reflux for 1.5 h.. The solvens is removed under reduced pressure, the residue suspended in 0.7 L water and the pH adjusted to 7. Extraction with dichloromethane yielded 57g 3-methoxy-6-pyridin-4-yl-pyridazine, which is used without further purification.

d) 4-Iodo-3-methoxy-6-pyridin-4-yl-pyridazine

45 ml 1.6M solution of n-butyllithium in hexane are added at -30°C to a 10,2 g 2,2,6,6-tertamethylpiperidine in 100 ml THF and the mixture stirred at 0°C for 30 min. After cooling to -75°C 11,2g 3-methoxy-6-pyridin-4-yl-pyridazine dissolved 300 ml THF are added and the solution stirred at -75°C for 35 min. The cold (-75°C) reaction mixture is subsequently added at a cold (-75°C) solution of 18,3 g iodine in 400 ml THF (tetrahydrofuran) and stirred at -75°C for 1.5 h. The reaction is quenched by adding 80 ml methanol /THF (1:1) at –75°C and 300 ml saturated aqueous $NaHCO_3$ at room temperature and extracted with dichloromethane. The organic layer is ished with 5% aqueous $Na_2S_2O_3$ and saturated sodium chloride solution, dried ($MgSO_4$) and the solvens removed. The crude product is purified by chromatography on silica gel to yield 14,4 g of 4-iodo-3-methoxy-6-pyridin-4-yl-pyridazine.

MS: (M+1) = 313.95

e) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester

Argon is passed for 30 min through a suspension of 55 mg 4-iodo-3-methoxy-6-pyridin-4-yl-pyridazine, 55 mg 1-(tert-butoxycarbonyl)indole-2-boronic acid, 53,5 mg potassium carbonate, and 18,5 mg triphenylphosphine in 0,8 ml DME (dimethoxyethane) and 0,7 ml water. 4 mg palladium (II) acetate is added and the mixture stirred under reflux for 3h. The product is isolated by extraction with ethyl acetate and purified by chromatography on silica gel yielding 27,5 mg 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester

MS: (M+1) = 403.15

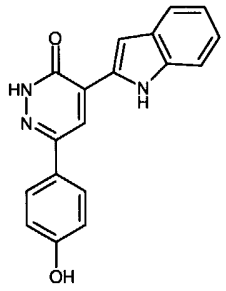
f) 4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

25mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester, 7,4 mg trimethylchlorosilane and 11,3 mg KI dissolved in 1 ml of acetonitril are stirred for 2h at 60°C. Subsequently 0.5 ml of a 4N solution of hydrochloric acid in dioxane is added and stirred for 2h at room temperature. The solution is diluted into DMF (dimethylformamide)/water and directly purified by HPLC (high performance liquid chromatography) on a RP18 (reversed phase 18) column giving 4,5mg 4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one.

MS: (M+1) = 289.

Example 2

6-(4-Hydroxy-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one



g) 6-Chloro-4-iodo-3-methoxy-pyridazine

6-Chloro-4-iodo-3-methoxy-pyridazine is synthesized following a procedure described in the literature (Mojovic, Ljubica; Turek, Alain; Ple, Nelly; Dorsy, Muriel; Ndzi, Bruno; Queguiner, Guy; Tetrahydron, **1995**, 52, p10417)

h) 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester

Argon is passed for 30 min through a suspension of 135 mg 6-chloro-4-iodo-3-methoxy-pyridazine, 130,5 mg 1-(tert-butoxycarbonyl)indole-2-boronic acid, 152 mg potassium carbonate, and 52,5 mg triphenylphosphine in 2,2 ml DME and 1,1 ml water. 11,2 mg palladium (II) acetate is added and the mixture stirred under reflux for 3h. The product is isolated by extraction with ethyl acetate and purified by chromatography on silica gel yielding 80 mg 2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester

i) 2-[6-(4-Hydroxy-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester

Argon is passed for 30 min through a suspension of 70 mg 6-chloro-4-iodo-3-methoxy-pyridazine, 53 mg 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, 59,4 mg potassium carbonate, and 20,1 mg triphenylphosphine in 0,8 ml DME and 0,7 ml water. 4,4 mg palladium (II) acetate is added and the mixture stirred under reflux for 3h. The product is isolated by extraction with ethyl acetate and purified by chromatography on silica gel yielding 45,8 mg 2-[6-(4-hydroxy-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester.

MS: (M+1) = 418

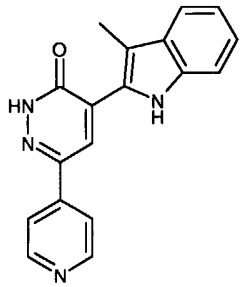
j) 6-(4-Hydroxy-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one

25mg of 2-[6-(4-hydroxy-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester, 8,6 mg trimethylchlorosilane and 13,5 mg KI dissolved in 1 ml of acetonitril are stirred for 2h at 60°C. Subsequently 0.75 ml of a 4N solution of hydrochloric acid in dioxane is added and stirred for 2h at room temperature. The solvens is evaporated and the residue purified by HPLC on a RP18 column giving 14,4 mg 4-(1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one.

MS: (M+1) = 304

Example 3

4-(3-Methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 3-Methyl-indole-1-carboxylic acid tert-butyl ester

1,88 g DMAP (dimethylaminopyridine) and 28,5g di-tert-butyl dicarbonate are added to a solution of 10,3g 3-methylindole in 300 ml dichloromethane and the solution is stirred for 4h at room temperature. Evaporation of the solvent and purification of the crude product on silica gel gives 16.5 g 3-methyl-indole-1-carboxylic acid tert-butyl ester.

MS: (M+1) = 232

b) 3-Methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert- butyl ester

To a solution of 462 mg 3-methyl-indole-1-carboxylic acid tert-butyl ester in 2,5 ml anhydrous tetrahydrofuran at –78 °C under argon is 1,2 ml of a 2M LDA (Li-diisopropylamine) solution in THF/hexane and stirred at 0°C for 30 min to complete the deprotonation. The reaction mixture is cooled to -78°C, 0,6 ml 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and stirred at 0°C for 60 min. The reaction is quenched by the addition of 2ml MeOH/water (1:1), diluted into water and extracted with ethylacetate. After evaporation of the solvent and purification on silica gel 385mg of 3-methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert- butyl ester are obtained.

MS: (M+1) = 358,6

c) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-methyl-indole-1-carboxylic acid tert- butyl ester

Argon is passed for 30 min through a suspension of 333 mg 4-iodo-3-methoxy-6-pyridin-4-yl-pyridazine, 380 mg 3-methyl-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid tert- butyl ester, 294 mg potassium carbonate, and 111,6 mg triphenylphosphine in 4,8 ml DME and 2,4 ml water. 24 mg palladium (II) acetate is added and the mixture stirred under reflux for 3h. The product is isolated by extraction with ethyl acetate and purified by chromatography on silica gel yielding 52,1 mg 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-methyl-indole-1-carboxylic acid tert- butyl ester.

MS: (M+1) = 403.15

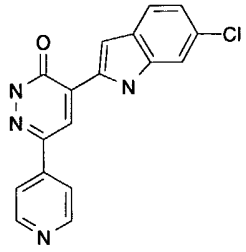
d) 4-(3-Methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

50 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-methyl-indole-1-carboxylic acid tert- butyl ester is dissolved in 0,75 ml ethanol and 0,75 ml 1N aqueous NaOH solution. The reaction mixture is stirred at 150°C in microwave apparatus (200W). The solution is neutralized by addition of 1N HCl, the solvent removed under reduced pressure and the crude product purified by HPLC chromatography (RP18 column, acetonitril/water, 0.05% HCOOH) yielding 21,1 mg 4-(3-methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one.

MS: (M+1) = 303

Example 4

4-(6-Chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

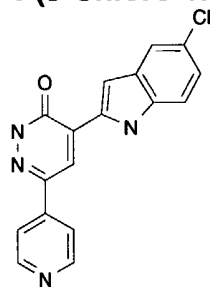


This compound is synthesized analogously to example 3.

MS: (M+1) = 322

Example 5

4-(5-Chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

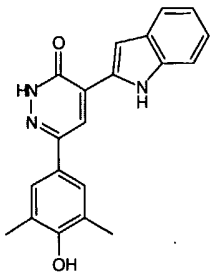


This compound is synthesized analogously to example 3.

MS: (M+1) = 322

Example 6

6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one



(a) 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-ethanol

47.7 ml of a 1.6M solution of n-butyl lithium in hexane is added dropwise at –75°C to 100 ml tetrahydrofuran followed by 12.9 ml 2,2,6,6-tetramethylpiperidine and the resulting solution is allowed to warm to 0°C and stirred for 30 min. The solution is cooled to –75°C and a solution of 5g 3-chloro-6-methoxypyridazine in 100 ml tetrahydrofuran is added at the same temperature. The reaction is stirred for 30 min at –75°C. A solution of 23.5 ml acetaldehyde in 50 ml tetrahydrofuran is cooled to –75°C and added to the reaction. The solution is stirred at –75°C for 90 min, then a mixture of 25 ml concentrated aqueous HCl, 100 ml ethanol and 125 ml tetrahydrofuran is added and the mixture is allowed to warm to room temperature. 60 ml of saturated aqueous sodium bicarbonate is slowly added, and the tetrahydrofuran is removed under reduced pressure. The resulting aqueous phase is extracted 3 times with dichloromethane. The organic phase is dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 3.85 g. LC-MS (ES+) 189 $(M+H)^+$. NMR analysis indicates that the product contained approximately 15% of 1-(3-chloro-6-methoxy-pyridazin-4-yl)-ethanol.

(b) 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-ethanone

3.85 g 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-ethanol is dissolved in 300 ml tetrahydrofuran and 35.5 g of manganese dioxide is added. The reaction is stirred for 48 h at RT. Solids are removed by filtration, and the solvent is removed under reduced pressure. The product is purified and separated from 1-(3-chloro-6-methoxy-pyridazin-4-yl)-ethanone by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 2.4 g. LC-MS (ES+) 187 $(M+H)^+$.

(c) 1-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-ethanone

250 mg of 1-(6-chloro-3-methoxy-pyridazin-4-yl)-ethanone and 232 mg of tetrakis(triphenylphosphine) palladium (0) are dissolved in 5 ml DME and the solution is stirred for 5 min at RT under argon. 400 mg of 2,6-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol and 1.4 ml of a 2M aqueous solution of sodium carbonate are added and the reaction solution is stirred at 95°C for 4 h. The reaction solution is filtered through a silica gel cartridge, eluting with dichloromethane. The solvent is removed under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 334 mg. LC-MS (ES+) 273 $(M+H)^+$.

(d) 4-[5-(1H-Indol-2-yl)-6-methoxy-pyridazin-3-yl]-2,6-dimethyl-phenol

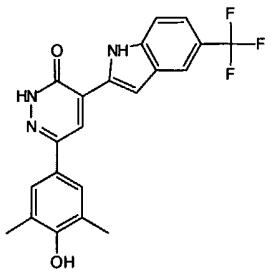
205 mg of 2-bromoaniline and 72 mg of anhydrous magnesium sulfate are suspended in 7 ml dimethylacetamide. 325 mg of 1-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-ethanone and 86.6µl acetic acid are added and the reaction is degassed with argon. 330 mg of tripotassium phosphate and 61mg of bis(tri-*tert*-butylphosphine) palladium (0) are added and the reaction is degassed with argon. The reaction is heated to 140°C for 5h. The solution is poured into water and extracted with ethyl acetate. The solvent is removed under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 105 mg. LC-MS (ES+) 346 $(M+H)^+$.

(e) 6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one

100 mg of 4-[5-(1H-indol-2-yl)-6-methoxy-pyridazin-3-yl]-2,6-dimethyl-phenol is suspended in 2 ml acetonitrile and 40µl of trimethylsilyl chloride and 53 mg of potassium iodide are added. The solution is heated to 80°C for 3h, then a further 120µl of trimethylsilyl chloride and 159 mg of potassium iodide are added. The solution is heated to 80°C for 3h then stirred at RT for 16 h. The reaction solution is diluted with water and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 15 mg. LC-MS (ES+) 332 $(M+H)^+$.

Example 7

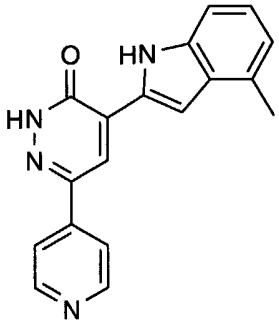
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(5-trifluoromethyl-1H-indol-2-yl)-2H-pyridazin-3- one



This compound is synthesized analogously to example 6, whereby the 2-bromoaniline in step (d) is replaced by 2-bromo-4-trifluoromethyl-phenylamine. Yield 3.9 mg. LC-MS (ES+) 400 $(M+H)^+$.

Example 8

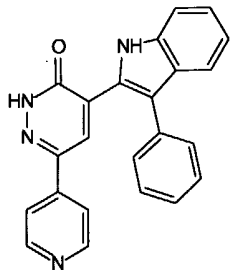
4-(4-Methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 3.

MS: (M+1) = 303

Example 9
4-(3-Phenyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole trifluoroacetate

A solution of 5.5 g 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester and 5ml TFA in 10 in 10 ml dichloromethane stirred for 18 h at room temperature. The solvent is evaporated and the crude product purified by suspended on water and collecting the precipitate.

Yield 5.4 g LC-MS (ES+) 303 (M+H)+.

b) 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole TFA salt

A supension of 2g 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole trifluoroacetate and 1.3 g N-Iodosuccinimide (NIS) in acetone is stirred for 4 h at

ambient temperature. The product is isolated by filtration, washed with aceton and used without further purification
Yield 2.2 g LC-MS (ES+) 429 (M+H)+.

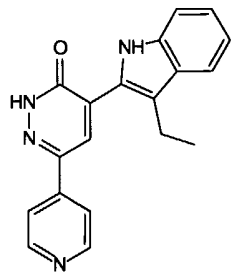
c) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-phenyl-1H-indole

Argon is passed for 30 min through a suspension of 270 mg 3-iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole TFA (trifluoroacetic acid) salt, 73 mg phenylboronic Acid, 220 mg potassium carbonate and 52.4 mg triphenylphosphine in 2 ml DME and 1 ml water. 11,2 mg palladium (II) acetate is added and the mixture stirred under reflux for 5h. The product is isolated by extraction with ethyl acetate and purified by chromatography on silica gel.
Yield 64 mg LC-MS (ES+) 379 (M+H)+.

d) 4-(3-Phenyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

63 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-phenyl-1H-indole is dissolved in 0,75 ml ethanol and 0,75 ml 1N aqueous NaOH solution. The reaction mixture is stirred at 150°C in microwave apparatus (200W). The reaction mixture is directly applied to HPLC chromatography to isolate the product (RP18 column, acetonitril/water, 0.05% HCOOH)
Yield 42 mg LC-MS (ES+) 365 (M+H)+.

Example 10
4-(3-Ethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-vinyl-1H-indole

A mixture of 430 mg 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole, 490 mg tributyl(vinyl)tin, 165 mg tetraethylammonium-chloride and 35 mg bis(triphenylphosphine)palladium(II) chloride in DMF is stirred at 80°C for 40 min. After cooling to room temperature, 15 ml aqueous potassium fluoride solution (30%) are added and the mixture stirred for 30 min at room temperature before

extraction with EtOAc. The organic layer is dried over $MgSO_4$ and the solvent evaporated ion prior to purication of the crude product by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% HCOOH).
Yield 233 mg. LC-MS (ES+) 329 $(M+H)^+$.

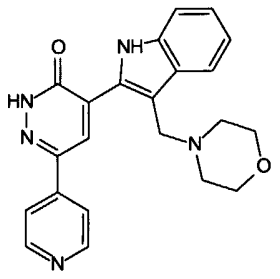
b) 3-Ethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole

12 mg Palladium, 10% on charcole are added to a solution of 70 mg 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-vinyl-1H-indole methanol and the reaction mixuture stirred under an hydrogen atmosphere for 4 hours. The catalyst is removed by filtration and the solvens by evaporation yielding the product which was used without further purification
Yield 61 mg. LC-MS (ES+) 331 (M+H)+.

c) 4-(3-Ethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

60 mg 3-Ethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole is dissolved in 0,5 ml ethanol and 0,5 ml 1N aqueous NaOH solution. The reaction mixture is stirred at 150°C in microwave apparatus (200W). The reaction mixture is directly applied to HPLC chromatography to isolate the product (RP18 column, acetonitril/water, 0.05% HCOOH)
Yield 19 mg. LC-MS (ES+) 317 (M+H)+.

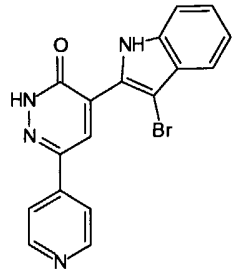
Example 11
4-(3-Morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



A solution of 14 µl formaldehyde (37% solution in water) and 17 µl morpholine in 0.5 ml glacial acetic acid is added dropwise at 0°C to 50 mg 4-(1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one suspended in 2.24 ml glacial acetic acid and 2.6 ml 1,4-dioxan. The resulting mixture is stirred for 3 h at room temparature, subsequently poured into ice / water and the pH is adjusted to 13.3 with 2N sodium hydroxide. The product is isolated by filtration.
Yield 15.4 mg. LC-MS (ES+) 388 (M+H)+.

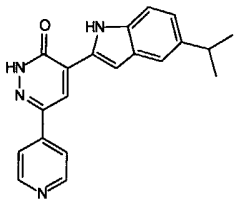
The compounds 38 - 42 are synthesized analogously to example 11.

Example 12
4-(3-Bromo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



22mg mg 4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one is suspended in 30 mL acetone and 2 mg N-bromosuccinimide is added. The reaction mixture is stirred for 3 hours at room temperature, the precipitated product isolated by filtration and washed with aceton. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (0.05% HCOOH). Yield 11.2 mg. LC-MS (ES+) 368 $(M+H)^+$.

Example 13
4-(5-Isopropyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 1-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-ethanol

To a solution of 0,93 g 2,2,6,6-tetramethylpiperidine in 30 ml THF is added 4,13 ml (15 % solution in toluene) *n*-butyllithium at -30°C. After being stirred at 0°C for 30 min, the reaction mixture is cooled to -78°C and a solution of 1,12 g 3-methoxy-6-pyridin-4-yl-pyridazine in 30 ml THF is added and stirred at -78°C for 30 min. At this temperature 3,17 g acetaldehyde are added and stirred for another 2 h. The reaction is quenched by the addition of 24 ml MeOH/THF 1:1 and warmed to ambient temperature. Than 30 ml saturated aq. $NaHCO_3$ are added and extracted

with CH_2Cl_2. The combined organic layers are washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by flash chromatography (ethyl acetate 100 %) to give 0,91 g (66%) of the desired product as a beige solid.

MS: (M+1) = 232

b) 1-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-ethanone

To a solution of 0,91 g 1-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-ethanol in 10 ml CH_2Cl_2 is added a suspension of 1,70 g Dess-Martin Periodinane in 10 ml CH_2Cl_2 at room temperature. After being stirred for 3 h, the suspension is extracted with 5 % aq. $Na_2S_2O_3$ solution. The organic layer is washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue is purified by chromatography to give 0,83 g (92%) of the desired product as a yellow solid.

MS: (M+1) = 230

c) 5-Isopropyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole

To a solution of 100 mg 1-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-ethanone, 120 mg K_3PO_4, 26,3 mg $MgSO_4$ and 22,3 mg palladium(0)-bis(tri-*tert*-butyl-phosphine) in 0,5 ml dry and degassed DMA are added 37 µl acetic acid and 93 mg 2-bromo-4-isopropylaniline at room temperature. The mixture is stirred at 140°C for 36 h. The reaction is cooled to room temperature, diluted with ethyl acetate, washed with water, dried over $MgSO_4$ and concentrated in vacuo (3 h high-vacuum). The residue (139 mg) is used without purification for the next step.

MS: (M+1) = 345

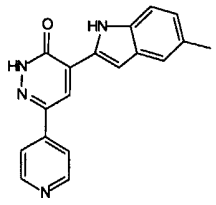
d) 4-(5-Isopropyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

To a solution of 139 mg (crude material) 5-isopropyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole in 2,5 ml EtOH is added 2,5 ml aq. NaOH (1 M). The mixture is heated for 10 min at 150°C using microwave. After cooling to room temperature the mixture is filtered and purified by HPLC to give 14 mg (11%) of the desired product as yellow solid.

MS: (M+1) = 331

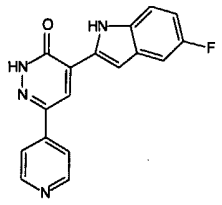
The following compounds 14 to 16 are synthesized using the same procedures.

Example 14
4-(5-Methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



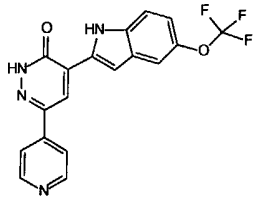
MS: (M+1) = 303

Example 15
4-(5-Fluoro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



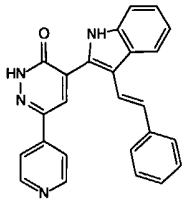
MS: (M+1) = 307

Example 16
6-Pyridin-4-yl-4-(5-trifluoromethoxy-1H-indol-2-yl)-2H-pyridazin-3-one



MS: (M+1) = 373

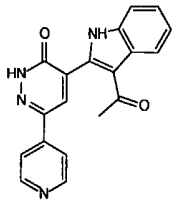
Example 17
6-Pyridin-4-yl-4-[3-((E)-styryl)-1H-indol-2-yl]-2H-pyridazin-3-one



MS: (M+1) = 391

This compound is synthesized analogously to example 9.

