N-(Aminoheteroaryl)-1*H*-indole-2-carboxamide derivatives, and preparation and therapeutic application thereof

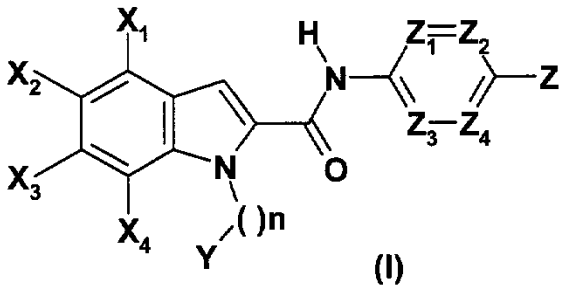
The invention relates to *N*-(aminoheteroaryl)-1*H*-indole-2-carboxamide-derived compounds which exhibit *in vitro* and *in vivo* antagonist activity with respect to receptors of TRPV1 (or VR1) type.

A first subject of the invention relates to the compounds corresponding to formula (I) below.

Another subject of the invention relates to processes for preparing the compounds of formula (I).

Another subject of the invention relates to the use of the compounds of formula (I), in particular in medicaments or in pharmaceutical compositions.

The compounds of the invention correspond to formula (I):



(I)

in which

X_1 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, cyano, $C(O)NR_1R_2$, nitro, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

X_2 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

X_3 and X_4 are, independently of one another, a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, nitro, NR_1R_2, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, NR_3COR_4, $NR_3SO_2R_5$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, at least one corresponding to a nitrogen atom and at least one corresponding to a $C(R_6)$ group; the nitrogen atom or one of the nitrogen atoms present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group;

n is equal to 0, 1, 2 or 3;

Y is an aryl or a heteroaryl optionally substituted with one or more groups selected from a halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, hydroxy, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, nitro, NR_1R_2, C_1-C_6-thioalkyl, thiol, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, NR_3COR_4, $NR_3SO_2R_5$, aryl-C_1-C_6-alkylene or aryl group, the aryl and the aryl-C_1-C_6-alkylene being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_7-alkylene group optionally substituted with one or two groups R_8;

B is a C_1-C_7-alkylene group optionally substituted with one or two groups R_9;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with a group R_{10} or R_{11},

the carbon atoms of the cyclic amine Z being optionally substituted with one or more groups R_{12} which may be identical to or different from one another;

R_1 and R_2 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl

group; or R_1 and R_2 form, together with the nitrogen atom which bears them, an azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiomorpholinyl, piperazinyl or homopiperazinyl group, this group being optionally substituted with a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_3 and R_4 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_5 is a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_6 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkylene, heteroaryl, hydroxyl, thiol, oxo or thio group;

R_7 is a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, aryl, aryl-C_1-C_6-alkylene or heteroaryl group;

R_8, R_9 and R_{10} are defined such that:

two groups R_8 can together form a bond or a C_1-C_6-alkylene group;

two groups R_9 can together form a bond or a C_1-C_6-alkylene group;

R_8 and R_9 can together form a bond or a C_1-C_6-alkylene group;

R_8 and R_{10} can together form a bond or a C_1-C_6-alkylene group;

R_9 and R_{10} can together form a bond or a C_1-C_6-alkylene group;

R_{11} is a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, hydroxyl, $COOR_5$, $C(O)NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

R_{12} is a fluorine atom, a C_1-C_6-alkyl group optionally substituted with a group R_{13}, a C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl or C_1-C_6-cycloalk-1,1-diyl group, a C_3-C_7-heterocycloalk-1,1-diyl group optionally substituted on a nitrogen atom with a group R_{11}, or a C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, $C(O)NR_1R_2$, NR_1R_2, NR_3COR_4, $OC(O)NR_1R_2$, NR_3COOR_5, $NR_3CONR_1R_2$, hydroxyl, thiol, oxo, thio, aryl-C_1-C_6-alkylene or aryl group, the aryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-

alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

R_{13} is a C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, $C(O)NR_1R_2$, NR_1R_2, NR_3COR_4, $OC(O)NR_1R_2$, NR_3COOR_5 or hydroxyl.

In the compounds of formula (I), the nitrogen atom(s) can be in oxidized form (N-oxide).
In the compounds of formula (I), the sulphur atom(s) can be in oxidized form (S(O) or $S(O)_2$).

By way of non-limiting examples of amines Z, mention may be made of aziridine, azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine, homopiperazine, azabicyclo[3.3.0]octanes, octahydrofuropyrroles, octahydropyrrolopyrroles, octahydroindole, octahydroisoindole, octahydropyrrolopyridines, decahydroquinoline, decahydroisoquinoline, decahydronaphthyridines, octahydropyridopyrazine, azabicylo[3.1.0]hexanes, azabicylo[3.2.0]heptanes, azabicylo[3.1.1]heptanes, diazabicylo[2.2.1]heptanes, azabicylo[3.2.1]octanes, diazabicylo[3.2.1]octanes and azabicylo[3.3.1]nonanes.