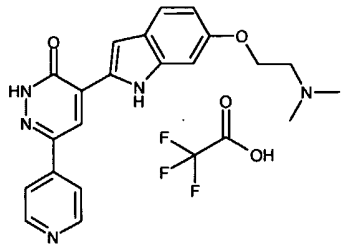
Example 18
4-(3-Acetyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



4 mg acetyl chlorid are added at 0°C to a supension of 80 mg aluminium chloride 1,2-dichloroethane, followed by 208 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole trifluoroacetate. The reaction mixture is stirred for 4 h at room temperature and for 3h at 50°C. It is worked up pouring into an ice/water mixture and filtration. The layers are separated, the organic is layer washed with Water, dried over $MgSO_4$ and the solvent removed. Reversed phase HPLC chromatography yielded 8.1 mg 4-(3-acetyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

MS: (M+1) = 331

Example 19
4-[1H-Indol-6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



a) 1-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole

A mixture of 5.5 g 6-hydroxyindole, 7.47 g *tert*-butyldimethylsilyl chloride, 7.03 g imidazole, and 25 mL dimethylformamide is stirred at ambient temperature for 20 h. The reaction is diluted with ethyl acetate, washed with water (2 x), dried ($MgSO_4$), and the solvent removed under reduced pressure to provide an oil. The oil is chromatographed , eluting with ethyl acetate/heptane, to afford 9.05 g (88%) of 6-(*tert*-butyldimethylsiloxy)-1H-indole as a white solid: TLC R_f 0.4 (silica, 1:9 ethyl acetate /heptane).

To a solution of 9 g 6-(*tert*-butyldimethylsiloxy)-1H-indole in 90 mL dichloromethane is added 0.89 g 4-(dimethylamino)pyridine and 12.7 g di-*tert*-butyl dicarbonate and the reaction stirred at ambient temperature for 4 h. The solvent is removed to give an oil. The oil is chromatographed on silica, eluting with 5:95 ethyl acetate/heptane, to provide 11.5 g (91%) of 1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole as a slightly yellow oil.

MS: (M+1) = 348.20.

b) 1-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole-2-boronic acid

To a solution of 1 g 1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole in 15 mL anhydrous tetrahydrofuran at –78 °C under nitrogen is added *tert*-butyllithium (2.30 mL of a 1.5 M solution in pentane) over 3 min and the reaction stirred at –78 °C. After 32 min, 0.66 mL trimethylborate are added in one portion and the reaction stirred at 0 °C. After 2h, 9 mL saturated aqueous ammonium chloride are added, the mixture diluted with 25 mL ether, and stirred at ambient temperature. The reaction is acidified with 4 mL of a solution made from 10% aqueous $KHSO_4$ (60 mL) and concentrated H_2SO_4 (2 mL). After stirring for 15 min, the layers are separated and the organics ished with water (15 mL) and brine (15 mL) successively, dried (Na_2SO_4), and the solvent removed under reduced pressure to yield a partially solidified material. The material is ished with hot hexanes (5 mL) and filtered. The collected solid is ished with hexanes (2 x 5 mL) to give 635 mg (56%) of 1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole-2-boronic acid as a white powder.

MS: M = 392.20.

c) 6-Hydroxy-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

600 mg 4-Iodo-3-methoxy-6-pyridin-4-yl-pyridazine, 974 mg 1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxy)indole-2-boronic acid, 2.5 g cesium

carbonate, and 78 mg [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in a mixture of 18 mL dioxane and 5.4 mL water. Argon is bubbled through the solution for 5 minutes. The mixtures is heated to reflux for 2 hours. After diluting with EtOAc, the organic phase is ished with water and brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product is dissolved in 30 mL THF. After addition of 1.51 g tetrabutylammonium fluoride trihydrate, the red solution is stirred for 2 hours. The reaction mixture is diluted with EtOAc, ished with saturated aqueous ammonium chloride, water, and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification by HPLC afforded 760 mg (95 %) 6-hydroxy-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester.

MS: (M+1) = 419.21

d) 6-(2-Dimethylaminoethoxy)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

100 mg 6-hydroxy-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester and 175 mg triphenylphosphine are dissolved in 7 mL toluene and 2 mL THF. After dropwise addition of 84 µL 2-dimethylaminoethanol and 123 µL diethyl azodicarboxylate, the reaction mixture is stirred at room temperature for 5 hours. The solvent is removed in vacuo and the residue dissolved in dichloromethane. The organic phase is ished with water and the aqueous phase extracted twice with dichloromethane. The combined organic phases are dried over $MgSO_4$ and concentrated in vacuo. Purification by HPLC afforded 35 mg (43%) 6-(2-dimethylaminoethoxy)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester.

MS: (M+1) = 490.31

e) 4-[1H-Indol- 6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

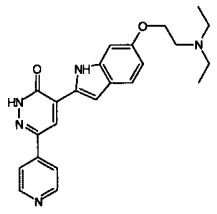
32 mg 6-(2-Dimethylaminoethoxy)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 0.5 ml ethanol. 0.5 ml 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 30 minutes. Purification by HPLC afforded 9 mg (28%) 4-

[1H-indol- 6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.

MS: (M+1) = 376.29

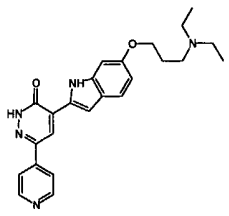
The following examples 20 - 23, 28 - 33, 44, 45, 49, 52 and 55 are synthesized analogously to example 19.

Example 20
4-[6-(2-Diethylamino-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



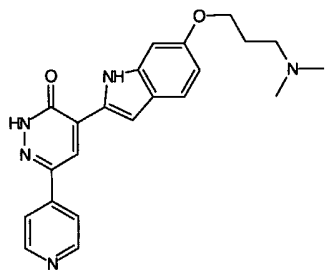
MS: (M+1) = 404

Example 21
4-[6-(3-Diethylamino-propoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



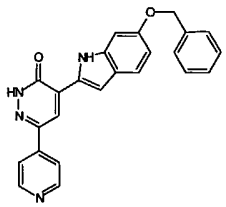
MS: (M+1) = 419

Example 22
4-[6-(3-Dimethylamino-propoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



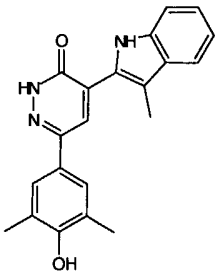
MS: (M+1) = 390

Example 23
4-(6-Benzyloxy-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 395

Example 24
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(3-methyl-1H-indol-2-yl)-2H-pyridazin-3-one



(a) 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-propan-1-ol

104.6 ml of a 1.6M solution of n-butyl lithium in hexane is added dropwise at –75°C to 200 ml tetrahydrofuran followed by 28.3 ml 2,2,6,6-tetramethylpiperidine and the resulting solution is allowed to warm to 0°C and stirred for 30 min. The solution is cooled to –75°C and a solution of 11g 3-chloro-6-methoxypyridazine in 100 ml tetrahydrofuran is added at the same temperature. The reaction is stirred for 30 min at –75°C. A solution of 65.9 ml propionaldehyde in 200 ml tetrahydrofuran is cooled to –75°C and added to the reaction. The solution is

stirred at –75°C for 90 min, then a mixture of 55 ml concentrated aqueous HCl, 220 ml ethanol and 275 ml tetrahydrofuran is added and the mixture is allowed to warm to room temperature. 150 ml of saturated aqueous sodium bicarbonate is slowly added, and the tetrahydrofuran is removed under reduced pressure. The resulting aqueous phase is extracted 3 times with dichloromethane. The organic phase is dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 12.25 g. LC-MS (ES+) 203 $(M+H)^+$. NMR analysis indicated that the product contained approximately 15% of 1-(3-chloro-6-methoxy-pyridazin-4-yl)-propan-1-ol.

(b) 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-propan-1-one

12.25 g 1-(6-Chloro-3-methoxy-pyridazin-4-yl)-propan-1-ol is dissolved in 410 ml tetrahydrofuran and 105 g of manganese dioxide is added. The reaction is stirred for 24 h at RT. Solids are removed by filtration, and the solution is treated with a further 105 g of manganese dioxide for 16 h at RT. Solids are removed by filtration, and the solvent is removed under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane. Yield 3.25 g. LC-MS (ES+) 201 $(M+H)^+$.

(c) 1-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-propan-1-one

2 g of 1-(6-chloro-3-methoxy-pyridazin-4-yl)-propan-1-one and 1.73 g of tetrakis(triphenylphosphine) palladium (0) are dissolved in 10 ml DME and the solution is stirred for 5 min at RT (room temperature) under argon. 3 g of 2,6-dimethyl-4-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenol and 10 ml of a 2M aqueous solution of sodium carbonate are added and the reaction solution is stirred at 95°C for 4 h. The reaction solution is poured into ethyl acetate and ished with saturated aqueous sodium bicarbonate. The organic phase is dried ($MgSO_4$), filtered and evaporated under reduced pressure. The product is purified by silica gel chromatography, eluting with a gradient of ethyl acetate in heptane, followed by purification by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 1.69 g. LC-MS (ES+) 287 $(M+H)^+$.

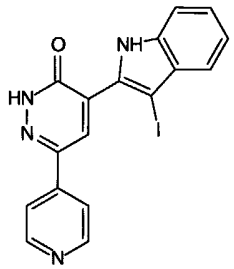
(d) 4-[6-Methoxy-5-(3-methyl-1H-indol-2-yl)-pyridazin-3-yl]-2,6-dimethyl-phenol

73.4 µl of 2-chloroaniline and 21 mg of anhydrous magnesium sulfate are suspended in 3 ml dimethylacetamide. 100 mg of 1-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-propan-1-one and 31.4 mg acetic acid are added and the reaction is degassed with argon. 96 mg of tripotassium phosphate and 35.7 mg of bis(tri-*tert*-butylphosphine) palladium (0) are added and the reaction is degassed with argon. The reaction is heated to 140°C for 16 h. The solution is filtered. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 35 mg.

(e) 6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(3-methyl-1H-indol-2-yl)-2H-pyridazin-3-one

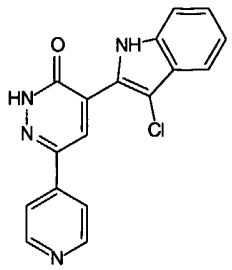
6 mg of 4-[6-methoxy-5-(3-methyl-1H-indol-2-yl)-pyridazin-3-yl]-2,6-dimethyl-phenol is suspended in 2 ml acetonitrile and 6.5 mg of trimethylsilyl chloride and 9.96 mg of potassium iodide are added. The solution is heated to 80°C for 3h. The reaction solution is diluted with water and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 3.8 mg. LC-MS (ES+) 346 $(M+H)^+$.

Example 25
4-(3-Iodo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



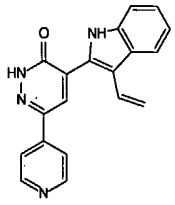
577mg 4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one is suspended in 30 mL acetone and 550 mg NIS is added. The reaction mixture is stirred for 3 hours at room temperature, the precipitated product isolated by filtration and washed with aceton. The material product is used without further purification
Yield 670 mg. LC-MS (ES+) 415 $(M+H)^+$.

Example 26
4-(3-Chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



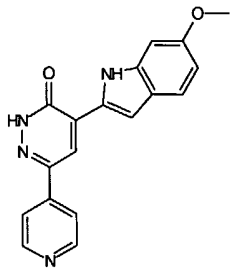
Example 26 is synthesized similarly to example 25 by using NCS (N-chlorosuccinimid) instead of NIS
Yield 42 mg. LC-MS (ES+) 324 $(M+H)^+$.

Example 27
6-Pyridin-4-yl-4-(3-vinyl-1H-indol-2-yl)-2H-pyridazin-3-one



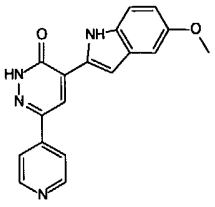
A mixture of 104 mg 4-(3-iodo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one (example 25), 123 mg tributyl(vinyl)tin, 41 mg tetraethylammonium-chloride and 9 mg bis(triphenylphosphine)palladium(II) chloride in DMF is stirred at 80°C for 40 min. After cooling to room temperature, 4 ml aqueous potassium fluoride solution (30%) are added and the mixture stirred for 30 min at room temperature before extraction with EtOAc. The organic layer is dried over $MgSO_4$ and the solvent evaporated ion prior to purication of the crude product by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% HCOOH).
Yield 28 mg. LC-MS (ES+) 315 $(M+H)^+$.

Example 28
4-(6-Methoxy-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 319

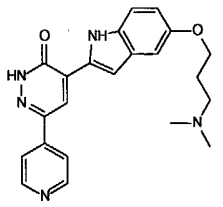
Example 29
4-(5-Methoxy-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 319

Example 30

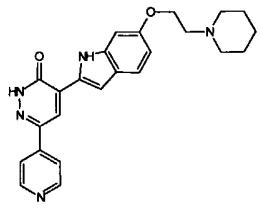
4-[5-(3-Dimethylamino-propoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 390

Example 31

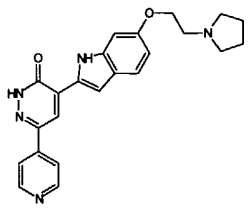
4-[6-(2-Piperidin-1-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 416

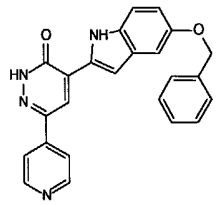
Example 32

6-Pyridin-4-yl-4-[6-(2-pyrrolidin-1-yl-ethoxy)-1H-indol-2-yl]-2H-pyridazin-3-one



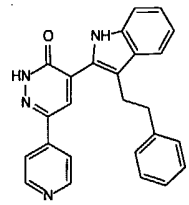
MS: (M+1) = 402

Example 33
4-(5-Benzyloxy-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



MS: (M+1) = 395

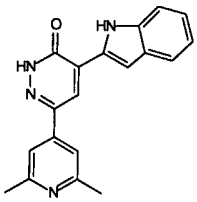
Example 34
4-(3-Phenethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 10.

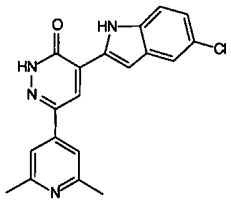
MS: (M+1) = 393

Example 35
6-(2,6-Dimethyl-pyridin-4-yl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one



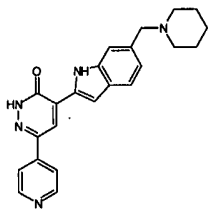
This compound is synthesized analogously to example 2.
MS: (M+1) = 317

Example 36
4-(5-Chloro-1H-indol-2-yl)-6-(2,6-dimethyl-pyridin-4-yl)-2H-pyridazin-3-one



This compound is synthesized analogously to example 2.
MS: (M+1) = 351

Example 37
4-(6-Piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 2-[1-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsiloxymethyl)indole-2-yl]-4,4,5,5-tetramethyl,1,3,2-dioxaborolane

5 g 1-(*tert*-Butoxycarbonyl)-6-(*tert*-butyldimethylsiloxymethyl)indole (prepared as described in WO03020276) is dissolved in 45 mL anhydrous THF and cooled to 0 °C. A solution of LDA in 10 mL THF (prepared at 0°C from 2.61 mL diisopropylamine and 10.86 mL butyllithium (1.6M in hexanes)) is added dropwise by cannula over 30 minutes. After stirring for 1 hour at 0 °C, water and 1N aqueous HCl are added. After stirring for 5 min, the reaction mixture is diluted with EtOAc and the aqueous layer reextracted with EtOAc. Drying ($MgSO_4$) and

concentration in vacuo affords 7.76 g crude product as a beige solide, which is directly used in the next step.

b) 6-Hydroxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

3.94 g 4-Iodo-3-methoxy-6-pyridin-4-yl-pyridazine, 6.74 g 2-[1-(*tert*-butoxy-carbonyl)-6-(*tert*-butyldimethylsiloxymethyl)indole-2-yl]-4,4,5,5-tetramethyl,1,3,2-dioxaborolane, 12.29 g cesium carbonate, and 513 mg [1,1'-bis(diphenyl-phosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in a mixture of 100 mL dioxane and 30.4 mL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 2 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo.

The crude product is dissolved in 95 mL THF. After addition of 9.91 g tetrabutylammonium fluoride trihydrate, the red solution is stirred for 2 hours. The reaction mixture is diluted with EtOAc, washed with saturated aqueous ammonium chloride, water, and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification on silica affords 3.9 g (72 %) 6-hydroxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester.

MS: (M+1) = 433.26

c) 6-Formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

2 g 6-Hydroxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 46 mL dichloromethane. After addition of 1.61 g activated manganese (IV) oxide the reaction mixture is heated to reflux for 1 hour. Then every two hours additional manganese (IV) oxide is added until the conversion is complete. The reaction mixture is diluted with dichloromethane and filtered over celite. 1.63 g (82%) crude product is obtained, which is directly used in the next reaction.

d) 6-(Piperidin-1-ylmethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

79 mg 6-Formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 14 mL dichloroethane. 182 µL piperidine and then 0.7 mL acetic acid are added. 334 mg sodium triacetoxyborohydride is added

in several portions over 6 hours. Saturated (sat.) aqueous (aq). $NaHCO_3$-solution is added and the reaction mixture is stirred until the CO_2-evolution stopped. The reaction mixture is diluted with dichloromethane, the aq. phase washed with dichloromethane, the combined org. phases dried ($MgSO_4$) and concentrated in vacuo. 76 mg (83%) crude product is obtained, which is directly used in the next step.

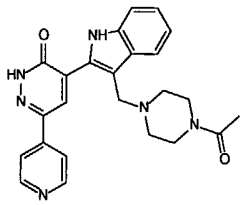
e) 4-[1H-Indole-6-(piperidin-1-ylmethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

76 mg 6-(Piperidin-1-ylmethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 0.6 mL ethanol. 0.5 mL 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 15 minutes. Purification by HPLC affords 25 mg (36%) 4-[1H-indole-6-(piperidin-1-ylmethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.

MS: (M+1) = 386.27

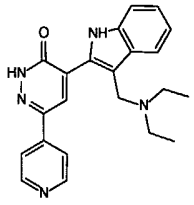
The compounds 43, 46 - 48, 50, 53 and 54 are synthesized analogously to example 37.

Example 38
4-[3-(4-Acetyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



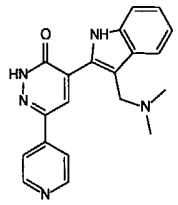
MS: (M+1) = 429

Example 39
4-(3-Diethylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



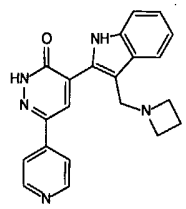
MS: (M+1) = 374

Example 40
4-(3-Dimethylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



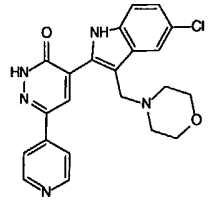
MS: (M+1) = 346

Example 41
4-(3-Azetidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



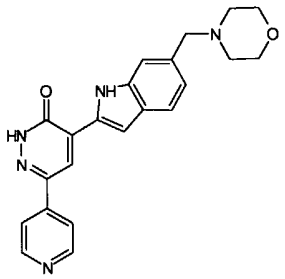
MS: (M+1) = 358

Example 42
4-(5-Chloro-3-morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



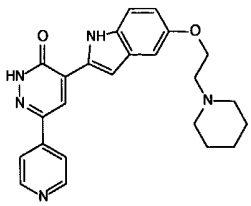
MS: (M+1) = 422

Example 43
4-(6-Morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



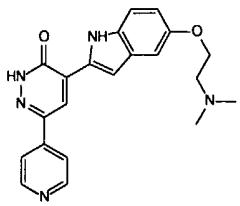
MS: (M+1) = 388

Example 44
4-[5-(2-Piperidin-1-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



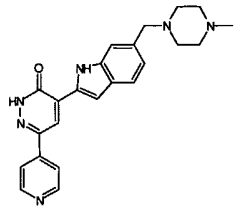
MS: (M+1) = 416

Example 45
4-[5-(2-Dimethylamino-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



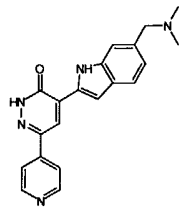
MS: (M+1) = 376

Example 46
4-[6-(4-Methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



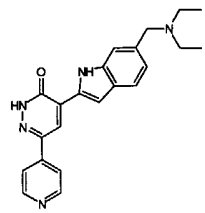
MS: (M+1) = 401

Example 47
4-(6-Dimethylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



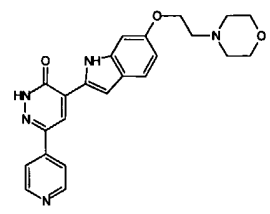
MS: (M+1) = 346

Example 48
4-(6-Diethylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



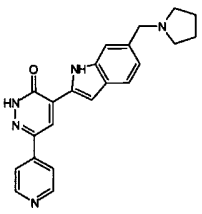
MS: (M+1) = 374

Example 49
4-[6-(2-Morpholin-4-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



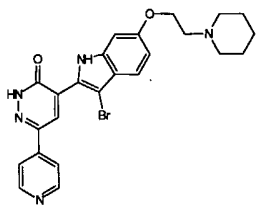
MS: (M+1) = 418

Example 50
6-Pyridin-4-yl-4-(6-pyrrolidin-1-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one



MS: (M+1) = 372

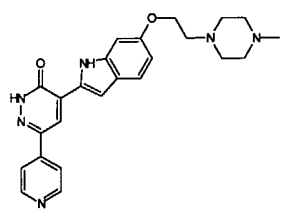
Example 51
4-[3-Bromo-6-(2-piperidin-1-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



24 mg 4-[1H-Indole-6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one is suspended in 1 mL acetone and 10 mg NBS was added. After stirring for 2 hours at rt (room temperature), the solvent is removed in vacuo. HPLC purification afforded 8 mg (29%) of 4-[1H-indole-3-bromo-6-(2-piperidylethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.