Among the compounds of formula (I) that are subjects of the invention, a first subgroup of compounds consists of the compounds for which X_1, X_2, X_3 and X_4 are selected, independently of one another, from a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl, C_1-C_6-thioalkyl or -$S(O)_2$-C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, a second subgroup of compounds consists of the compounds for which X_1, X_2, X_3 and X_4 are selected, independently of one another, from a hydrogen or halogen atom or a C_1-C_6-alkyl or C_1-C_6-fluoroalkyl group.

Among the compounds of formula (I) that are subjects of the invention, a third subgroup of compounds consists of the compounds for which X_1, X_2, X_3 and X_4 are selected, independently of one another, from a hydrogen, fluorine or chlorine atom or a methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, thiomethyl or -$S(O)_2CH_3$ group.

Among the compounds of formula (I) that are subjects of the invention, a fourth subgroup of compounds consists of the compounds for which
X_1 is a hydrogen or halogen atom or a C_1-C_6-alkyl group;
X_2 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl or -$S(O)_2$-C_1-C_6-alkyl group;

X_3 and X_4 are, independently of one another, a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, NR_1R_2 or C_1-C_6-thioalkyl group;
R_1 and R_2 are, independently of one another, a C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, a fifth subgroup of compounds consists of the compounds for which
X_1 is a hydrogen, fluorine or chlorine atom or a methyl group;
X_2 is a hydrogen, fluorine or chlorine atom or a methyl, isopropyl, tert-butyl, trifluoromethyl or $-S(O)_2CH_3$ group;
X_3 and X_4 are, independently of one another, a hydrogen, fluorine or chlorine atom or a methyl, ethyl, isopropyl, tert-butyl, trifluoromethyl, -O-isopropyl, NR_1R_2 or thiomethyl group;
R_1 and R_2 are, independently of one another, a methyl group.

Among the compounds of formula (I) that are subjects of the invention, a sixth subgroup of compounds consists of the compounds for which Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, at least two of them corresponding to a $C(R_6)$ group; the nitrogen atom or one of the nitrogen atoms present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, a seventh subgroup of compounds consists of the compounds for which Z_1 and Z_3 are a $C(R_6)$ group and Z_2 and Z_4 are a nitrogen atom; R_6 being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, an eighth subgroup of compounds consists of the compounds for which Z_1 and Z_3 are a $C(R_6)$ group and Z_2 and Z_4 are a nitrogen atom; R_6 corresponding to a hydrogen atom.

Among the compounds of formula (I) that are subjects of the invention, a ninth subgroup of compounds consists of the compounds for which Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $C(R_6)$ group; the nitrogen atom present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, a tenth subgroup of compounds consists of the compounds for which Z_4 is a nitrogen atom and Z_1, Z_2 and Z_3 are, independently of one another, a $C(R_6)$ group; the nitrogen atom present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, an eleventh subgroup of compounds consists of the compounds for which Z_4 is a nitrogen atom and Z_1, Z_2 and Z_3 are, independently of one another, a $C(R_6)$ group; R_6 is a hydrogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl or C_1-C_6-alkoxyl group.

Among the compounds of formula (I) that are subjects of the invention, a twelfth subgroup of compounds consists of the compounds for which Z_4 is a nitrogen atom and Z_1, Z_2 and Z_3 are, independently of one another, a $C(R_6)$ group; R_6 is a hydrogen atom or a methyl, trifluoromethyl or methoxy group.

Among the compounds of formula (I) that are subjects of the invention, a thirteenth subgroup of compounds consists of the compounds for which n is equal to 1.

Among the compounds of formula (I) that are subjects of the invention, a fourteenth subgroup of compounds consists of the compounds for which Y is an aryl or a heteroaryl optionally substituted with one or more groups selected from a halogen atom or a C_1-C_6-alkyl or NR_1R_2 group;
R_1 and R_2 form, together with the nitrogen atom which bears them, an azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiomorpholinyl, piperazinyl or homopiperazinyl group, this group being optionally substituted with a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group.

Among the compounds of formula (I) that are subjects of the invention, a fifteenth subgroup of compounds consists of the compounds for which Y is a phenyl or a pyridinyl, the phenyl being optionally substituted with a group selected from a fluorine atom or a methyl or NR_1R_2 group;
R_1 and R_2 form, together with the nitrogen atom which bears them, a pyrrolidinyl group.

Among the compounds of formula (I) that are subjects of the invention, a sixteenth subgroup of compounds consists of the compounds for which

Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_4-alkylene group optionally substituted with one or two groups R_8;

B is a C_1-C_4-alkylene group optionally substituted with one or two groups R_9;

L is a bond or an oxygen atom;

it being possible for the nitrogen atom of the cyclic amine Z to be in N-oxide form;

the carbon atoms of the cyclic amine Z being optionally substituted with a group R_{12};

R_8 and R_9 are defined such that:

two groups R_8 can together form a bond; or

two groups R_9 can together form a bond; or

R_8 and R_9 can together form a bond;

R_{12} is an NR_1R_2, NR_3COOR_5 or hydroxyl group;

R_1 and R_2, are, independently of one another, a hydrogen atom;

R_3 is a hydrogen atom;

R_5 is a C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, a seventeenth subgroup of compounds consists of the compounds for which

Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;

it being possible for the nitrogen atom of the cyclic amine Z to be in N-oxide form;

the carbon atoms of the cyclic amine Z being optionally substituted with a group R_{12};

R_{12} is an NR_1R_2, NR_3COOR_5 or hydroxyl group;

R_1 and R_2 are, independently of one another, a hydrogen atom;

R_3 is a hydrogen atom;

R_5 is a C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, an eighteenth subgroup of compounds consists of the compounds for which

Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;

it being possible for the nitrogen atom of the cyclic amine Z to be in N-oxide form;

the carbon atoms of the cyclic amine Z being optionally substituted with a group R_{12};

R_{12} is an NR_1R_2, NR_3COOR_5 or hydroxyl group;

R_1 and R_2 are, independently of one another, a hydrogen atom;

R_3 is a hydrogen atom;
R_5 is a tert-butyl group.

Among the compounds of formula (I) that are subjects of the invention, a nineteenth subgroup of compounds consists of the compounds for which
Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;
the carbon atoms of the azetidine being optionally substituted with a hydroxyl group;
the carbon atoms of the pyrrolidine being optionally substituted with an NR_1R_2, NR_3COOR_5 or hydroxyl group; it being possible for the nitrogen atom of the pyrrolidine to be in N-oxide form;
R_1 and R_2 are, independently of one another, a hydrogen atom;
R_3 is a hydrogen atom;
R_5 is a C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, a twentieth subgroup of compounds consists of the compounds for which
Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;
the carbon atoms of the azetidine being optionally substituted with a hydroxyl group;
the carbon atoms of the pyrrolidine being optionally substituted with an NR_1R_2, NR_3COOR_5 or hydroxyl group; it being possible for the nitrogen atom of the pyrrolidine to be in N-oxide form;
R_1 and R_2 are, independently of one another, a hydrogen atom;
R_3 is a hydrogen atom;
R_5 is a tert-butyl group.

Among the compounds of formula (I) that are subjects of the invention, a twenty-first subgroup of compounds consists of the compounds for which
Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_7-alkylene group optionally substituted with one or two groups R_8;
B is a C_1-C_7-alkylene group optionally substituted with one or two groups R_9;
L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with a group R_{10} or R_{11},

the carbon atoms of the cyclic amine Z being optionally substituted with one or more groups R_{12}, which may be identical to or different from one another, R_{12} being a C_1-C_6-alkyl group optionally substituted with a group R_{13}, NR_1R_2 or NR_3COOR_5;

R_1 and R_2 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl group;

R_3 is a hydrogen atom or a C_1-C_6-alkyl group;

R_5 is a C_1-C_6-alkyl group;

R_8, R_9 and R_{10} are defined such that:

two groups R_8 can together form a bond or a C_1-C_6-alkylene group; or

two groups R_9 can together form a bond or a C_1-C_6-alkylene group; or

R_8 and R_9 can together form a bond or a C_1-C_6-alkylene group; or

R_8 and R_{10} can together form a bond or a C_1-C_6-alkylene group; or

R_9 and R_{10} can together form a bond or a C_1-C_6-alkylene group;

R_{11} being as defined in the formula (I).

Among the compounds of formula (I) that are subjects of the invention, a twenty-second subgroup of compounds consists of the compounds for which

Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_7-alkylene group;

B is a C_1-C_7-alkylene group;

L is a bond, or a sulphur, oxygen or nitrogen group; the nitrogen atom being optionally substituted with a group R_{11},

the carbon atoms of the cyclic amine Z being optionally substituted with one or more groups R_{12}, which may be identical to or different from one another;

R_{11} and R_{12} being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, a twenty-third subgroup of compounds consists of the compounds for which Z is an azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiomorpholinyl, piperazinyl or homopiperazinyl group, this group being optionally substituted with one or more groups R_{12}, which may be identical to or different from one another; R_{12} being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, a twenty-fourth subgroup of compounds consists of the compounds for which Z is a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl group, this group being optionally substituted with

one or more groups R_{12}, which may be identical to or different from one another; R_{12} being a C_1-C_6-alkyl group optionally substituted with a group R_{13}, NR_1R_2 or NR_3COOR_5;
R_1 and R_2 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl group;
R_3 is a hydrogen atom or a C_1-C_6-alkyl group;
R_5 is a C_1-C_6-alkyl group.