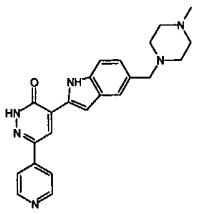
MS: (M+1) = 494.03

Example 52
4-{6-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one



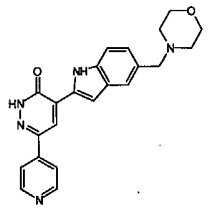
MS: (M+1) = 431

Example 53
4-[5-(4-Methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



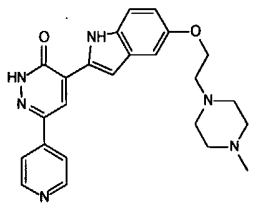
MS: (M+1) = 401

Example 54
4-(5-Morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



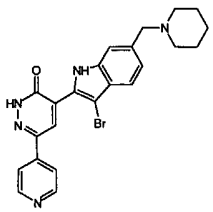
MS: (M+1) = 388

Example 55
4-{5-[2-(4-Methyl-piperazin-1-yl)-ethoxy]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one



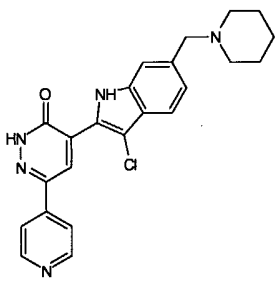
MS: (M+1) = 431

Example 56
4-(3-Bromo-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



33 mg 4-[1H-Indole-6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one is suspended in 1.2 mL acetone and 14 mg NBS is added. After stirring for 2 hours at rt, the solvent is removed in vacuo. HPLC purification affords 12 mg (31%) of 4-[1H-indole-3-bromo-6-(piperidylmethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.
MS: (M+1) = 464.

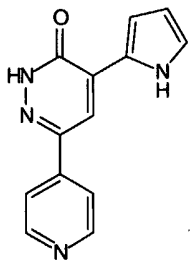
Example 57
4-(3-Chloro-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



33 mg 4-[1H-Indole-6-(2-dimethylaminoethoxy)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one is suspended in 1.2 mL acetone and 10.5 mg NCS is added. The reaction mixture is stirred for 24 hours at room temperature and then heated to 50 °C for 2 hours. After addition of 5 mg NCS, the reaction mixture is heated to 50 °C for an additional hour. Then the solvent is removed in vacuo. HPLC purification afforded 8 mg (23%) of 4-[1H-indole-3-chloro-6-(piperidylmethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.
MS: (M+1) = 420.17

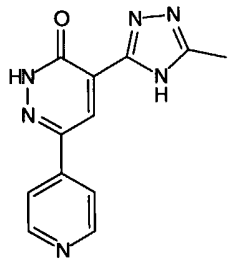
The following compounds 60 and 61 are synthesized analogously to example 57.

Example 58
6-Pyridin-4-yl-4-(1H-pyrrol-2-yl)-2H-pyridazin-3-one



This compound is synthesized analogously to example 1.
MS: (M+1) = 239

Example 59
4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



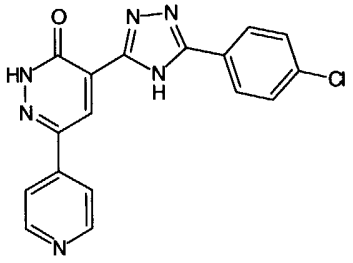
a) 3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide
10 g of 3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazine-4-carboxylic acid ethyl ester are dissolved in 150 ml of ethanol, 4.2 ml of hydrazine hydrate is added and the mixture is refluxed for 5 hours. After cooling to room temperature, the solid is collected by filtration and dried in vacuo at 40 °C.
Yield: 6 g, MS: (M+1) = 232

b) 4-(5-Methyl-4H-[1,2,4]triazol-3-yl)-6-pyridin-4-yl-2H-pyridazin-3-one
A mixture of 100 mg of 3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide, 130 mg thioacetamide, 87 mg triethylamine , 1 ml of pyridine and 5 ml of butanol is refluxed for 15 hours. After cooling and stirring at room temperature a solid precipitated is collected by filtration, washed with cold isopropanol and dried in vacuo.
Yield: 26 mg, MS: (M+1) = 255

This compound is synthesized analogously to example 1.

MS: (M+1) = 239

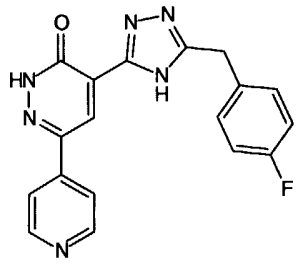
Example 60
4-[5-(4-Chloro-phenyl)-4H-[1,2,4]triazol-3-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



A mixture of 0.5 g 2-(4-fluoro-phenyl)-acetimidic acid methyl ester, 0.24 g of 3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazine-4-carboxylic acid hydrazide and 3 ml of N-methylpyrrolidone is heated at 130 °C for 2 hours. After cooling to room temperature 10 ml of water are added and the product extracted with ethyl acetate and purified by chromatography (silicagel, dichloromethane/methanol).

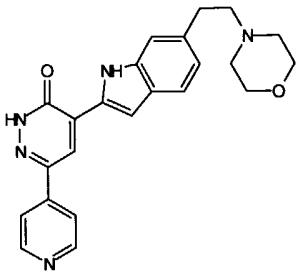
Yield: 35 mg, MS: (M+1) = 349

Example 61
4-[5-(4-Fluoro-benzyl)-4H-[1,2,4]triazol-3-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 60.
MS: (M+1) = 349

Example 62
4-[6-(2-Morpholin-4-yl-ethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3- one



MS: (M+1) = 363

a) 6-(2-methoxyvinyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

1.23 g Methoxymethyltriphenylphoshonium chloride is suspended in 10 mL THF and cooled to –78 °C. 2.20 mL butyllithium (1.6 M in hexanes) is added dropwise and the resulting mixture is stirred for 30 min at –78 °C and then warmed in an ice bath to 0°C. After addition of a solution of 734 mg 6-formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see above) in 5 mL THF the reaction mixture is heated to reflux for 5 hours. After cooling to rt, the reaction mixture is diluted with heptanes, washed with water, dried ($MgSO_4$) and concentrated in vacuo. The resulting 280 mg crude enol ether is directly used in the next step.

b) 6-(2-Oxoethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

180 mg 6-(2-Methoxyvinyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester are dissolved in 10 mL acetonitrile. Then 196 mg potassium iodide and 125 µL chlorotrimethylsilane are added. The reaction mixture is stirred for 2 hours at rt. The solvent is removed in vacuo and the obtained solid is dissolved in dichloromethane/water. The aqueous phase is extracted five times with dichloromethane, the combined org. phases are dried ($MgSO_4$) and the solvent removed in vacuo. 200 mg crude product are obtained as a mixture of 6-(2-oxoethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester and 6-(2-oxoethyl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)indole-1-carboxylic acid *tert*-butyl ester. The mixture is directly used in the next step.

c) 6-(2-Piperidylethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

54 mg of a mixture of 6-(2-oxoethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester and 6-(2-oxoethyl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)indole-1-carboxylic acid *tert*-butyl ester are dissolved in 9 mL dichloroethane. 160 µL morpholine and then 0.46 mL acetic acid are added. 129 mg sodium triacetoxyborohydride are added in several portions over 4 hours. Sat. aq. $NaHCO_3$-solution is added and the reaction mixture is stirred until the CO_2-evolution stopped. The reaction mixture is diluted with dichloromethane, the aq. phase washed with dichloromethane, the combined org. phases dried ($MgSO_4$) and concentrated in vacuo. 8 mg (13%) crude product (mixture of 6-(2-piperidylethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester and 2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-6-(2-piperidyl-ethyl)-indole-1-carboxylic acid *tert*-butyl ester is obtained, which is directly used in the next step.

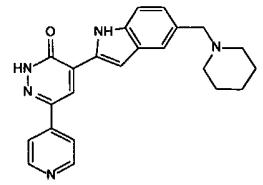
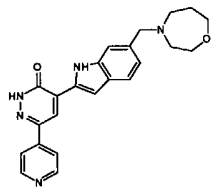
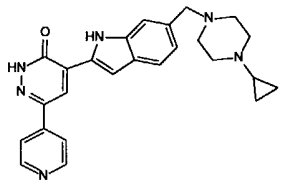
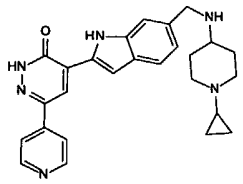
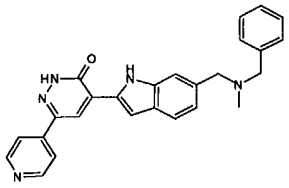
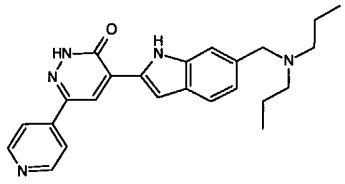
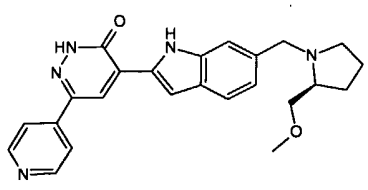
e) 4-[1H-Indole-6-(piperidylethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

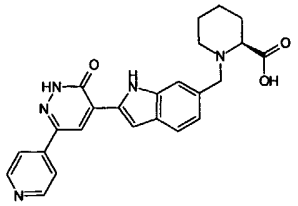
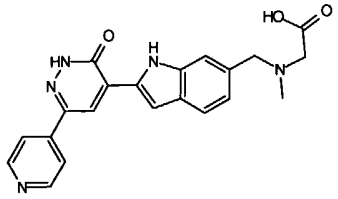
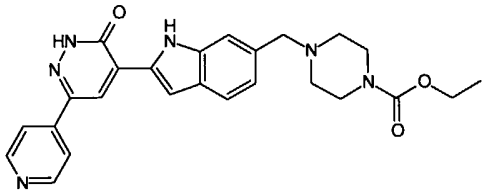
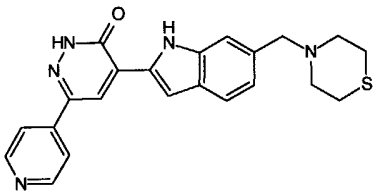
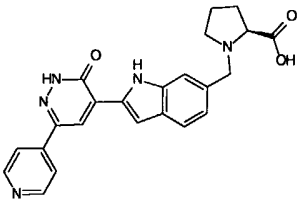
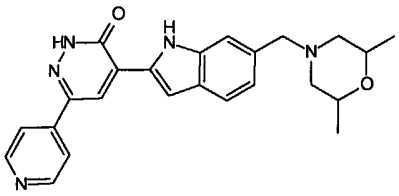
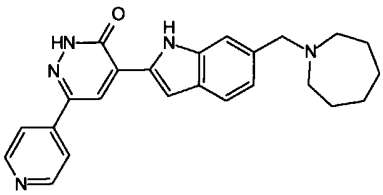
8 mg of a mixture of 6-(2-piperidylethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester and 2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-6-(2-piperidyl-ethyl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 0.4 mL ethanol. 0.56 ml 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 15 minutes. Purification by HPLC afforded 5 mg (61%) 4-[1H-indole-6-(piperidylethyl)-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.

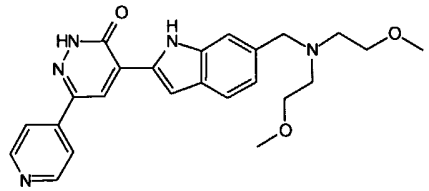
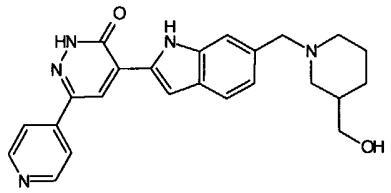
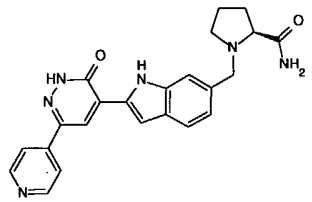
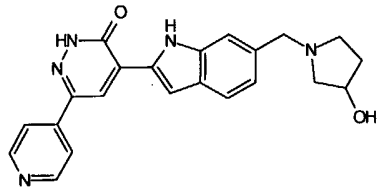
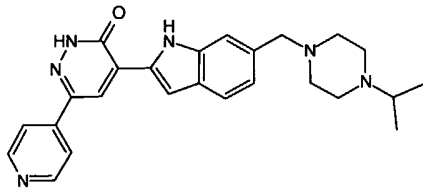
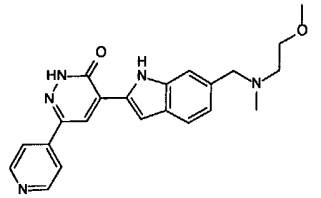
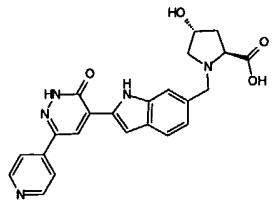
MS: (M+1) = 402.20

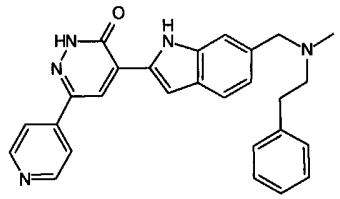
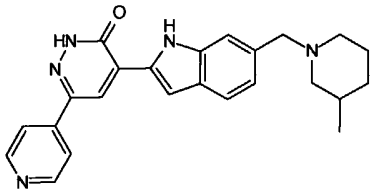
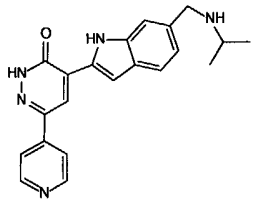
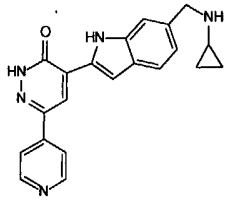
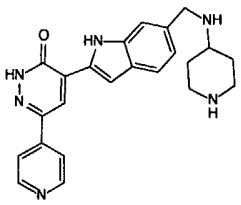
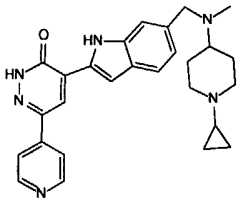
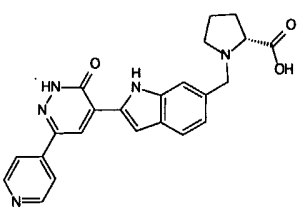
Examples 63 – 112

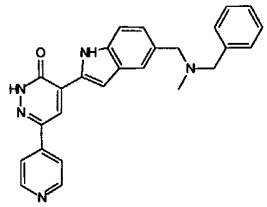
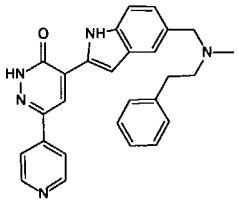
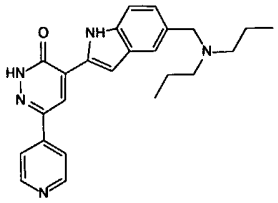
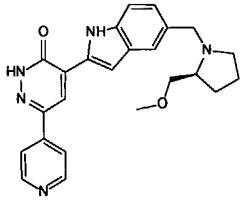
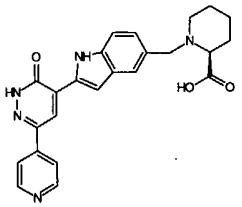
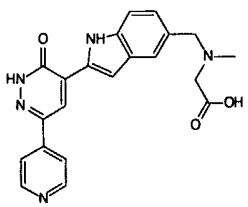
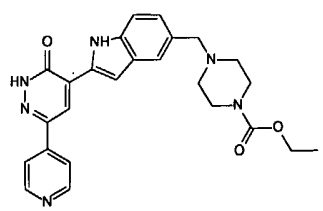
These examples are synthesized analogously to example 37.

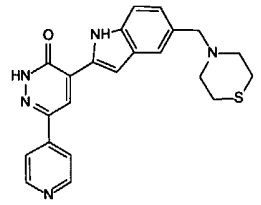
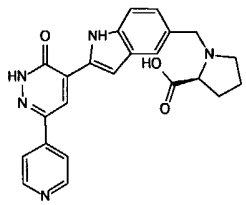
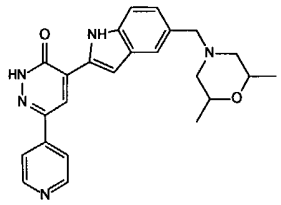
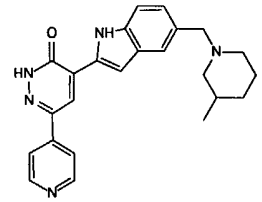
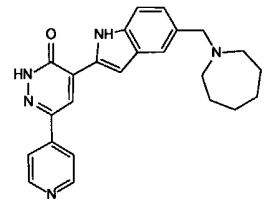
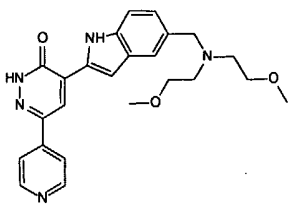
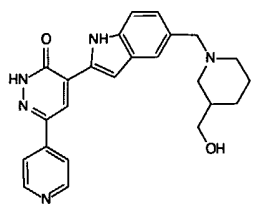
Example	No	CHEMICAL NAME	MS (M+1)
	63	4-(5-Piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	386
	64	4-(6-[1,4]Oxazepan-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	402
	65	4-[6-(4-Cyclopropyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	427
	66	4-{6-[(1-Cyclopropyl-piperidin-4-ylamino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one	441
	67	4-{6-[(Benzyl-methyl-amino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one	422
	68	4-(6-Dipropylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	402
	69	4-[6-((S)-2-Methoxymethyl-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416

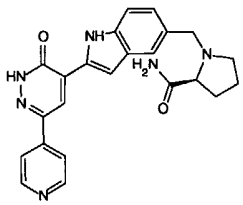
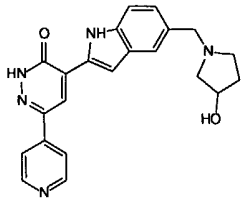
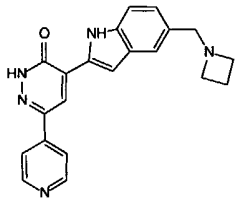
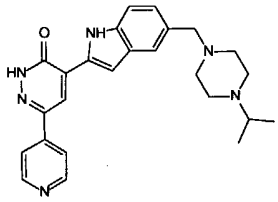
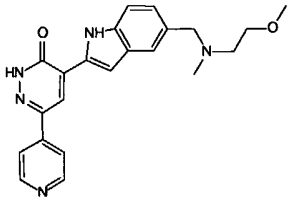
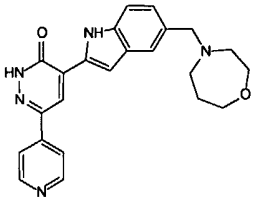
Example	No	CHEMICAL NAME	MS (M+1)
	70	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-piperidine-2-carboxylic acid	430
	71	{Methyl-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-amino}-acetic acid	390
	72	4-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-piperazine-1-carboxylic acid ethyl ester	459
	73	6-Pyridin-4-yl-4-(6-thiomorpholin-4-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one	404
	74	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid	416
	75	4-[6-(2,6-Dimethyl-morpholin-4-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416
	76	4-(6-Azepan-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	400

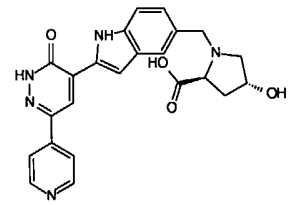
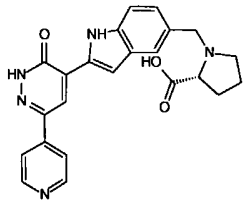
Example	No	CHEMICAL NAME	MS (M+1)
	77	4-(6-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	434
	78	4-[6-(3-Hydroxymethyl-piperidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416
	79	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid amide	415
	80	4-[6-(3-Hydroxy-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	388
	81	4-[6-(4-Isopropyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	429
	82	4-(6-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	390
	83	(2S,4R)-4-Hydroxy-1-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid	432

Example	No	CHEMICAL NAME	MS (M+1)
	84	4-{6-[(Methyl-phenethyl-amino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one	436
	85	4-[6-(3-Methyl-piperidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	400
	86	4-[6-(Isopropylamino-methyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	360
	87	4-(6-Cyclopropylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	358
	88	4-[6-(Piperidin-4-ylaminomethyl)-1H-indol-2-yl]-6-pyridin-4-yl 2H-pyridazin-3-one	401
	89	4-(6-{[(1-Cyclopropyl-piperidin-4-yl)-methyl-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	455
	90	(R)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid	416

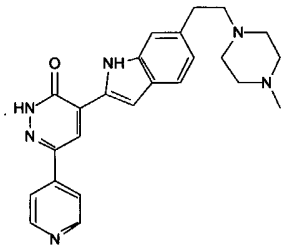
Example	No	CHEMICAL NAME	MS (M+1)
	91	4-{5-[(Benzyl-methyl-amino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one	422
	92	4-{5-[(Methyl-phenethyl-amino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one	436
	93	4-(5-Dipropylaminomethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	402
	94	4-[5-((S)-2-Methoxymethyl-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416
	95	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-piperidine-2-carboxylic acid	430
	96	{Methyl-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-amino}-acetic acid	390
	97	4-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-piperazine-1-carboxylic acid ethyl ester	459

Example	No	CHEMICAL NAME	MS (M+1)
	98	6-Pyridin-4-yl-4-(5-thiomorpholin-4-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one	404
	99	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-pyrrolidine-2-carboxylic acid	416
	100	4-[5-(2,6-Dimethyl-morpholin-4-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416
	101	4-[5-(3-Methyl-piperidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	400
	102	4-(5-Azepan-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	400
	103	4-(5-{[Bis-(2-methoxy-ethyl)-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	434
	104	4-[5-(3-Hydroxymethyl-piperidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	416

Example	No	CHEMICAL NAME	MS (M+1)
	105	(S)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-pyrrolidine-2-carboxylic acid amide	415
	106	4-[5-(3-Hydroxy-pyrrolidin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	388
	107	4-(5-Azetidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	358
	108	4-[5-(4-Isopropyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one	429
	109	4-(5-{[(2-Methoxy-ethyl)-methyl-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	390
	110	4-(5-[1,4]Oxazepan-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one	402

	111	(2S,4R)-4-Hydroxy-1-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-pyrrolidine-2-carboxylic acid	432
	112	(R)-1-[2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-5-ylmethyl]-pyrrolidine-2-carboxylic acid	416

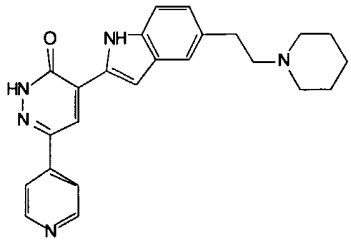
Example 113
4-{6-[2-(4-Methyl-piperazin-1-yl)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 62.

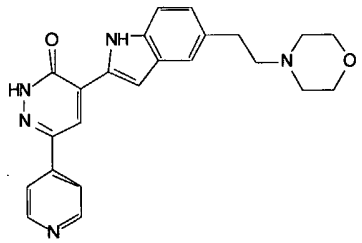
MS: (M+1) = 415.

Example 114
4-[5-(2-Piperidin-1-yl-ethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



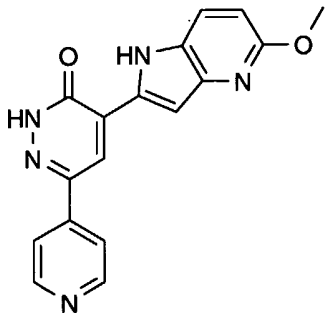
This compound is synthesized analogously to example 62 starting from 5-formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see above).
MS: (M+1) = 400.

Example 115
4-[5-(2-Morpholin-4-yl-ethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



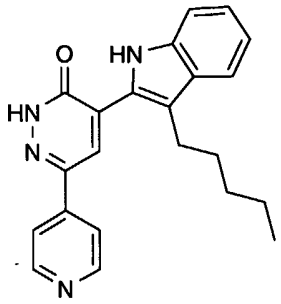
This compound is synthesized analogously to example 62 starting from 5-formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see above).
MS: (M+1) = 402.

Example 116
4-(5-Methoxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



This example is synthesized analogously to example 1
MS: (M+1) = 320.

Example 117
4-(3-Pentyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-pent-1-enyl-1H-indole

This compound is prepared as described for example 9c by using 1-pentenylboronic Acid

b) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-pentyl-1H-indole

20 mg Palladium catalyst (10% on Charcoal) is added to a solution of 145 mg 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-pent-1-enyl-1H-indole in 1 ml ethanol and the suspension is stirred under a hydrogen atmosphere for 8 hours. The crude product is isolated by filtration and removal of the solvent and purified by silicagel chromatography (ethylacetate/ n-hepatane)

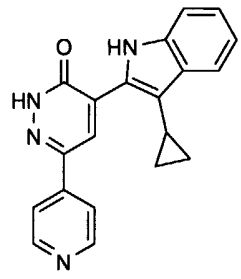
4-(3-Pentyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

62 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-pentyl-1H-indole are deprotected as described for compound 9d

MS: (M+1) = 359.

Example 118

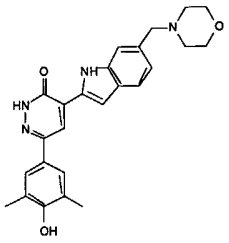
4-(3-Cyclopropyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



This example is synthesized analogously to example **1**

MS: (M+1) = 329

Example 119
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(6-morpholin-4-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one



a) 6-(*tert*-Butyldimethylsiloxymethyl)-2-(6-chloro-3-methoxy-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

2.385 g 6-Chloro-4-iodo-3-methoxy-pyridazine, 4.30 g 2-[1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxymethyl)indole-2-yl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (see example 37), 11.50 g cesium carbonate, and 360 mg [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in a mixture of 66 mL dioxane and 19.4 mL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 2 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification on silica (Flashmaster, heptane/EtOAc) gives 3.3 g (74%) 6-(*tert*-butyldimethylsiloxymethyl)-2-(6-chloro-3-methoxy-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester.

b) 6-(*tert*-Butyldimethylsiloxymethyl)-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester

3.30 g 6-(*tert*-Butyldimethylsiloxymethyl)-2-(6-chloro-3-methoxy-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester, 2.11 g 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, 1.37 g sodium carbonate, and 756 mg tetrakis(triphenylphosphine)palladium(0) are dissolved in a mixture of 53 mL dimethoxyethane and 6.5 mL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 5 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification on silica (Flashmaster, heptane/EtOAc) gives 3.06 g (79%) 6-(*tert*-butyldimethylsiloxymethyl)-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester.

c) 6-Hydroxymethyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester

3.06 g 6-(*tert*-Butyldimethylsiloxymethyl)-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 50 mL THF. After addition of 4.1 g tetrabutylammonium fluoride trihydrate, the red solution is stirred for 2 hours. The reaction mixture is diluted with EtOAc, washed with saturated aqueous ammonium chloride, water, and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification on silica affords 2.04 g (82%) 6-hydroxymethyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester.

d) 6-Formyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester

A dry flask is charged with 0.399 mL oxalyl chloride and 69 mL dichloromethane. After cooling to –78 °C 0.304 mL DMSO is added dropwise. After stirring for 15 minutes at this temperature, 2.04 g (6-hydroxymethyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester in 46 mL dichloromethane are slowly added by syringe. After stirring for 60 minutes at –78 °C 2.98 mL triethylamine is added. The reaction mixture is stirred for 60 minutes at –78 °C, allowed to warm to 0°C and quenched by addition of sat. aq. NH_4Cl-solution. The reaction mixture is diluted with dichloromethane, washed with sat. aq. NH_4Cl-solution and brine, dried ($MgSO_4$) and concentrated in vacuo. 1.96 g (97%) crude 6-formyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester are obtained.

e) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-6-(4-morpholin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester

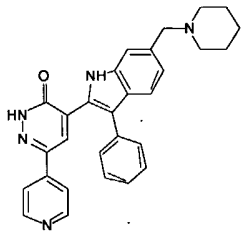
176 mg 6-Formyl-2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid *tert*-butyl ester are dissolved in 28 mL dichloroethane. 0.33 mL morpholine and then 1.4 mL acetic acid are added. 394 mg sodium triacetoxyborohydride is added in several portions over 3 hours. Sat. aq. $NaHCO_3$-solution is added and the reaction mixture is stirred until the CO_2-evolution stopped. The reaction mixture is diluted with dichloromethane, the aq. phase washed with dichloromethane, the combined org. phases dried ($MgSO_4$) and concentrated in vacuo. 202 mg (99%) crude product is obtained, which is directly used in the next step.

f) 6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-morpholin-1-ylmethyl)-1H-indol-2-yl]- 2H-pyridazin-3-one

101 mg 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid tert-butyl ester are dissolved in 3.0 mL acetonitrile. 80 µL TMSCl (trimethylsilylchloride) and 105 mg potassium iodide are added. The reaction mixture is heated to reflux for 3 hours. Purification by HPLC affords 18 mg (18%) 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-morpholin-1-ylmethyl)-1H-indol-2-yl]- 2H-pyridazin-3-one as its trifluoroacetate salt.

MS: (M+1) = 431

Example 120
4-(3-Phenyl-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-piperidin-1-ylmethyl-1H-indole

1.30 g 6-(Piperidin-1-ylmethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see example 37) are dissolved in 2 mL dichloromethane. 0.97 mL trifluoroacetic acid and 4 drops of water are added. The reaction mixture is stirred overnight at rt. Concentration in vacuo affords 1.05 g (100%) crude product.

b) 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-piperidin-1-ylmethyl-1H-indole

1.05 g 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-piperidin-1-ylmethyl-1H-indole are suspended in 30 mL acetone and 690 mg NIS is added. After stirring for 30 minutes at rt, the solvent is removed in vacuo. HPLC purification affords 560 mg (43%) 3-iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-piperidin-1-ylmethyl-1H-indole and 287 mg (27%) starting material.

c) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-phenyl-6-piperidin-1-ylmethyl-1H-indole

68 mg 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-piperidin-1-ylmethyl-1H-indole, 17 mg phenylboronic acid, 86 mg potassium phosphate tribasic n-hydrate, and 12 mg tetrakis(triphenylphosphine)palladium(0) are dissolved in a mixture of 2.0 mL toluene and 72 µL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to 90 °C for 2.5 hours. Concentration in vacuo affords 62 mg crude product.

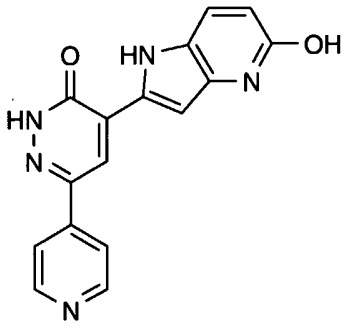
d) 4-(3-Phenyl-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

62 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-phenyl-6-piperidin-1-ylmethyl-1H-indole are dissolved in 0.5 mL ethanol. 0.75 mL 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 15 minutes. Purification by HPLC affords 36 mg (58%) 4-(3-phenyl-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoro-acetate salt.

MS: (M+1) = 462.

Example 121

4-(5-Hydroxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3- one



a) 5-Methoxy-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-pyrrolo[3,2-b]pyridine-1- carboxylic acid tert-butyl ester

This compound is synthesized as described for example 1e.

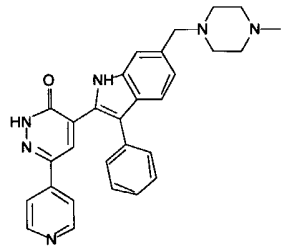
b) 4-(5-Hydroxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

34 mg 4-(5-Hydroxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 19 mg trimethylchlorosilane and 32 mg KI dissolved in 1 ml of acetonitril are

stirred for 2h at 60°C. 10 mg trimethylchlorosilane and 16 mg KI are added to and the mixture stirred for additional 8 hours to complete the reaction. After cooling to room temperature 0.5 ml of a 4N solution of hydrochloric acid in dioxane is added and the resulting mixture stirred for 2h at room temperature. The solution is diluted into DMF/water and directly purified by HPLC on a RP18 column giving 5.4 mg 4-(5-hydroxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3- one.

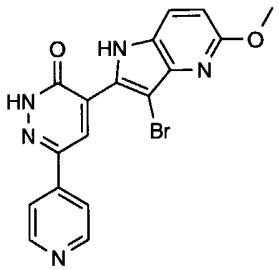
MS: (M+1) = 306.

Example 122
4-[6-(4-Methyl-piperazin-1-ylmethyl)-3-phenyl-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



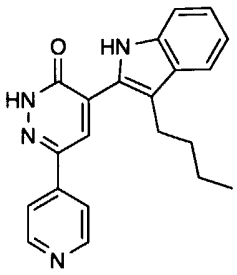
This compound is synthesized analogously to example 120.
MS: (M+1) = 477.

Example 123
4-(3-Bromo-5-methoxy-1H-pyrrolo[3,2-b]pyridin-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is prepared analogously example 12 starting from compound 116.
MS: (M+1) = 367

Example 124
4-(3-Butyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 3-Butyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole

0.39 ml of n-butyllithium solution (1.6M in hexane) is added at -75°C to a 0.5 M solution of zinc chloride in THF and the resulting mixture stirred for 30 min at room temperature. This solution is added via a syringe to a solution of 107 mg 3-iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole (9b) and 10mg 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride (1:1 complex with CH_2Cl_2) in THF and stirred for 4 h at 70°C. The reaction mixture is quenched by adding saturated NH_4Cl-solution and extracted with ethylacete. The combined organic layers are dried over $MgSO_4$, the solvens removed in vacuo. Reversed phase chromatography (RP18, water (0.05% HCOOH) / acetonitrile (0.05% HCOOH)) 30 mg product.

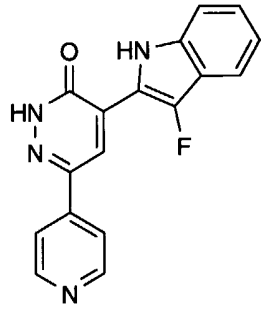
MS: (M+1) = 345

b) 4-(3-Butyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

22 mg 3-Butyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole are deprotected as described for compound 9d.

MS: (M+1) = 345

Example 125
4-(3-Fluoro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



43 mg 4-(1H-Indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one (example 1) are dissolved in 1,2 ml of a 1:1 DMSO / acetonitrile mixture and cooled to 0°C. Then 0.25 equiv. of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis tetrafluoroborate is and the resulting mixture stirred for 30 min at 0°C. The addition

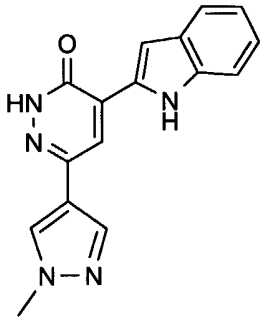
of 0.25 equiv. of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis tetrafluoroborate and stirring at 0°C is repeated several times until the reaction is complete. The product is isolated by RP HPLC chromatography (RP18 water (0.05% HCOOH) / acetonitrile (0.05% HCOOH))

Yield: 7.3 mg

MS: (M+1) = 307

Example 126

4-(1H-Indol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one



a) 2-[3-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester

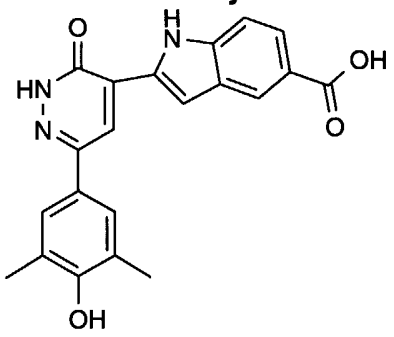
250 mg of 2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester and 72 mg of tetrakis(triphenylphosphine) palladium (0) are dissolved in 12 ml DME and the solution is stirred for 5 min at RT under argon. 95 mg of 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan)-1H-pyrazole and 0.41 ml of a 2M aqueous solution of sodium carbonate are added and the reaction solution is stirred at 95°C for 5 h. The reaction solution is filtered through a silica gel cartridge, eluting with dichloromethane. The solvent is removed under reduced pressure. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 142 mg. LC-MS (ES+) 406 $(M+H)^+$.

b) 4-(1H-Indol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one

2-[3-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester is dissolved in 8ml dioxan and 8ml aqueous 2N NaOH and heated by microwave irradiation for 90 min at 150°C. The solution is neutralized with aqueous HCl and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 35 mg. LC-MS (ES+) 292 $(M+H)^+$.

Example 127

2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid



a) 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester

This compound is prepared from 500 mg of 6-chloro-4-iodo-3-methoxy-pyridazine analogously to example 2. Yield 200 mg. LC-MS (ES+) 331.9$(M+H)^+$.

b) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indole-5-carboxylic acid ethyl ester

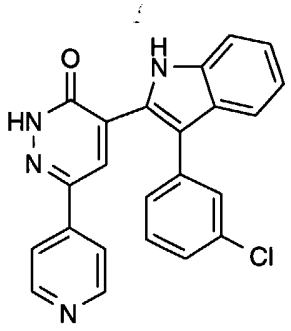
This compound is prepared from (a) above, analogously to example 6 (c). Yield 140 mg. LC-MS (ES+) 418 $(M+H)^+$.

c) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid

The product from (b) above is dissolved in 4ml dioxan and 2ml aqueous 2N NaOH and heated by microwave irradiation for 90 min at 150°C. The solution is neutralized with aqueous HCl and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 20 mg. LC-MS (ES+) 376 $(M+H)^+$.

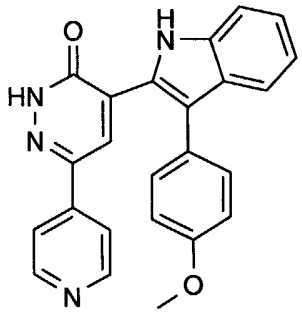
Example 128

4-[3-(3-Chloro-phenyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



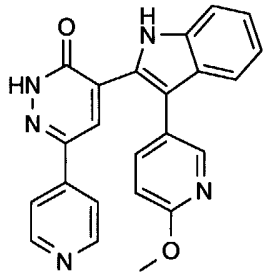
This compound is prepared as described for example 9.
MS: (M+1) = 399

Example 129
4-[3-(4-Methoxy-phenyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



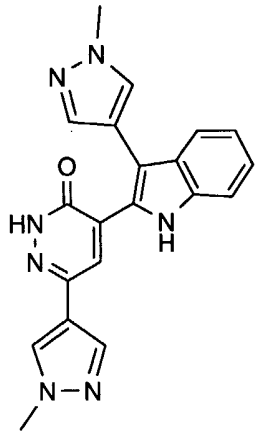
This compound is prepared as described for example 9.
MS: (M+1) = 395

Example 130
4-[3-(6-Methoxy-pyridin-3-yl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is prepared as described for example 9.
MS: (M+1) = 396

Example 131
6-(1-Methyl-1H-pyrazol-4-yl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one



a) 3-Bromo-2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester

100 mg of 2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester is dissolved in 5ml dimethoxythane and 75mg of N-bromosuccinimide is added. The solution is stirred at RT for 16h. The resulting solution is used in the subsequent reaction without further purification.

b) 2-[3-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4- yl)-indole-1-carboxylic acid tert-butyl ester

3-Bromo-2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester is treated analogously to example 126 (a). Yield 40 mg. LC-MS (ES+) 486 $(M+H)^+$.

c) 2-[3-Methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4- yl)-1H-indole

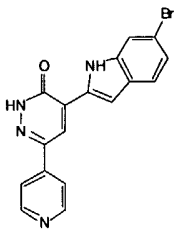
40 mg of 2-[3-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4- yl)-indole-1-carboxylic acid tert-butyl ester is treated analogously to Example 127 (c). Yield 9 mg. LC-MS (ES+) 386 $(M+H)^+$.

d) 6-(1-Methyl-1H-pyrazol-4-yl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one

9 mg of 2-[3-methoxy-6-(1-methyl-1H-pyrazol-4-yl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4- yl)-1H-indole is treated analogously to example 6 (e). Yield 6 mg. LC-MS (ES+) 372 $(M+H)^+$.

Example 132

4-(6-Bromo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 6-Bromo-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid *tert*-butyl ester

1.1 g 6-Bromo-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid *tert*-butyl ester and 1.515 mL 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane are dissolved in 6.0 mL THF and cooled to 0 °C. LDA (from 0.70 mL diisopropylamine and 2.9 mL 1.6 M butyllithium (in hexanes) in 10 mL THF) is added dropwise over 1 hour. Then the reaction mixture is stirred for 1 hour at 0°C, quenched with water/1N HCl (5.5 mL each) and stirred until two clear phases appear. The aq. phase is extracted twice with EtOAc, the combined org. phases dried ($MgSO_4$) and the solvent removed in vacuo. This affords 1.45 g (92%) crude product.

b) 6-Bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester

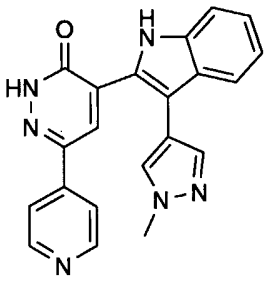
1.075 g 4-Iodo-3-methoxy-6-pyridin-4-yl-pyridazine, 1.45 g 6-bromo-2-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-indole-1-carboxylic acid *tert*-butyl ester, 4.48 g cesium carbonate, and 140 mg [1,1'-bis(diphenylphosphino)ferrocene]dichloro-palladium(II) complex with dichloromethane (1:1) are dissolved in a mixture of 30 mL dioxane and 8.8 mL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 2 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. Purification on silica (Flashmaster, methylenechloride/MeOH) gives 1.59 g (96%) 6-bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester.

c) 4-(6-Bromo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

40 mg 6-Bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester are dissolved in 0.5 mL ethanol. 0.58 mL 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave

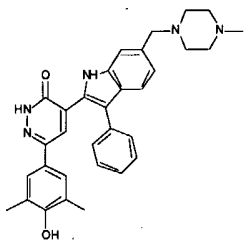
oven for 15 minutes. Purification by HPLC affords 20 mg (50%) 4-(6-bromo-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one.
MS: (M+1) = 367.

Example 133
4-[3-(1-Methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is prepared as described for example 9.
MS: (M+1) = 369

Example 134
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-3-phenyl-1H-indol-2-yl]-2H-pyridazin-3-one



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid tert-butyl ester

293 mg 6-Formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see example 119) is dissolved in 52 mL dichloromethane. 635 µL *N*-methylpiperazine and then 2.6 mL acetic acid are added. 656 mg sodium triacetoxyborohydride is added in several portions over 3 hours. Sat. aq. $NaHCO_3$-solution is added and the reaction mixture is stirred until the CO_2-evolution stopped. The reaction mixture is diluted with dichloromethane, the aq. phase washed with dichloromethane, the combined org. phases dried ($MgSO_4$) and concentrated in vacuo. 344 mg (100%) crude product is obtained, which is directly used in the next step.

b) 4-{5-[3-Iodo-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-methoxy-pyridazin-3-yl}- 2,6-dimethyl-phenol

344 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-yl-methyl)-indole-1-carboxylic acid tert-butyl ester is dissolved in 4 mL THF. 324 µL 30% NaOMe in MeOH is added. The reaction mixture is stirred for 3 hours at rt. After concentration in vacuo, the crude indole is dissolved in 10.8 mL acetone and 166 mg NIS is added. The reaction mixture was stirred for 30 minutes at rt and then concentrated in vacuo. Purification by HPLC affords 64 mg (18%) 4-{5-[3-iodo-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-methoxy-pyridazin-3-yl}-2,6-dimethyl-phenol.

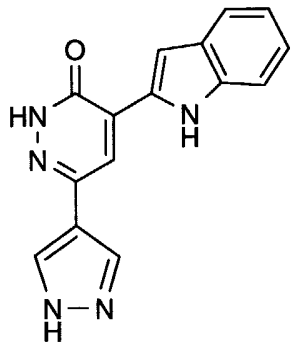
c) 4-{6-Methoxy-5-[6-(4-methyl-piperazin-1-ylmethyl)-3-phenyl-1H-indol-2-yl]-pyridazin-3-yl}-2,6-dimethyl-phenol

48 mg 4-{5-[3-Iodo-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-methoxy-pyridazin-3-yl}-2,6-dimethyl-phenol, 14 mg phenylboronic acid, 72 mg potassium phosphate tribasic n-hydrate, and 10 mg tetrakis(triphenylphosphine)palladium(0) are dissolved in a mixture of 1.9 mL toluene and 55 µL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to 90 °C for 2.5 hours. Concentration in vacuo affords 48 mg crude product.

d) 6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-3-phenyl-1H-indol-2-yl]-2H-pyridazin-3-one

48 mg 4-{6-Methoxy-5-[6-(4-methyl-piperazin-1-ylmethyl)-3-phenyl-1H-indol-2-yl]-pyridazin-3-yl}-2,6-dimethyl-phenol are dissolved in 1.2 mL acetonitrile. 34 µL TMSCl and 45 mg potassium iodide are added. The reaction mixture is heated to reflux for 3 hours. Again 34 µL TMSCl and 45 mg potassium iodide are added and the reaction mixture stirred for an additional 2 hours. Purification by HPLC affords 16 mg (34%) 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-yl-methyl)-3-phenyl-1H-indol-2-yl]-2H-pyridazin-3-one as its trifluoroacetate salt.
MS: (M+1) = 520.

Example 135
4-(1H-Indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one



a) 2-[3-Methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester

150 mg of 2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester is treated analogously to example 126 (a) using 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan)-1H-pyrazole. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 54 mg. LC-MS (ES+) 392 $(M+H)^+$.

b) 2-[3-Methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-1H-indole

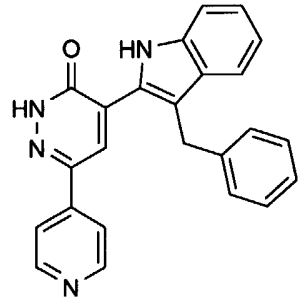
54 mg of 2-[3-methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester is treated analogously to example 127 (c). Yield 35 mg.

c) 4-(1H-Indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one

35 mg of 2-[3-methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-1H-indole is treated analogously to example 6 (e). Yield 7 mg. . LC-MS (ES+) 278 $(M+H)^+$.

Example 136

4-(3-Benzyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

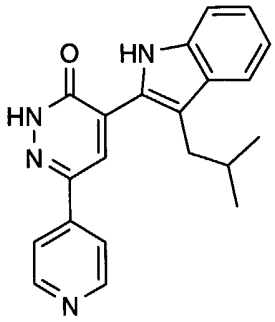


This compound was prepared analogously compound 124 using commercially available benzylzinc bromide.

MS: (M+1) = 379.

Example 137

4-(3-Isobutyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

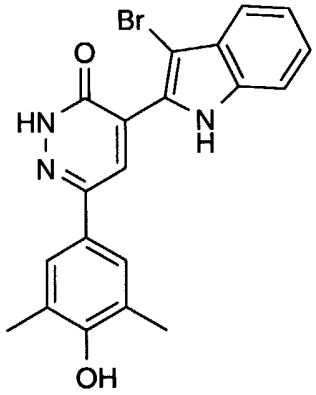


This compound is prepared analogously compound 124 using commercially available of 2-methylpropylzinc bromide

MS: (M+1) = 345.

Example 138

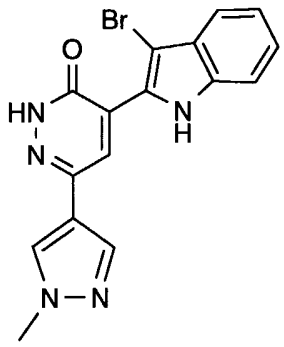
4-(3-Bromo-1H-indol-2-yl)-6-(4-hydroxy-3,5-dimethyl-phenyl)-2H-pyridazin-3-one



10 mg of 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one is dissolved in 400µl of acetone and 5.3 mg of N-bromosuccinimide is added. The solution is stirred at RT for 20 min and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 4 mg. LC-MS (ES+) 409/411 $(M)^+$.

Example 139

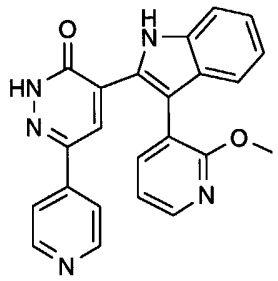
4-(3-Bromo-1H-indol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one



30 mg of 4-(1H-Indol-2-yl)-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one is dissolved in 4 ml of acetone and 22 mg of N-bromosuccinimide is added. The solution is stirred at RT for 20 min and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 14 mg. LC-MS (ES+) 370/372 $(M+H)^+$.

Example 140

4-[3-(2-Methoxy-pyridin-3-yl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

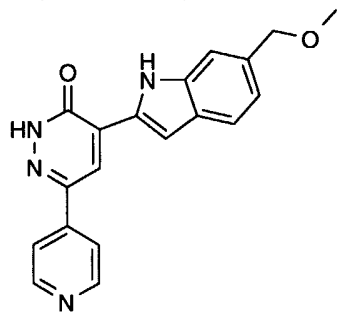


This compound is prepared as described for example 9.

MS: (M+1) = 396

Example 141

4-(6-Methoxymethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one



a) 6-Methoxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole

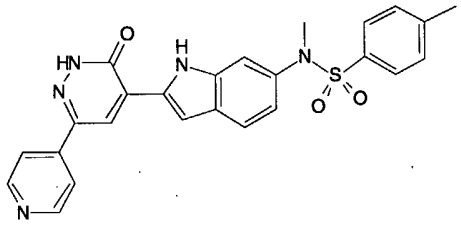
This compounds is isolated as side product during the reductive amination reaction described for example 37.

b) 4-(6-Methoxymethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

6-Methoxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole is deprotected as described for compound 9d.

Example 142

4,*N*-Dimethyl-*N*-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-yl]-benzenesulfonamide



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-[methyl-(toluene-4-sulfonyl)-amino]-indole-1-carboxylic acid *tert*-butyl ester

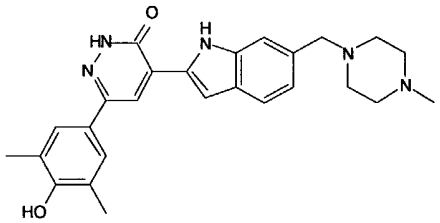
Under argon, 340 mg 6-Bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester (see example 132), 157 mg *N*-methyl-*para*-toluenesulfonamide, 322 mg cesium carbonate, 32 mg $Pd_2(dba)_3$, and 30 mg xantphos are dissolved in 6.8 mL toluene. Argon is bubbled through the solution for 5 minutes. The reaction mixture is heated to 130 °C for 1 hour in a microwave oven. Then the reaction mixture is diluted with EtOAc and washed with water. The organic phase is dried ($MgSO_4$) and the solvent removed in vacuo. Purification by HPLC affords 155 mg (37%) 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-[methyl-(toluene-4-sulfonyl)-amino]-indole-1-carboxylic acid *tert*-butyl ester.

b) 4,*N*-Dimethyl-*N*-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-yl]-benzenesulfonamide

155 mg 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-[methyl-(toluene-4-sulfonyl)-amino]-indole-1-carboxylic acid *tert*-butyl ester are dissolved in 2.25 mL ethanol. 1.85 mL 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 15 minutes. Purification by HPLC affords 61 mg

(39%) 4,*N*-dimethyl-*N*-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-yl]-benzenesulfonamide.
MS: (M+1) = 472.

Example 143
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



a) 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-6-hydroxymethyl-indole-1-carboxylic acid *tert*-butyl ester

2.234 g 3-Chloro-4-iodo-3-methoxy-pyridazine, 4.03 g 2-[1-(*tert*-butoxycarbonyl)-6-(*tert*-butyldimethylsiloxymethyl)indole-2-yl]-4,4,5,5-tetramethyl,1,3,2-dioxaborolane (see example 37), 5.38 g cesium carbonate, and 337 mg [1,1'-bis(diphenyl-phosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in a mixture of 72 ml dioxane and 21 ml water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 2 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo.
The crude product is dissolved in 80 ml THF. After addition of 4.16 g tetrabutylammonium fluoride trihydrate, the red solution is stirred for 2 hours. The reaction mixture is diluted with EtOAc, washed with saturated aqueous ammonium chloride, water, and brine, dried with $MgSO_4$ and concentrated in vacuo. 3.21 g (100%) crude product are obtained.
MS: (M+1) = 390.

b) 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-6-formyl-indole-1-carboxylic acid *tert*-butyl ester

2.7 g 6-Hydroxymethyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 80 mL dichloromethane. After addition of 3.61 g activated manganese (IV) oxide the reaction mixture is heated to reflux

for 1 hour. Then every two hours additional manganese (IV) oxide is added until the conversion is complete. The reaction mixture is diluted with dichloromethane and filtered over celite. 2.68 g (100%) crude product is obtained, which is directly used in the next reaction.

c) 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester

2.68 g 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-6-formyl-indole-1-carboxylic acid *tert*-butyl ester is dissolved in 300 mL dichloromethane. 4.73 mL *N*-methylpiperazine and then 30 mL acetic acid are added. 4.40 g sodium triacetoxyborohydride is added in several portions over 3 hours. Sat. aq. $NaHCO_3$-solution is added and the reaction mixture is stirred until the CO_2-evolution stopped. The reaction mixture is diluted with dichloromethane, the aq. phase washed with dichloromethane, the combined org. phases dried ($MgSO_4$) and concentrated in vacuo. HPLC purification affords 2.019 g (50%) 2-(6-chloro-3-methoxy-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester as its trifluoro-acetate salt.

MS: (M+1) = 472.

d) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester

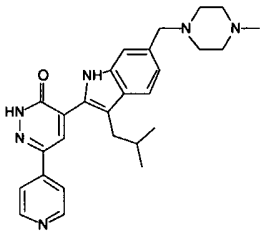
500 mg 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester, 233 mg 2,6-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol, 180 mg sodium carbonate, and 98 mg tetrakis(triphenylphosphine)palladium(0) are dissolved in a mixture of 6.7 mL dimethoxyethane and 0.85 mL water. Argon is bubbled through the solution for 5 minutes. The mixture is heated to reflux for 5 hours. After diluting with EtOAc, the organic phase is washed with water and brine, dried with $MgSO_4$ and concentrated in vacuo. 475 mg crude product are obtained.

e) 6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one

475 mg 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-6-(4-methyl-piperazin-1-ylmethyl)-indole-1-carboxylic acid *tert*-butyl ester are dissolved in 10 mL acetonitrile. 432 µL TMSCl and 565 mg potassium iodide are added. The reaction mixture is heated to reflux for 3 hours. After cooling to rt, 1 mL conc. HCl

is added and the reaction mixture stirred for 1 hour. Then the mixture was concentrated in vacuo. Purification by HPLC and addition of 1 N aq. HCl before lyophilisation affords 53 mg (13%) 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one as its chloride salt.
MS: (M+1) = 444.

Example 144
4-[3-Isobutyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



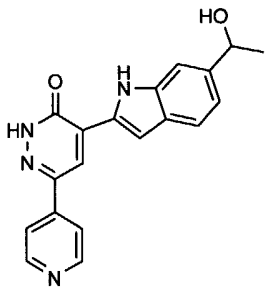
a) 3-Isopropyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole

220 mg 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole (see example 120), 3.36 mL isobutylzinc bromide (0.5M in THF), and 14 mg [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in 2.2 mL THF. Argon is bubbled through the solution for 5 minutes. The reaction mixture is heated to 70 °C for 7 hours. Concentration in vacuo affords 98 mg crude product.

b) 4-[3-Isobutyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

98 mg 3-Isopropyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole are dissolved in 1.23 mL ethanol. 1.18 mL 1 N aqueous sodium hydroxide are added. The reaction mixture is heated to 150 °C in a microwave oven for 15 minutes. Purification by HPLC affords 39 mg (41%) 4-[3-isobutyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.
MS: (M+1) = 457.

Example 145
4-[6-(1-Hydroxy-ethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



a) 6-(1-Hydroxy-ethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl

0.4 ml of a 1.4M methyl magnesium bromide solution in toluene/THF is added dropwise at 0°C to a solution of 215 mg 6-formyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester (37c) in THF and the solution stirred over night. The reaction mixture is diluted with ethylacetate, the combined organic layers extracted with brine and water and the solvent removed in vacuo. The crude product is used without further purification.

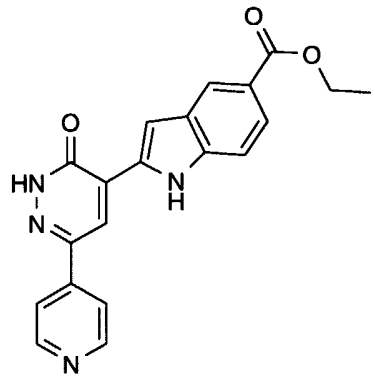
b) .4-[6-(1-Hydroxy-ethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

1-[2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indol-6-yl]-ethanol is deprotected as described for compound 9d.

MS: (M+1) = 333.

Example 146

2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester



a) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester

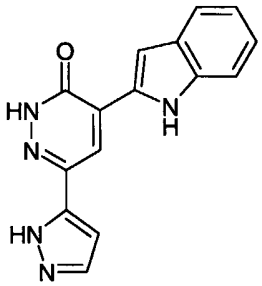
1.34g of 4-iodo-3-methoxy-6-pyridin-4-yl-pyridazine is treated analogously to example 127 (a). Yield: 1.0g. LC-MS (ES+) 375 $(M)^+$.

b) 2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester

200 mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester is treated analogously to example 6 (e). Yield: 82mg. LC-MS (ES+) 361 $(M+H)^+$.

Example 147

4-(1H-Indol-2-yl)-6-(2H-pyrazol-3-yl)-2H-pyridazin-3-one

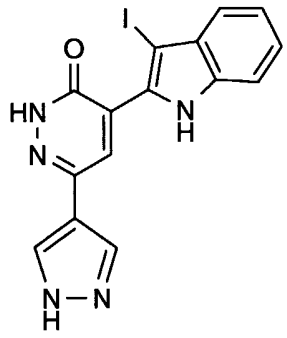


This compound is prepared as described for example 6

MS: (M+1) = 278.

Example 148

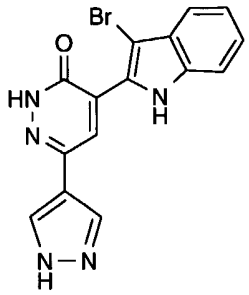
4-(3-Iodo-1H-indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one



125 mg of 2-[3-methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-1H-indole is treated analogously to example 6 (e). Yield: 6mg. LC-MS (ES+) 403 $(M+H)^+$.

Example 149

4-(3-Bromo-1H-indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one



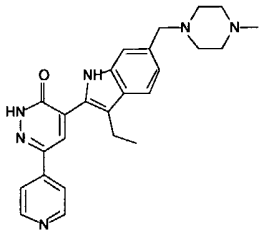
a) 4-(1H-Indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one

125 mg of 2-[3-methoxy-6-(1H-pyrazol-4-yl)-pyridazin-4-yl]-1H-indole is treated analogously to example 6 (e). Yield: 39mg. LC-MS (ES+) 278 $(M+H)^+$.

b) 4-(3-Bromo-1H-indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one

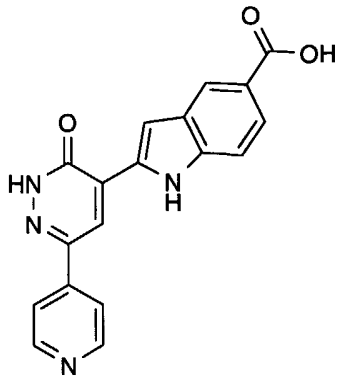
39 mg of 4-(1H-indol-2-yl)-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one is dissolved in dimethoxyethane and 28 mg of N-bromosuccinimide is added. The solution is stirred for 3h at RT. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 11 mg. LC-MS (ES+) 355/357 $(M+H)^+$.

Example 150
4-[3-Ethyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 144.
MS: (M+1) = 429.

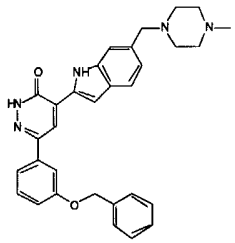
Example 151
2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid



26 mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester is treated analogously to example 126 (b). Yield: 9mg. LC-MS (ES+) 333 $(M+H)^+$.

Example 152

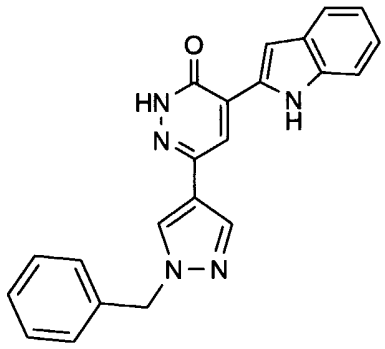
6-(3-Benzyloxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



This compound is synthesized analogously to example 143.
MS: (M+1) = 506.

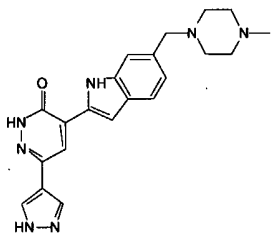
Example 153

6-(1-Benzyl-1H-pyrazol-4-yl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one



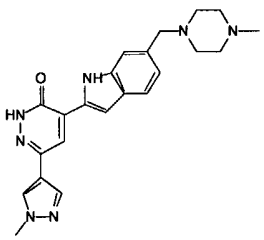
This compound is synthesized analogously to example 126 using 1-benzyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan)-1H-pyrazole.. Yield: 100mg. LC-MS (ES+) 368 $(M+H)^+$.

Example 154
4-[6-(4-Methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one



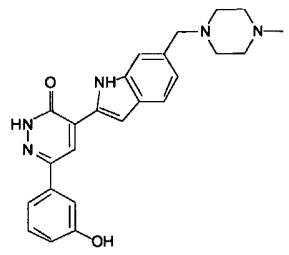
This compound is synthesized analogously to example 143.
MS: (M+1) = 390.

Example 155
4-[6-(4-Methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-(1-methyl-1H-pyrazol-4-yl)-2H-pyridazin-3-one



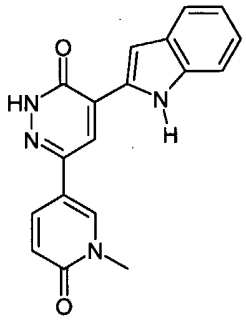
This compound is synthesized analogously to example 143.
MS: (M+1) = 404.

Example 156
6-(3-Hydroxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



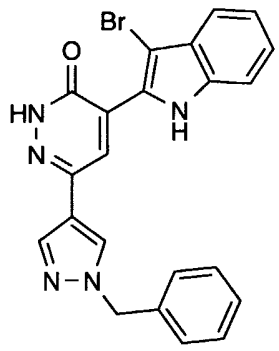
This compound is synthesized analogously to example 143.
MS: (M+1) = 416.

Example 157
4-(1H-Indol-2-yl)-6-(1-methyl-6-oxo-1,6-dihydro-pyridin-3-yl)-2H-pyridazin-3-one



This compound is prepared as described for example 6
MS: (M+1) = 319

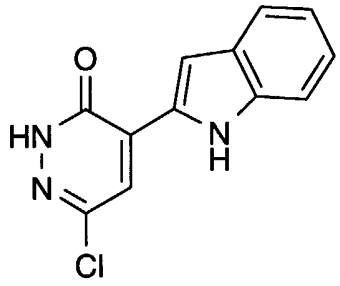
Example 158
6-(1-Benzyl-1H-pyrazol-4-yl)-4-(3-bromo-1H-indol-2-yl)-2H-pyridazin-3-one



This compound is synthesized from 6-(1-benzyl-1H-pyrazol-4-yl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one analogously to example 149 (b). Yield: 100mg. LC-MS (ES+) 446/448 $(M+H)^+$.

Example 159

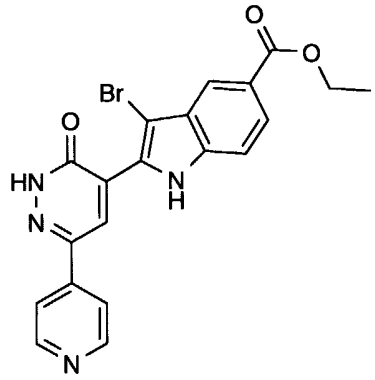
6-Chloro-4-(1H-indol-2-yl)-2H-pyridazin-3-one



2g of 2-(6-chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester is treated for 16h at 85°C with 2.76g of KI and 1.8g of trimethylsilylchloride in 200ml acetonitrile. On completion of the reaction the reaction solution is poured into water and the precipitated product is isolated by filtration. Yield: 1.33 g. LC-MS (ES+) 246 $(M+H)^+$.

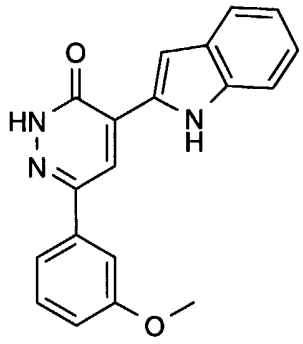
Example 160

3-Bromo-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester



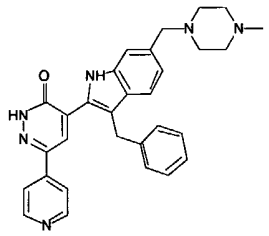
78 mg of 2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester is treated analogously to example 149 (b). Yield: 54 mg. LC-MS (ES+) 439 $(M+H)^+$.

Example 161
4-(1H-Indol-2-yl)-6-(3-methoxy-phenyl)-2H-pyridazin-3-one



This compound is prepared, using 3-methoxyphenyl boronic acid, analogously to example 2. Yield: 23 mg. LC-MS (ES+) 318 $(M+H)^+$.

Example 162
4-[3-Benzyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one



a) 3-Benzyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole

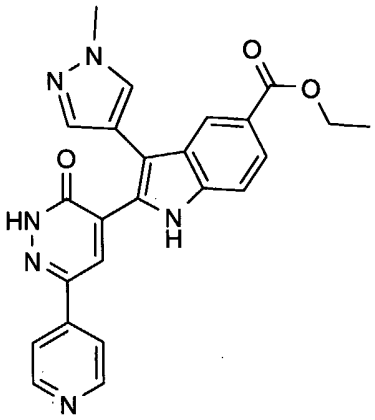
250 mg 3-Iodo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole (see example 120), 4.63 mL benzylzinc bromide (0.5M in THF), and 19 mg [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) complex with dichloromethane (1:1) are dissolved in 2.5 mL THF. Argon is bubbled through the solution for 5 minutes. The reaction mixture is heated to 70 °C for 7 hours. Concentration in vacuo affords the crude product.

b) 4-[3-Benzyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one

100 mg crude 3-benzyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-(4-methyl-piperazin-1-ylmethyl)-1H-indole are dissolved in 2.4 mL acetonitrile. 75 µL TMSCl

and 99 mg potassium iodide are added. The reaction mixture is heated to reflux for 3 hours. Then again 75 µL TMSCl and 99 mg potassium iodide are added and the reaction mixture is refluxed for additional 2 hours. Purification by HPLC affords 31 mg (32%) 4-[3-benzyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one as its trifluoroacetate salt.
MS: (M+1) = 491.

Example 163
3-(1-Methyl-1H-pyrazol-4-yl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester



(a) 3-Bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester
800 mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester is treated analogously to example 149 (b). Yield: 960mg. LC-MS (ES+) 453 $(M+H)^+$.

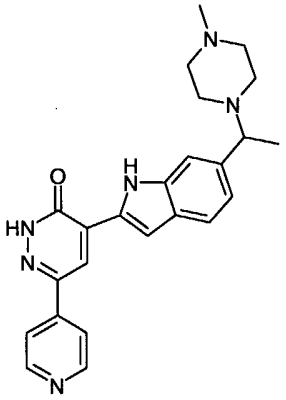
(b) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-indole-5- carboxylic acid ethyl ester
960mg of 3-bromo-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester is treated analagously to example 126 (a). Yield: 400 mg. LC-MS (ES+) 455 $(M+H)^+$.

(c) 3-(1-Methyl-1H-pyrazol-4-yl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid ethyl ester

50 mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-indole-5- carboxylic acid ethyl ester is treated analagously to example 6 (e). Yield: 14 mg. LC-MS (ES+) 441 $(M+H)^+$.

Example 164

4-{6-[1-(4-Methyl-piperazin-1-yl)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one



a) 6-Acetyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert- butyl ester

200 mg Dess-Martin periodinane (1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one) is added to a solution of 210 mg 6-(1-hydroxy-ethyl)-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butylester (145a) in 4 ml dichloromethan and the mixture stirred for 2.5 hours at room temperature. Than the solution is extracted with a 5% Na_2S0_3 solution and water, dried using a silicagel catridge and the solvent removed in vacuo. The crude product is purified by chromatography on silica gel (heptane/ethylacetat)

Yield 160 mg

b) 2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-[1-(4-methyl-piperazin-1-yl)-ethyl]-indole- 1-carboxylic acid tert-butyl ester

180 mg resin bound (2,57mmol/g) sodium cyano borhydride are added to a solution of 80 mg 6-acetyl-2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert- butyl ester, 22mg N-methyl-piperazine and 0.062 ml acidic acid and the mixture stirred over night at 65°C. The crude product is isolated by filtration and evoparation of the solvent and is used without further purification.

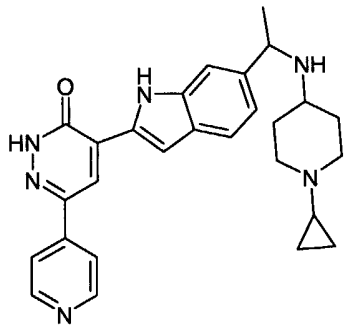
c) 4-{6-[1-(4-Methyl-piperazin-1-yl)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one

2-(3-Methoxy-6-pyridin-4-yl-pyridazin-4-yl)-6-[1-(4-methyl-piperazin-1-yl)-ethyl]-indole- 1-carboxylic acid tert-butyl ester is deprotected analogously example 37.

MS: (M+1) = 415.

Example 165

4-{6-[1-(1-Cyclopropyl-piperidin-4-ylamino)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one

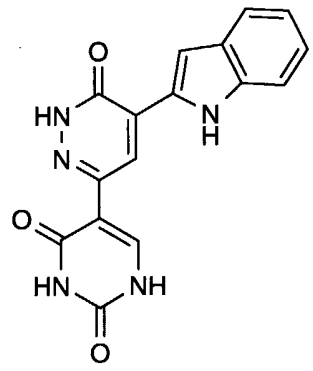


Example 165 is prepared analogously example 164

MS: (M+1) = 455.

Example 166

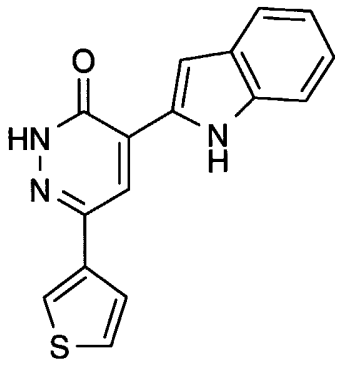
5-[5-(1H-Indol-2-yl)-6-oxo-1,6-dihydro-pyridazin-3-yl]-1H-pyrimidine-2,4-dione



This compound is prepared, using 2,4-di(tert-butoxy)pyrimidin-5-yl boronic acid hydrate, analogously to example 2. Yield: 62 mg. LC-MS (ES+) 322 $(M+H)^+$.

Example 167

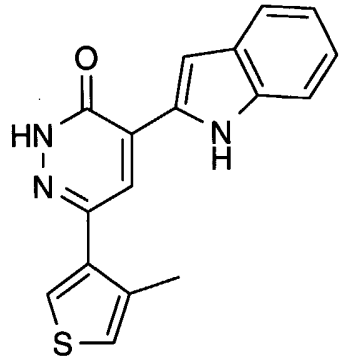
4-(1H-Indol-2-yl)-6-thiophen-3-yl-2H-pyridazin-3-one



This compound is prepared, using 3-thiophene boronic acid, analogously to example 2. Yield: 15 mg. LC-MS (ES+) 294 $(M+H)^+$.

Example 168

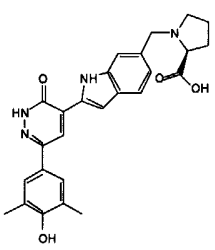
4-(1H-Indol-2-yl)-6-(4-methyl-thiophen-3-yl)-2H-pyridazin-3-one



This compound is prepared, using 4-methyl-3-thiophene boronic acid, analogously to example 2. Yield: 37 mg. LC-MS (ES+) 308 $(M+H)^+$.

Example 169

***(S)*-1-{2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indol-6-ylmethyl}-pyrrolidine-2-carboxylic acid**

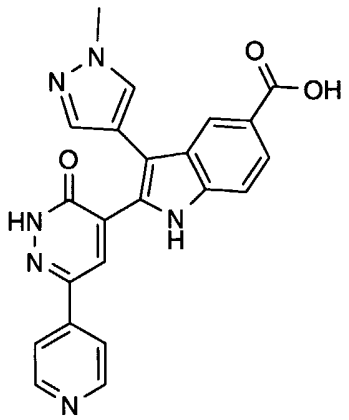


This compound is synthesized analogously to example 119.

MS: (M+1) = 459.

Example 170

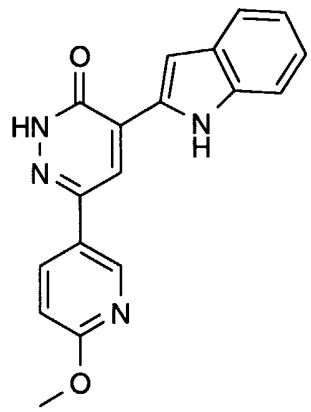
3-(1-Methyl-1H-pyrazol-4-yl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid



350 mg of 2-(3-methoxy-6-pyridin-4-yl-pyridazin-4-yl)-3-(1-methyl-1H-pyrazol-4-yl)-1H-indole-5- carboxylic acid ethyl ester is dissolved in 4ml ethanol and 4ml aqueous 2N NaOH and heated by microwave irradiation for 10 min at 150°C. The solution is neutralized with aqueous HCl and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 39 mg. LC-MS (ES+) 413 $(M+H)^+$.

Example 171

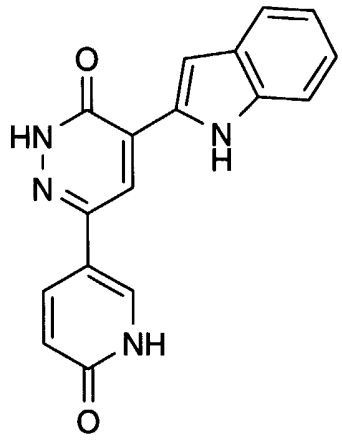
4-(1H-Indol-2-yl)-6-(6-methoxy-pyridin-3-yl)-2H-pyridazin-3-one



This compound is prepared, using 2-methoxy-5-pyridine boronic acid, analogously to example 2. Yield: 9 mg. LC-MS (ES+) 319 $(M+H)^+$.

Example 172

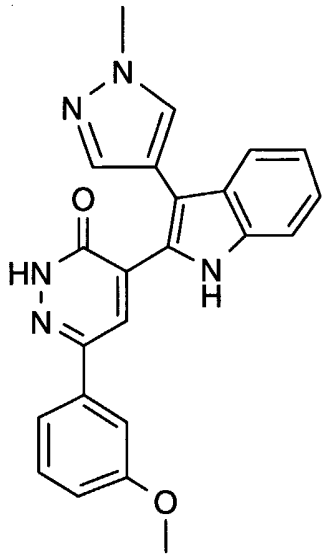
4-(1H-Indol-2-yl)-6-(6-oxo-1,6-dihydro-pyridin-3-yl)-2H-pyridazin-3-one



This compound is prepared analogously to example 171. Yield: 25 mg. LC-MS (ES+) 305 $(M+H)^+$.

Example 173

6-(3-Methoxy-phenyl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one



(a) 3-Bromo-2-[3-methoxy-6-(3-methoxy-phenyl)-pyridazin-4-yl]-indole-1-carboxylic acid tert- butyl ester

185mg of 2-[3-Methoxy-6-(3-methoxy-phenyl)-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester is treated analogously to example 149 (b) Yield: 122 mg. LC-MS (ES+) 510 $(M+H)^+$.

(b) 2-[3-Methoxy-6-(3-methoxy-phenyl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4-yl)-indole-1- carboxylic acid tert-butyl ester

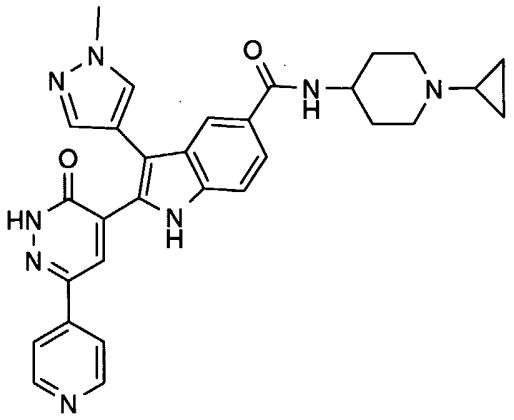
119 mg of 3-bromo-2-[3-methoxy-6-(3-methoxy-phenyl)-pyridazin-4-yl]-indole-1-carboxylic acid tert- butyl ester is treated analagously to example 126 (a). Yield: 68 mg. LC-MS (ES+) 512 $(M+H)^+$.

(c) 6-(3-Methoxy-phenyl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one

64 mg of 2-[3-methoxy-6-(3-methoxy-phenyl)-pyridazin-4-yl]-3-(1-methyl-1H-pyrazol-4-yl)-indole-1- carboxylic acid tert-butyl ester is treated analagously to example 6 (e). Yield: 15 mg. LC-MS (ES+) 398 $(M+H)^+$.

Example 174

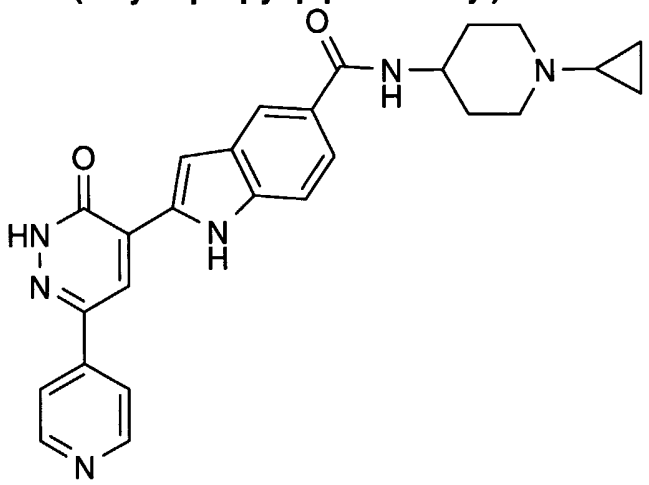
3-(1-Methyl-1H-pyrazol-4-yl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide



100 mg of 3-(1-methyl-1H-pyrazol-4-yl)-2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid is dissolved in 3ml of dichloromethane and 139mg of N-ethylmorpholine and 43.6mg of TOTU (O-((ethoxycarbonyl)-cyanomehyleneamino)-N,N,N',N'-tetramethyluroniumtetrafluoro) is added. After 5 minutes 34 mg of 1-cyclopropyl-piperidin-4-ylamine is added. The reaction is stirred for 48h at RT. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 47 mg. LC-MS (ES+) 535 $(M+H)^+$.

Example 175

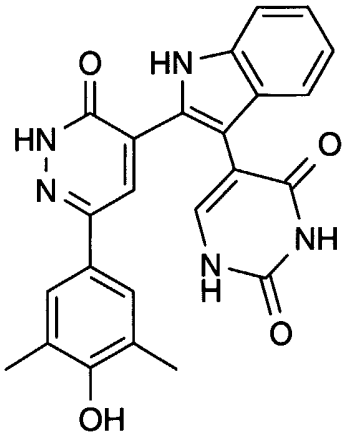
2-(3-Oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide



This compound is prepared, using 48 mg of 2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indole-5-carboxylic acid, analogously to example 174. Yield 37 mg. LC-MS (ES+) 455 $(M+H)^+$.

Example 176

5-{2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indol-3-yl}-1H-pyrimidine-2,4-dione



a) 4-[5-(3-Bromo-1H-indol-2-yl)-6-methoxy-pyridazin-3-yl]-2,6-dimethyl-phenol

471 mg of 4-[5-(1H-indol-2-yl)-6-methoxy-pyridazin-3-yl]-2,6-dimethyl-phenol is treated analogously to example 149 (b). Yield 280 mg. LC-MS (ES+) 424 $(M+H)^+$.

b) 5-{2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indol-3-yl}-1H- pyrimidine-2,4-dione

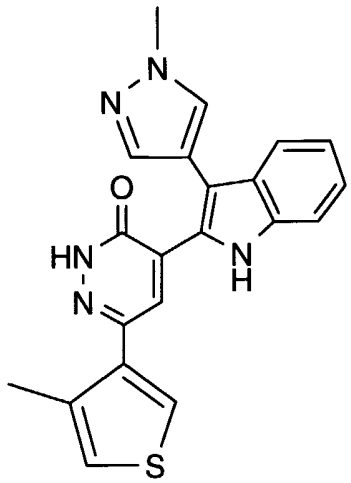
111 mg of 4-[5-(3-bromo-1H-indol-2-yl)-6-methoxy-pyridazin-3-yl]-2,6-dimethyl-phenol is treated analogously to example 6 (c), using 2,4-di(tert-butoxy)pyrimidin-5-yl boronic acid hydrate. Yield 100 mg. LC-MS (ES+) 455 $(M+H)^+$.

c) 5-{2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indol-3-yl}-1H-pyrimidine-2,4-dione

95 mg of 5-{2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indol-3-yl}-1H- pyrimidine-2,4-dione is treated analogously to example 6 (e). Yield 18 mg. LC-MS (ES+) 442 $(M+H)^+$.

Example 177

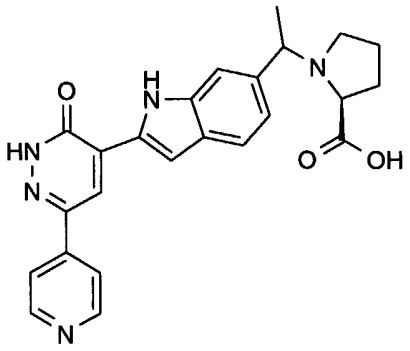
4-[3-(1-Methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-(4-methyl-thiophen-3-yl)-2H-pyridazin-3-one



The compound is prepared analogously to example 173. Yield 13 mg. LC-MS (ES+) 388 $(M+H)^+$.

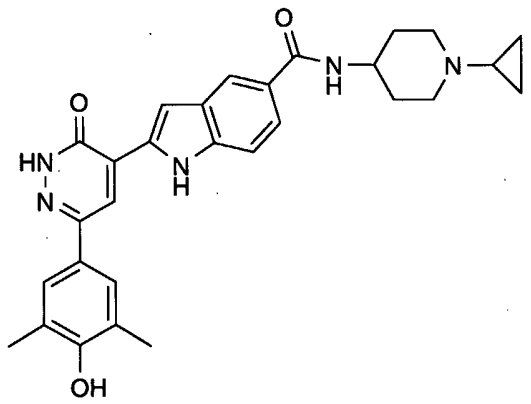
Example 178

4-[3-(1-Methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-(4-methyl-thiophen-3-yl)-2H-pyridazin-3-one



Example 178 is prepared analogously example 164.
MS: (M+1) = 430.

Example 179
2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide



a) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indole-5-carboxylic acid
480 mg of 2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indole-5-carboxylic acid ethyl ester is dissolved in 4ml ethanol and 4ml aqueous 2N NaOH and heated by microwave irradiation for 10 min at 150°C. The solution is neutralized with aqueous HCl and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 155 mg. LC-MS (ES+) 390 $(M+H)^+$.

b) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide

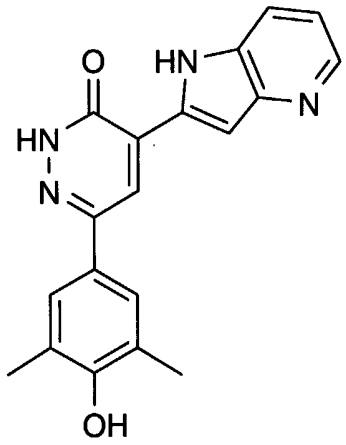
This compound is prepared analogously to example 174. Yield 200 mg. LC-MS (ES+) 512 $(M+H)^+$.

c) 2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide

This compound is prepared from 2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-methoxy-pyridazin-4-yl]-1H-indole-5-carboxylic acid (1-cyclopropyl-piperidin-4-yl)-amide analogously to example 6 (e). Yield 60 mg. LC-MS (ES+) 498 $(M+H)^+$.

Example 180

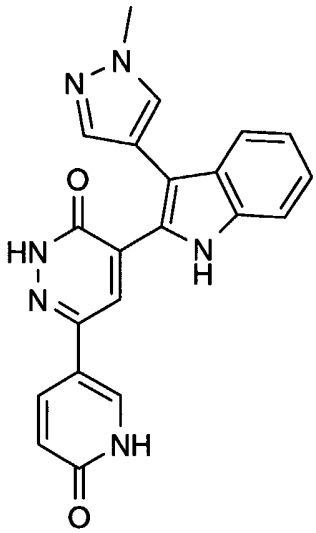
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(1H-pyrrolo[3,2-b]pyridin-2-yl)-2H-pyridazin-3-one



This compound is synthesized analogously to example 6, using 3-amino-2-bromopyridine. Yield 15 mg. LC-MS (ES+) 333 $(M+H)^+$.

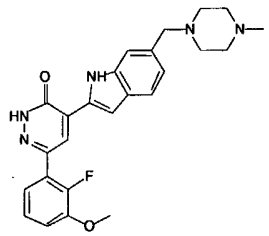
Example 181

4-[3-(1-Methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-(6-oxo-1,6-dihydro-pyridin-3-yl)-2H-pyridazin-3-one



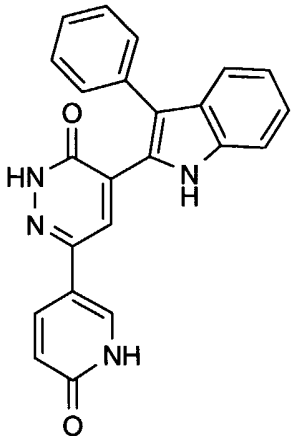
This compound is synthesized, starting from 4-(1H-indol-2-yl)-6-(6-methoxy-pyridin-3-yl)-2H-pyridazin-3-one, analogously to example 173. Yield 0.5 mg. LC-MS (ES+) 385 $(M+H)^+$.

Example 182
6-(2-Fluoro-3-methoxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



This compound is synthesized analogously to example 143.
MS: (M+1) = 448.

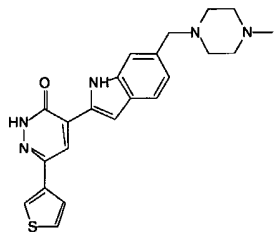
Example 183
6-(6-Oxo-1,6-dihydro-pyridin-3-yl)-4-(3-phenyl-1H-indol-2-yl)-2H-pyridazin-3-one



This compound is synthesized, starting from 4-(1H-Indol-2-yl)-6-(6-methoxy-pyridin-3-yl)-2H-pyridazin-3-one, and using phenyl boronic acid, analogously to example 173. Yield 30 mg. LC-MS (ES+) 381 $(M+H)^+$.

Example 184

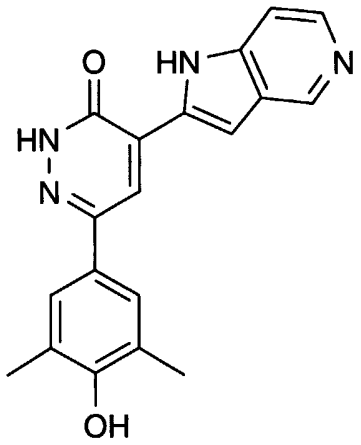
4-[6-(4-Methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-thiophen-3-yl-2H-pyridazin-3-one



This compound is synthesized analogously to example 143.
MS: (M+1) = 406.

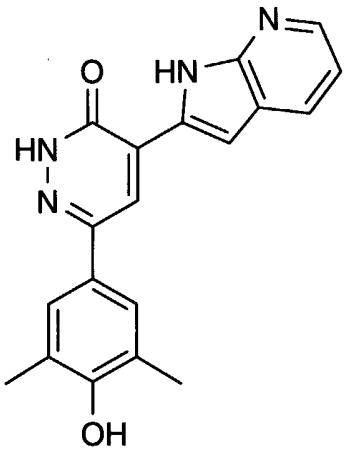
Example 185

6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(1H-pyrrolo[3,2-c]pyridin-2-yl)-2H-pyridazin-3-one



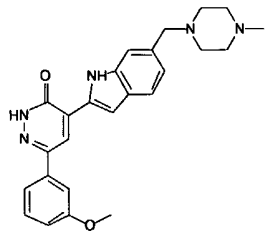
This compound is synthesized analogously to example 6, using 4-amino-3-bromopyridine. Yield 8 mg. LC-MS (ES+) 333 $(M+H)^+$.

Example 186
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-(1H-pyrrolo[2,3-b]pyridin-2-yl)-2H-pyridazin-3-one



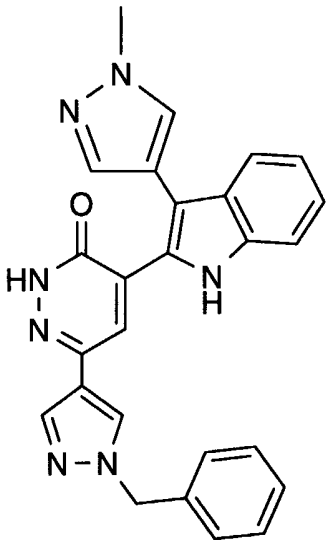
This compound is synthesized analogously to example 6, using 2-amino-3-bromopyridine. Yield 18 mg. LC-MS (ES+) 333 $(M+H)^+$.

Example 187
6-(3-Methoxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



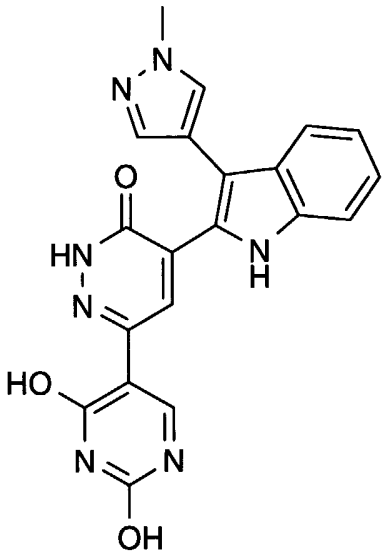
This compound is synthesized analogously to example 143.
MS: (M+1) = 430.

Example 188
6-(1-Benzyl-1H-pyrazol-4-yl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one



This compound is synthesized, starting from 2-[6-(1-benzyl-1H-pyrazol-4-yl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester, analogously to example 173. Yield 9 mg. LC-MS (ES+) 448 $(M+H)^+$.

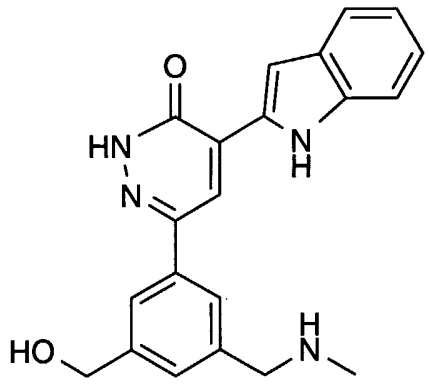
Example 189
6-(2,4-Dihydroxy-pyrimidin-5-yl)-4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-2H-pyridazin-3-one



This compound is synthesized, starting from 2-[6-(2,4-dihydroxy-pyrimidin-5-yl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert-butyl ester, analogously to example 173. Yield 3.5 mg. LC-MS (ES+) 402 $(M+H)^+$.

Example 190

6-(3-Hydroxymethyl-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one



a) 2-[6-(3,5-Diformyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert- butyl ester

This compound is synthesized, starting from 2,3-diformylphenyl boronic acid, analogously to Example 126(a). Yield 172 mg. LC-MS (ES+) 458 $(M+H)^+$.

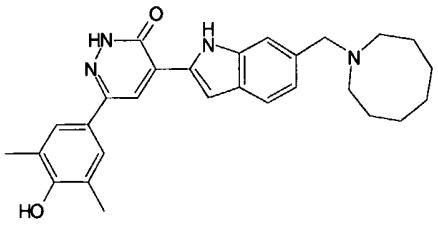
b) 2-[6-(3-Hydroxymethyl-5-methylaminomethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1- carboxylic acid tert-butyl ester

170 mg of 2-[6-(3,5-diformyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1-carboxylic acid tert- butyl ester is dissolved in 5ml of methanol and 0.093ml of methylamine solution in THF is added. The solution is stirred for 5 min at RT then 22 mg of acetic acid and 26 mg of sodium cyanoborohydride is added. The reaction is stirred for 4h at 60°C. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 19 mg. LC-MS (ES+) 475 $(M+H)^+$.

(c) 6-(3-Hydroxymethyl-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one

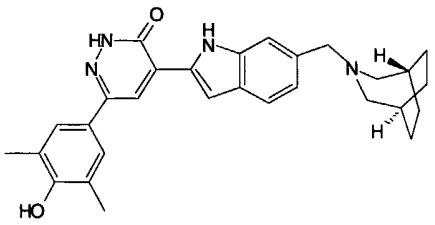
18 mg of 2-[6-(3-hydroxymethyl-5-methylaminomethyl-phenyl)-3-methoxy-pyridazin-4-yl]-indole-1- carboxylic acid tert-butyl ester is dissolved in 3 ml of acetonitrile and 19 mg of potassium iodide and 12 mg of chlorotrimethylsilane are added. The reaction is heated to 85°C for 5h. The reaction is quenched by the addition of a drop of water, the solvent is removed under reduced pressure and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 3.5 mg. LC-MS (ES+) 361 $(M+H)^+$.

Example 191
4-(6-Azocan-1-ylmethyl-1H-indol-2-yl)-6-(4-hydroxy-3,5-dimethyl-phenyl)-2H-pyridazin-3-one



This compound is synthesized analogously to example 119.
MS: (M+1) = 457.

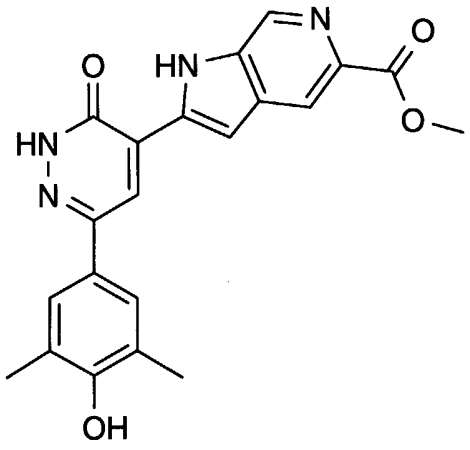
Example 192
4-[6-(3-Aza-bicyclo[3.2.2]non-3-ylmethyl)-1H-indol-2-yl]-6-(4-hydroxy-3,5-dimethyl-phenyl)-2H-pyridazin-3-one



This compound is synthesized analogously to example 119.
MS: (M+1) = 469.

Example 193

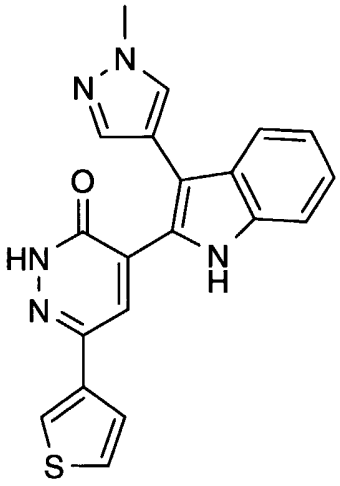
2-[6-(4-Hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-pyrrolo[2,3-c]pyridine-5-carboxylic acid methyl ester



This compound was synthesized analogously to Example 6, using 5-amino-4-bromopyridine-2-carboxylic acid methyl ester. Yield 9 mg.

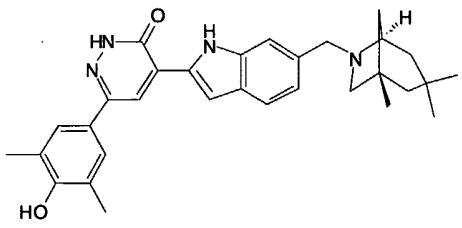
Example 194

4-[3-(1-Methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-thiophen-3-yl-2H-pyridazin-3-one



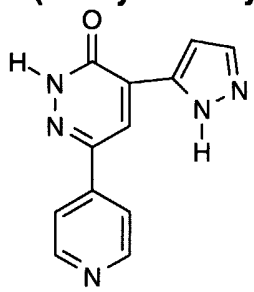
This compound is synthesized, starting from 2-(3-Methoxy-6-thiophen-3-yl-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester, analogously to Example 173. Yield 5.5 mg. LC-MS (ES+) 374 $(M+H)^+$.

Example 195
6-(4-Hydroxy-3,5-dimethyl-phenyl)-4-[6-((1S,5R)-1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one



This compound is synthesized analogously to example 119.
MS: (M+1) = 497.

Example 196
4-(2H-Pyrazol-3-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

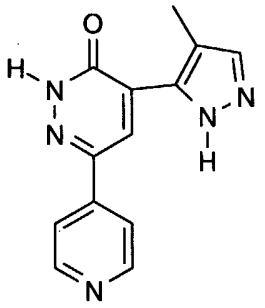


This compound is prepared analogously to example 1

MS: (M+1) = 240.

Example 197

4-(4-Methyl-2H-pyrazol-3-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

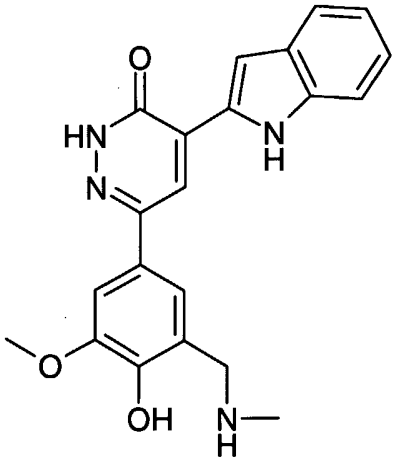


This compound is prepared analogously to example 1

MS: (M+1) = 254

Example 198

6-(4-Hydroxy-3-methoxy-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3- one



a) 5-Bromo-3-methoxy-2-(2-trimethylsilanyl-ethoxymethoxy)-benzaldehyde

2 g of 5-Bromo-2-hydroxy-3-methoxy-benzaldehyde is dissolved in 200 ml of DMF and 4.78 g of potassium carbonate and 2.3 g of 2-trimethylsilyl-ethoxymethyl chloride are added. The reaction is stirred at RT for 18h. The solvents are removed under reduced pressure, the residue is dissolved in ethyl acetate and washed with water. After drying over magnesium sulfate, filtration and evaporation, the product is purified by silica gel chromatography eluting with a gradient of ethyl acetate in heptane. Yield 1.8 g.

b) 3-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-(2-trimethylsilanyl- ethoxymethoxy)-benzaldehyde

500 mg of 5-Bromo-3-methoxy-2-(2-trimethylsilanyl-ethoxymethoxy)-benzaldehyde is dissolved in 40ml of dioxane and 101 mg of (1,1'-bis(diphenylphosphino)ferrocene)palladium(II) chloride and 77 mg of 1,1'-bis(diphenylphosphino)ferrocene are added. The solution is de-gassed with argon and 407 mg of potassium acetate and 527 mg of bis(pinacolato)diboron are added. The solution is heated for 13 h at 70°C. The solution is evaporated, the residue taken up in dichloromethane and the product is purified by silica gel chromatography eluting with a gradient of ethyl acetate in heptane. Yield 502 mg.

c) 2-{6-[3-Formyl-5-methoxy-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-3-methoxy-pyridazin- 4-yl}-indole-1-carboxylic acid tert-butyl ester

400 mg of 3-Methoxy-5-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-2-(2-trimethylsilanyl- ethoxymethoxy)-benzaldehyde and 353 mg of 2-(6-Chloro-3-methoxy-pyridazin-4-yl)-indole-1-carboxylic acid tert-butyl ester is reacted analogously to the procedure described in Example 126(a). Yield 377 mg. LC-MS (ES+) 606 $(M+H)^+$.

d) 2-{3-Methoxy-6-[3-methoxy-5-methylaminomethyl-4-(2-trimethylsilanyl-ethoxymethoxy)- phenyl]-pyridazin-4-yl}-indole-1-carboxylic acid tert-butyl ester

175 mg of 2-{6-[3-Formyl-5-methoxy-4-(2-trimethylsilanyl-ethoxymethoxy)-phenyl]-3-methoxy-pyridazin- 4-yl}-indole-1-carboxylic acid tert-butyl ester is dissolved in 5ml of methanol and 0.16ml of methylamine solution in THF is added. The solution is stirred for 10 min at RT then 19 mg of acetic acid and 20 mg of sodium cyanoborohydride is added. The reaction is stirred for 20h at RT. The product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 118 mg. LC-MS (ES+) 621 $(M+H)^+$.

e) 6-(4-Hydroxy-3-methoxy-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3- one

118 mg of 2-{3-Methoxy-6-[3-methoxy-5-methylaminomethyl-4-(2-trimethylsilanyl-ethoxymethoxy)- phenyl]-pyridazin-4-yl}-indole-1-carboxylic acid tert-butyl ester is dissolved in 5 ml of dichloromethane and 5 ml of trifluoroacetic acid and the solution is stirred for 4h at RT. The solvents are removed under reduced pressure.

The residue is dissolved in 26 ml of acetonitrile and 117 mg of potassium iodide and 76 mg of chlorotrimethylsilane are added. The reaction is heated to 85°C for 3h. The reaction is quenched by the addition of a drop of water, the solvent is removed under reduced pressure and the product is purified by preparative RP-HPLC eluting with a gradient of 0-100% acetonitrile in water (+0.01% trifluoroacetic acid). Yield 13 mg. LC-MS (ES+) 377 $(M+H)^+$.

Functional measurements for determination of IC_{50}-values

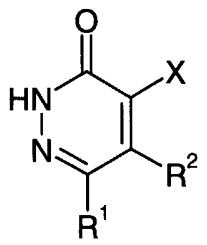
GSK-3β

GSK-ß activity is measured using human recombinant GSK-3ß and a primed (pre-phosphorylated) substrate peptide (derived from glycogen synthase and containing the phosphorylation sites 3a, b, and c) on basis of the AlphaScreen technology in 384-well plate format (small volume plate, white, GREINER). In a final volume of 11 µl, 2 µl of compound (1 nM-100 mM in kinase buffer, DMSO (dimethylsulfoxide) kept constant at 0.9%), 2 µl of GSK- 3ß solution (0.18 nM) and 2 µl of biot. phospho-glycogen synthase peptide (34 nM) in kinase buffer (20 mM Hepes, pH 7,4, 10 mM $MgCl_2$, 200 mM EDTA (ethylenediaminotetraacetate), 1 mM DTT (dithiotriol), 0,1 mg/ml BSA (bovine serum albumin), 10 µM ATP (adenosinetriphosphate)) are incubated at room temperature for 60 min. After adding 2,5 ml donor beads (20 µg/ml) and 2,5 ml antibody (anti-phospho-glycogen synthase 1:2000) -coated acceptor beads (40 µg/ml) in AlphaScreen detection buffer (20 mM Hepes, pH 7,4, 10 mM $MgCl_2$, 40 mM EDTA, 1 mM DTT, 0,1 mg/ml BSA, plates are incubated at room temperature (in the dark!) over night and then placed in a reader (Alphaquest or Fusion) to measure final fluorescence. IC50-values are calculated form the fitted curved corrected for blank values (absence of GSK-3ß) and preformed in triplicate.

GSK3ß (µmol)	Example
0,59	6
0,102	11
0,025	26
0,004	65
0,01	74
0,014	87
0,012	89
0,007	116
0,011	118
1,5	126
0,007	133
2	147
0,021	156
0,018	165
0,078	176
0,018	180

Claims

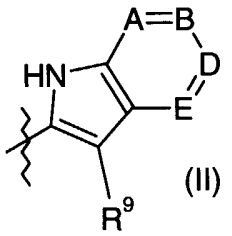
1. A compound of the general formula (I)



(I)

wherein:

X is a residue selected from the group consisting of:



(II)

, tetrazolyl and unsubstituted and at least monosubstituted triazolyl, imidazolyl, pyrrolyl and pyrazolyl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where not more than three of the substituents A, B, D and E may be N;

R^1 is halogen;

unsubstituted or at least monosubstituted C_1-C_{10}-alkyl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-O-C(O)R^7$, $-NR^7R^8$, $-NR^8C(O)R^7$, $-C(O)NR^7R^8$, $-NR^8C(S)R^7$, $-C(S)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-NR^8SO_2R^7$, $-SO_2NR^7R^8$, $-O-SO_2R^7$, $-SO_2-O-R^7$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or OH;

or unsubstituted or at least monosubstituted heterocyclyl, aryl oder heteroaryl,

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-O-C(O)R^7$, $-NR^7R^8$, $-NR^8C(O)R^7$, $-C(O)NR^7R^8$, $-NR^8C(S)R^7$, $-C(S)NR^7R^8$, $-SR^7$, $-S(O)R^7$, $-SO_2R^7$, $-NR^8SO_2R^7$, $-SO_2NR^7R^8$, $-O-SO_2R^7$, $-SO_2-O-R^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or OH;

R^2 is hydrogen or C_1-C_{10}-alkyl;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, halogen, -CN, NO_2, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^7 and R^8 are independently from each other:

H;

or unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl, C_2-C_{10}-alkyinyl, aryl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), $-C(O)NH_2$, trifluoromethyl, trifluoromethoxy, -CN, $-NH_2$, $-NH(C_1$-C_{10}-alkyl) and $-N(C_1$-C_{10}-alkyl)$_2$,

and the C_1-C_{10}-alkyl-, aryl, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is selected from the group consisting of:

hydrogen, halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^{10} is unsubstituted or at least monosubstituted C_1-C_{10}-alkyl, aryl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, C_2-C_{10}-alkenyl or C_2-C_{10}-alkyinyl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, aryl, halogen, -OH, oxo, C_1-C_{10}-alkoxy, (C_1-C_{10}-alkyl)thio-, -C(O)OH, -C(O)O-(C_1-C_6-alkyl), $-C(O)NH_2$, trifluoromethyl, trifluoromethoxy, -CN, $-NH_2$, $-NH(C_1$-C_{10}-alkyl) and $-N(C_1$-C_{10}-alkyl)$_2$,

and the C_1-C_{10}-alkyl-, aryl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, -C(O)-(C_1-C_6-alkyl), oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

Heteroaryl is a 5 to 10-membered, aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

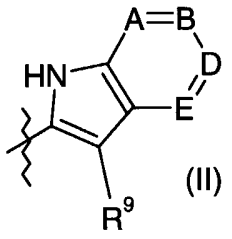
Aryl is a 6 to 10-membered, aromatic mono- or bicyclus;

Heterocyclyl is a 4- to 10-membered, non-aromatic, mono- or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S,

or a physiologically acceptable salt thereof;
with the provisio that R^1 is not unsubstituted or at least monosubstituted pyrazolo[1,5-a]pyridinyl

2. A compound according to claim 1, wherein in formula (I)

X is a residue selected from the group consisting of:



(II)

, and unsubstituted and at least monosubstituted pyrrolyl and triazolyl

where the substituents are selected from the group consisting of: halogen, -CN, $-NO_2$, R^{10}, $-(CH_2)_n-NR^7R^8$ where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-O-C(O)R^8$, $-NR^7R^8$, $-NR^7C(O)R^8$, $-C(O)NR^7R^8$, $-NR^7C(S)R^8$, $-C(S)NR^7R^8$, $-SR^8$, $-S(O)R^8$, $-SO_2R^8$, $-NR^7SO_2R^8$, $-SO_2NR^7R^8$, $-O-SO_2R^8$, $-SO_2-O-R^8$, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or -OH;

and each of said residues is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where not more than two of the substituents A, B, D and E may be N;

R^1 is: unsubstituted or at least monosubstituted C_1-C_6-alkyl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkoxy, $-NH_2$, $-NH(C_1$-C_6-alkyl), $-N(C_1$-C_6-alkyl)$_2$, heterocyclyl-(C_1-C_6-alkyl)-NH-, aryl-(C_1-C_6-alkyl)-NH-, heterocyclyl, aryl and heteroaryl,

and the aryl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_4-alkyl, C_1-C_4-alkoxy, fluor, chloro, trifluoromethyl, trifluoromethoxy or -OH;

or unsubstituted or at least monosubstituted heterocyclyl, aryl or heteroaryl,

where the substituents are selected from the group consisting of: halogen, R^{10}, $-(CH_2)_n$-NR^7R^8 where n is 1 to 3, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^7H$, $-NR^7(C_1$-C_6-alkyl), $-C(O)NR^7H$, $-SR^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments aryl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^2 is hydrogen or C_1-C_6-alkyl;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, $-(CH_2)_n$-NR^7R^8 where n is 1 to 3, $-OR^8$, $-C(O)R^8$, $-C(O)OR^8$, $-NR^8H$, $-NR^8(C_1$-C_6-alkyl), $-C(O)NR^8H$, $-SR^8$, $-SO_2NR^8H$, $-SO_2R^8$, aryl, heteroaryl, heterocyclyl, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluormethyl, Trifluoromethoxy or -OH;

R^7 und R^8 are independently from each other:

H;

or unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, heterocyclyl, phenyl or heteroaryl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, -C(O)OH, -C(O)O-(C_1-C_3-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, oxo, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^9 is selected from the group consisting of:

hydrogen, halogen, -CN, R^{10}, -$(CH_2)_n$-NR^7R^8 where n is 1 to 3, -OR^8, -C(O)O-(C_1-C_6-alkyl), -C(O)-(C_1-C_6-alkyl), -SR^8, -C(O)NR^8H, aryl, heteroaryl, heterocyclyl, trifluoromethyl and trifluoromethoxy,

and the CH_2-fragments, aryl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluormethyl, trifluoromethoxy or -OH;

R^{10} is unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)- or C_2-C_6-alkenyl,

where the substituents are selected from the group consisting of: halogen, -C_1-C_6-alkyl, C_1-C_6-alkoxy, -OH, -C(O)-C_1-C_3-alkyl, -C(O)OH,

-C(O)O-(C_1-C_3-alkyl), -C(O)NH_2, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

Heteroaryl is imidazolyl, thiophenyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzo[b]thiophenyl, thiazolo[3,2-b][1,2,4]-triazolyl, pyrrolyl, chinolinyl, isochinolinyl, 1,2,3,4-tetrahydrochinolinyl, benzimidazolyl, indolyl or 1,3-benzodioxolyl;

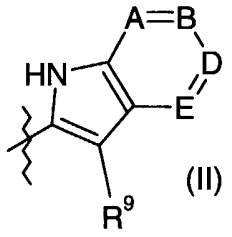
Aryl is naphthyl, indanyl or phenyl;

Heterocyclyl is acetidinyl, azepanyl, thiomorpholinyl, 1,4-oxazepanyl, azocanyl, 3-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.2.1]octyl, dihydropyridinonyl, pyrimidindionyl 4-oxo-azepanyl, 1,4-diazepanyl, tetrahydrofuranyl, 1,3-dioxolanyl, morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

or a physiologically acceptable salt thereof.

3. A compound according to claim 1 or 2, wherein in formula (I)

X is



(II)

,

which residue is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where only one of the substituents A, B, D and E may be N;

R^1 is unsubstituted or at least monosubstituted phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, dihydropyridinonyl, imidazoyl, 1H-pyrrolo[2,3-b]pyridinyl, benzo[b]thiophenyl, benzodioxolyl or thiazolo[3,2-b][1,2,4]-triazolyl,

where the substituents are selected from the group consisting of: halogen, R^{10}, $-OR^7$, $-C(O)R^7$, $-C(O)OR^7$, $-NR^7H$, $-NR^7(C_1\text{-}C_6\text{-alkyl})$, $-C(O)NR^7H$, $-SR^7$, aryl, heteroaryl, trifluoromethyl and trifluoromethoxy,

and aryl and heteroaryl may in turn be at least monosubstituted with $C_1\text{-}C_6$-alkyl, $C_1\text{-}C_6$-alkoxy, halogen, trifluoromethyl, trifluoromethoxy or -OH;

R^2 is hydrogen;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, R^{10}, $-(CH_2)_n\text{-}NR^7R^8$ where n is 1 to 3, $-OR^8$, -C(O)OH, $-C(O)O\text{-}(C_1\text{-}C_6\text{-alkyl})$, $-C(O)NR^8H$, difluoromethyl, trifluoromethyl and trifluoromethoxy,

R^7 and R^8 are independently from each other:

H;

or unsubstituted or at least monosubstituted $C_1\text{-}C_6$-alkyl, phenyl-($C_1\text{-}C_6$-alkyl)-, heterocyclyl-($C_1\text{-}C_6$-alkyl)-, heteroaryl-($C_1\text{-}C_6$-alkyl)-, heterocyclyl, phenyl or heteroaryl,

where the substituents are selected from the group consisting of: fluoro, chloro, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, -C(O)OH, -C(O)O-(C_1-C_3-alkyl), -C(O)NH_2, trifluoromethyl, trifluoromethoxy, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, oxo, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

R^9 is selected from the group consisting of:

hydrogen; halogen; -C(O)-(C_1-C_3-alkyl); (C_1-C_6-alkyl)thio-; trifluoromethyl; trifluoromethoxy;

unsubstituted and at least monosubstituted C_1-C_6-alkyl and C_2-C_6-alkenyl,

where the substituents are selected from the group consisting of: heteroaryl, heterocyclyl, phenyl, -OH, C_1-C_6-alkoxy, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and phenyl, heterocyclyl and heteroaryl may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -CO-(C_1-C_3-alkyl), fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

and heteroaryl and phenyl, which in turn may be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluormethyl, trifluoromethoxy or -OH

R^{10} is unsubstituted or at least monosubstituted C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)- or C_2-C_6-alkenyl,

where the substituents are selected from the group consisting of: halogen, -C_1-C_6-alkyl, C_1-C_6-alkoxy, -OH, -C(O)-C_1-C_3-alkyl, -C(O)OH,

-C(O)O-(C_1-C_3-alkyl), -C(O)NH_2, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and the C_1-C_6-alkyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

Heteroaryl is imidazolyl, thiophenyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzo[b]thiophenyl, thiazolo[3,2-b][1,2,4]-triazolyl, pyrrolyl, chinolinyl, isochinolinyl, 1,2,3,4-tetrahydrochinolinyl, benzimidazolyl, indolyl or 1,3-benzodioxolyl;

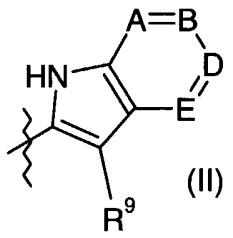
Aryl is naphthyl, indanyl or phenyl;

Heterocyclyl is acetidinyl, azepanyl, thiomorpholinyl, 1,4-oxazepanyl, azocanyl, 3-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.2.1]octyl, dihydropyridinonyl, pyrimidindionyl 4-oxo-azepanyl, 1,4-diazepanyl, tetrahydrofuranyl, 1,3-dioxolanyl, morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

or a physiologically acceptable salt thereof.

4. A compound according to any of claims 1 or 3, wherein in formula (I)

X is



(II)

,

which residue is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3 or N;

B is CR^4 or N;

D is CR^5 or N;

E is CR^6 or N;

where only one of the substituents A, B, D and E may be N;

R^1 is: unsubstituted or at least monosubstituted phenyl, pyridinyl, pyrimidinyl, pyrazolyl, thiophenyl, oxazolyl, isoxazolyl, dihydropyridinonyl, imidazolyl, 1H-pyrrolo[2,3-b]pyridinyl, benzo[b]thiophenyl, benzodioxolyl or thiazolo[3,2-b][1,2,4]-triazolyl,

where the substituents are selected from the group consisting of: halogen, C_1-C_6-alkyl, phenyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)- -OH, C_1-C_6-alkoxy, (C_1-C_6-alkyl)thio-, -O-phenyl, $-NH_2$, $-N(C_1$-C_6-alkyl)$_2$, $-NH(C_1$-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NH-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NH-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl-NH-, heterocyclyl-(C_1-C_6-alkyl)-NH-, heteroaryl-(C_1-C_6-alkyl)-NH-, phenyl-(C_1-C_6-alkyl)-NH-, trifluoromethyl, trifluoromethoxy, phenyl and heteroaryl,

and the phenyl-, heterocyclyl- and heteroaryl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^2 is hydrogen;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, fluoro, chloro, -CN, C_1-C_6-alkyl, heterocyclyl-(C_1-C_6-alkyl)-, heteroaryl-(C_1-C_6-alkyl)-, phenyl-(C_1-C_6-alkyl)-, H_2N-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-, -OH, C_1-C_6-alkoxy, heterocyclyl-(C_1-C_6-alkyl)-O-, heteroaryl-(C_1-C_6-alkyl)-O-, phenyl-(C_1-C_6-alkyl)-O-, H_2N-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-O-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-O-, -C(O)OH, -C(O)O-

(C_1-C_6-alkyl), heterocyclyl-HN-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (heterocyclyl)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (heterocyclyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)HN-(C_1-C_3-alkyl)-, (phenyl-(C_1-C_3-alkyl)-)(C_1-C_3-alkyl)N-(C_1-C_3-alkyl)-, -C(O)NH_2, -C(O)N(C_1-C_6-alkyl)$_2$, -C(O)NH(C_1-C_6-alkyl), H_2N-(C_1-C_6-alkyl)-NHC(O)-, HO-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)HN-(C_1-C_6-alkyl)-NHC(O)-, (C_1-C_6-alkyl)$_2$N-(C_1-C_6-alkyl)-NHC(O)-, heterocyclyl-(C_1-C_6-alkyl)-NHC(O)-, heteroaryl-(C_1-C_6-alkyl)-NHC(O)-, phenyl-(C_1-C_6-alkyl)-NHC(O)-, difluoromethyl, trifluoromethyl and trifluoromethoxy,

and the heteroaryl-, heterocyclyl- and phenyl-fragments of said substituents may in turn be at least monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, -C(O)OH, fluoro, chloro, trifluoromethyl, trifluoromethoxy or -OH;

R^9 is selected from the group consisting of:

hydrogen; bromo; chloro; -C(O)-(C_1-C_3-alkyl);

unsubstituted and at least monosubstituted C_1-C_4-alkyl and C_2-C_4-alkenyl,

where the substituents are selected from the group consisting of: phenyl azetidinyl, pyridinyl, pyrazolyl, pyrimidinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl, pyrrolidinyl, -NH_2, -NH(C_1-C_6-alkyl) and -N(C_1-C_6-alkyl)$_2$,

and phenyl, azetidinyl, pyridinyl, pyrazolyl, pyrimidinyl, morpholinyl, piperazinyl, piperidinyl, imidazolyl and pyrrolidinyl may in turn be monosubstituted with C_1-C_3-alkyl, C_1-C_3-alkoxy, trifluoromethyl, trifluoromethoxy, fluoro, chloro or -OH;

and phenyl, imidazolyl and pyridinyl, which may in turn be at least monosubstituted with C_1-C_6-alkyl, C_1-C_6-alkoxy, oxo, halogen, trifluoromethyl, trifluoromethoxy or –OH;

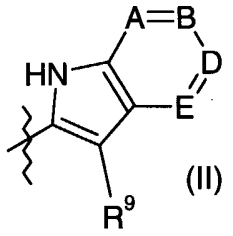
Heteroaryl is imidazolyl, thiophenyl, furanyl, oxazolyl, isoxazolyl, pyridinyl, pyrimidinyl, pyrazolyl, benzo[b]thiophenyl, thiazolo[3,2-b][1,2,4]-triazolyl, pyrrolyl, chinolinyl, isochinolinyl, 1,2,3,4-tetrahydrochinolinyl, benzimidazolyl, indolyl or 1,3-benzodioxolyl;

Heterocyclyl is acetidinyl, azepanyl, thiomorpholinyl, 1,4-oxazepanyl, azocanyl, 3-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.2.1]octyl, dihydropyridinonyl, pyrimidindionyl 4-oxo-azepanyl, 1,4-diazepanyl, tetrahydrofuranyl, 1,3-dioxolanyl, morpholinyl, pyrrolidinyl, piperazinyl or piperidinyl;

or a physiologically acceptable salt thereof.

5. A compound according to any of claims 1 or 4, wherein in formula (I)

X is



(II)

,

which residue is bound to the pyridazinone fragment via the carbonatom being in α-position to the NH-fragment of said residue;

A is CR^3;

B is CR^4;

D is CR^5;

E is CR^6 or N;

R^1 is: pyridin-4-yl, 2-ethylamino-pyrimidin-4-yl, 3,5-dimethyl-4-hydroxyphenyl, 2-(1-phenylethylamino)-pyrimidin-4-yl, 2-(2-morpholin-4-ylethylamino)-pyrimidin-4-yl, 2-methylamino-pyrimidin-4-yl, 6-

methyl-2-(2-morpholin-4-ylethylamino)-pyrimidin-4-yl, 3-methoxy-4-hydroxy-phenyl, 2-methylsulfanyl-pyrimidin-4-yl, 4-butylamino-pyrimidin-4-yl, 3-hydroxy-phenyl, thiophen-3-yl, 1H-pyrazol-4-yl, 4-hydroxy-3-methoxy-5-methylaminomethyl-phenyl, 4-hydroxy-phenyl or 2,6-dimethyl-pyrimidin-4-yl;

R^2 is hydrogen;

R^3, R^4, R^5 and R^6 are independently from each other selected from the group consisting of:

hydrogen, fluoro, chloro, -C(O)OH, 2-dimethylamino-ethoxy, 2-diethylamino-ethoxy, methoxy, ethoxy, 2-piperidin-1-yl-ethoxy, piperidin-1-ylmethyl, 2-piperidin-1-yl-ethoxy, 2-(4-methyl-piperazin-1-yl)-ethoxy, 4-methyl-piperazin-1-ylmethyl, 2-morpholin-4-yl-ethoxy, 4-cyclopropyl-piperazin-1-ylmethyl, (1-cyclopropyl-piperidin-4-ylamino)-methyl, 2-carboxy-pyrrolidin-1-ylmethyl, [(1-cyclopropyl-piperidin-4-yl)methylamino]-methyl, morpholin-4-ylmethyl, 1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl, methyl, ethyl, trifluoromethyl and trifluoromethoxy;

R^9 is: hydrogen, chloro, acetyl, methyl, ethyl, isobutyl, 1-methyl-1H-pyrazol-4-yl, morpholin-4-ylmethyl and phenyl;

or a physiologically acceptable salt thereof.

6. A compound according to any of claims 1 or 5, selected from the group consisting of:

4-(5-chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(5-trifluoromethyl-1H-indol-2-yl)-2H-pyridazin-3- one, 4-(3-phenyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-ethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-morpholin-4-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-acetyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-chloro-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[5-(2-piperidin-1-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-

2H-pyridazin-3-one, 4-{6-[2-(4-methyl-piperazin-1-yl)-ethoxy]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[5-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-(3-methyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(2-morpholin-4-yl-ethoxy)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(4-cyclopropyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-{6-[(1-cyclopropyl-piperidin-4-ylamino)-methyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, (S)-1-[2-(3-oxo-6-pyridin-4-yl-2,3-dihydro-pyridazin-4-yl)-1H-indol-6-ylmethyl]-pyrrolidine-2-carboxylic acid, 4-(6-{[(1-cyclopropyl-piperidin-4-yl)-methyl-amino]-methyl}-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(6-morpholin-4-ylmethyl-1H-indol-2-yl)-2H-pyridazin-3-one, 2-[6-(4-hydroxy-3,5-dimethyl-phenyl)-3-oxo-2,3-dihydro-pyridazin-4-yl]-1H-indole-5-carboxylic acid, 4-[3-(1-methyl-1H-pyrazol-4-yl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[3-isobutyl-6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-pyridin-4-yl-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-(1H-pyrazol-4-yl)-2H-pyridazin-3-one, 6-(3-hydroxy-phenyl)-4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-2H-pyridazin-3-one, 4-{6-[1-(1-cyclopropyl-piperidin-4-ylamino)-ethyl]-1H-indol-2-yl}-6-pyridin-4-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3,5-dimethyl-phenyl)-4-(1H-pyrrolo[3,2-b]pyridin-2-yl)-2H-pyridazin-3-one, 4-[6-(4-methyl-piperazin-1-ylmethyl)-1H-indol-2-yl]-6-thiophen-3-yl-2H-pyridazin-3-one, 6-(4-hydroxy-3-methoxy-5-methylaminomethyl-phenyl)-4-(1H-indol-2-yl)-2H-pyridazin-3- one and 4-(3-chloro-6-piperidin-1-ylmethyl-1H-indol-2-yl)-6-pyridin-4-yl-2H-pyridazin-3-one

or a physiologically acceptable salt thereof.

7. A compound according to any of claims 1 to 6 or a physiologically acceptable salt thereof for use as pharmaceutical.

8. The use of a compound according to any of claims 1 to 6 or a physiologically acceptable salt thereof for the manufacture of a medicament for prophylaxis and/or treatment of diseases in which phosphorylation of the Tau protein is observed.

9. The use of a compound according to any of claims 1 to 6 or a physiologically acceptable salt thereof for the manufacture of a medicament which is an inhibitor of GSK-3β.

10. The use of a compound according to any of claims 1 to 6 or a physiologically acceptable salt thereof for the manufacture of a medicament for prophylaxis and/or treatment of neurodegenerative diseases, strokes, cranial and spinal traumas and peripheral neuropathies, obesity, metabolic diseases, type II diabetes, essential hypertension, atherosclerotic cardiovascular diseases, polycystic ovary syndrome, syndrome X or immunodeficiency.

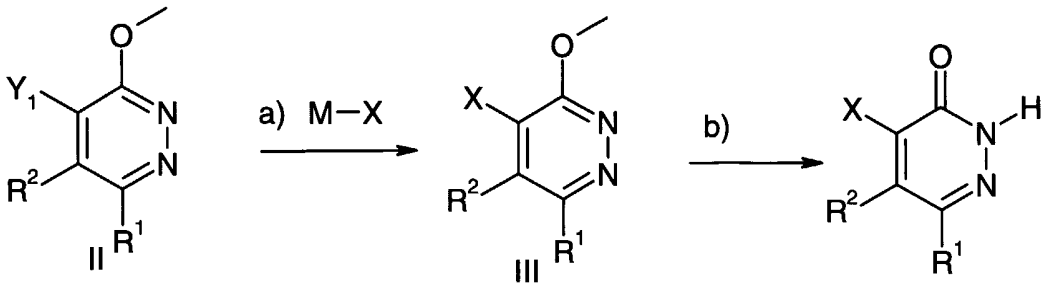
11. The use according to claim 10, wherein the neurodegenerative disease is Alzheimer's disease, Parkinson's disease, frontoparietal dementia, corticobasal degeneration or Pick's disease.

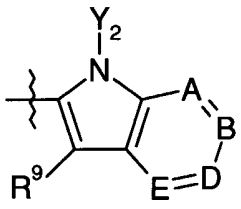
12. The use according to claim 10 for prophylaxis and/or treatment of type-II-diabetes or Alzheimer's disease.

13. A pharmaceutical preparation comprising an effective dose of at least one compound or a physiologically acceptable salt thereof as defined in any of claims 1 to 6 and a physiologically acceptable carrier.

14. A pharmaceutical preparation according to claim 13, which pharmaceutical preparation is in the form of a pill, tablet, lozenge, coated tablet, granule, capsule, hard or soft gelatin capsule, aqueous solution, alcoholic solution, oily solution, syrup, emulsion suspension, pastille, suppository, solution for injection or infusion, ointment, tincture, cream, lotion, powder, spray, transdermal therapeutic systems, nasal spray, aerosol mixture, microcapsule, implant, rod or plaster.

15. A method for the synthesis of a compound of formula (I) according to any of claims 1 to 6, wherein



X =  , pyrolyl, imidazolyl, pyrazolyl

a compound of formula (II) is converted with M-X by metal catalysed coupling, where X is $B(OH)_2$, $B(C_1\text{-}C_{10}\text{-alkoxy})_2$, $Sn(C_1\text{-}C_{10}\text{-alkyl})_3$ or $Zn\text{-}(C_1\text{-}C_{10}\text{-alkyl})$, Y_1 is Cl, Br or I and Y_2 is H or a protecting group, to provide a compound of formula (III), followed by elimination of the methylgroup and optionally the protecting group Y_2 to provide a compound of formula (I).

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/005346

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/14 C07D403/04 A61K31/501 A61K31/5377 A61P3/00
A61P25/00 C07D403/14 C07D409/14 C07D413/14 C07D471/04
A61K31/553 A61K31/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	PATENT ABSTRACTS OF JAPAN vol. 1997, no. 12, 25 December 1997 (1997-12-25) & JP 09 216883 A (FUJISAWA PHARMACEUT CO LTD), 19 August 1997 (1997-08-19) abstract; claim 1; example 13	1-15
A	US 2002/119963 A1 (COOPER CHRISTOPER B ET AL) 29 August 2002 (2002-08-29) abstract; claims 1,17,32,33	1-15
A	WO 02/22605 A (KNEGTEL RONALD ; BEBBINGTON DAVID (GB); CHARRIER JEAN DAMIEN (GB); GOL) 21 March 2002 (2002-03-21) claims	1-15

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 August 2005	14/09/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hanisch, I

Form PCT/ISA/210 (second sheet) (January 2004)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 02/066020 A (FISHMAN PNINA ; CAN FITE BIOPHARMA LTD (IL); KHALILI KAMEL (US)) 29 August 2002 (2002-08-29) page 4, line 1 - page 5, line 11; claims 1,20-24,45-49	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/005346

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 09216883 A	19-08-1997	NONE	
US 2002119963 A1	29-08-2002	US 2003083352 A1	01-05-2003
		US 2004192750 A1	30-09-2004
		AU 7094401 A	13-02-2002
		BG 107469 A	30-09-2003
		BR 0112862 A	01-07-2003
		CA 2418115 A1	07-02-2002
		CN 1444567 A	24-09-2003
		CZ 20030225 A3	18-02-2004
		EE 200300049 A	15-10-2004
		EP 1305295 A1	02-05-2003
		HR 20030048 A1	30-04-2003
		HU 0303069 A2	01-03-2004
		WO 0210141 A1	07-02-2002
		JP 2004505111 T	19-02-2004
		MX PA03000939 A	24-06-2003
		NO 20030472 A	27-03-2003
		NZ 523272 A	27-08-2004
		PL 365134 A1	27-12-2004
		SK 1042003 A3	04-05-2004
		ZA 200300819 A	20-04-2004
WO 0222605 A	21-03-2002	AT 294797 T	15-05-2005
		AU 9091201 A	26-03-2002
		AU 9091401 A	26-03-2002
		AU 9094401 A	26-03-2002
		AU 9101301 A	26-03-2002
		AU 9267001 A	26-03-2002
		AU 9455801 A	26-03-2002
		AU 9687101 A	26-03-2002
		AU 9687501 A	26-03-2002
		BR 0114088 A	17-06-2003
		CA 2422299 A1	21-03-2002
		CA 2422354 A1	21-03-2002
		CA 2422367 A1	21-03-2002
		CA 2422371 A1	21-03-2002
		CA 2422377 A1	21-03-2002
		CA 2422378 A1	21-03-2002
		CA 2422379 A1	21-03-2002
		CA 2422380 A1	21-03-2002
		CN 1469874 A	21-01-2004
		CN 1469875 A	21-01-2004
		CN 1473161 A	04-02-2004
		DE 60110616 D1	09-06-2005
		EP 1317447 A1	11-06-2003
		EP 1317444 A1	11-06-2003
		EP 1317448 A1	11-06-2003
		EP 1318997 A1	18-06-2003
		EP 1317449 A1	11-06-2003
		EP 1317450 A1	11-06-2003
		EP 1317452 A1	11-06-2003
		EP 1318814 A2	18-06-2003
		HU 0302172 A2	29-09-2003
		HU 0302173 A2	29-09-2003
		HU 0302411 A2	28-11-2003
		HU 0401819 A2	28-12-2004
		JP 2004509113 T	25-03-2004

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/005346

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0222605 A		JP 2004509114 T	25-03-2004
		JP 2004525075 T	19-08-2004
		JP 2004512277 T	22-04-2004
		JP 2004509115 T	25-03-2004
		JP 2004509116 T	25-03-2004
		JP 2004509117 T	25-03-2004
		JP 2004509118 T	25-03-2004
		MX PA03002289 A	06-06-2003
		MX PA03002291 A	06-06-2003
		MX PA03002292 A	06-06-2003
WO 02066020 A	29-08-2002	US 2002115635 A1	22-08-2002
		EP 1363644 A2	26-11-2003
		WO 02066020 A2	29-08-2002
		JP 2004520404 T	08-07-2004
		US 2002165197 A1	07-11-2002