Among the compounds of formula (I) that are subjects of the invention, a twenty-fifth subgroup of compounds consists of the compounds for which X_1, X_2, X_3, X_4, Z_1, Z_2, Z_3, Z_4, n, Y and Z are as defined in the subgroups above.

Among the compounds of formula (I) that are subjects of the invention, a twenty-sixth subgroup of compounds consists of the compounds for which
X_1, X_2, X_3 and X_4 are selected, independently of one another, from a hydrogen or halogen atom or a C_1-C_6-alkyl or C_1-C_6-fluoroalkyl group; and/or
Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $C(R_6)$ group; the nitrogen atom present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I); and/or
n is equal to 1; and/or
Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_7-alkylene group;
B is a C_1-C_7-alkylene group;
L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with a group R_{11},
the carbon atoms of the cyclic amine Z being optionally substituted with one or more groups R_{12}, which may be identical to or different from one another;
R_{11} and R_{12} being as defined in formula (I).

Among the compounds of formula (I) that are subjects of the invention, mention may be made of the following compounds:
1. *N*-{6-[((*R*)-3-tert-butoxycarbonylamino)pyrrolidin-1-yl]pyridin-3-yl}-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

2. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

3. *N*-{6-[(*R*)-3-aminopyrrolidin-1-yl]pyridin-3-yl}-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

4. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

5. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-trifluoromethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

6. *N*-[4-methyl-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

7. *N*-[6-(3-hydroxypyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

8. *N*-[5-methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

9. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-6-trifluoromethyl-1*H*-indole-2-carboxamide

10. *N*-[6-(pyrrolidin-1-yl)-4-methylpyridin-3-yl]-5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

11. *N*-[5-methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

12. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-[3-(pyrrolidin-1-yl)benzyl]-1*H*-indole-2-carboxamide

13. *N*-[6-(piperidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

14. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-trifluoromethyl-1*H*-indole-2-carboxamide

15. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-[(6-methylpyridin-2-yl)methyl]-1*H*-indole-2-carboxamide

16. *N*-[4-methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

17. *N*-[6-(morpholin-4-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide hydrochloride (1:1)

18. *N*-[4-methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

19. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-[(2-methylpyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

20. *N*-[6-(1-oxypyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

21. *N*-[2-(pyrrolidin-1-yl)pyrimidin-5-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
22. *N*-[6-(3-azabicyclo[3.2.0]hept-3-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
23. *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-fluoro-1*H*-indole-2-carboxamide
24. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
25. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-trifluoromethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
26. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-fluoro-1*H*-indole-2-carboxamide
27. *N*-[2-methyl-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
28. *N*-[6-(3-azabicyclo[3.1.0]hex-3-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
29. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-1-(3-fluorobenzyl)-5-trifluoromethyl-1*H*-indole-2-carboxamide
30. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-1-(3-fluorobenzyl)-6-trifluoromethyl-1*H*-indole-2-carboxamide
31. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(benzyl)-1*H*-indole-2-carboxamide
32. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-4,6-dimethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
33. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-tert-butyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
34. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-isopropyloxy-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
35. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-methylsulphonyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
36. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-dimethylamino-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
37. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-methylthio-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
38. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-4-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
39. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-7-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

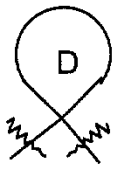
40. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
41. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-4-chloro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
42. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-chloro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
43. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-chloro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
44. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
45. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-4-methyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
46. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-methyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
47. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-methyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
48. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-isopropyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
49. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-tert-butyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
50. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-ethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
51. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-isopropyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
52. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-trifluoromethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide
53. *N*-[6-(pyrrolidin-1-yl)-4-(trifluoromethyl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

In the context of the present invention, the expression:

- "C_t-C_z where t and z can take the values of 1 to 7" is intended to mean a carbon-based chain that can contain from t to z carbon atoms, for example "C_1-C_3" is intended to mean a carbon-based chain which can contain from 1 to 3 carbon atoms;
- "an alkyl" is intended to mean: a linear or branched, saturated aliphatic group. By way of examples, mention may be made of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, etc., groups;
- "an alkylene" is intended to mean: a linear or branched, saturated divalent alkyl group, for example a C_1-C_3-alkylene group is a linear or branched, divalent carbon-based chain containing from 1 to 3 carbon atoms, for example a methylene, ethylene, 1-

methylethylene or propylene;

- "a cycloalkyl" is intended to mean: a cyclic carbon-based group. By way of examples, mention may be made of cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc., groups;
- "a heterocycloalkyl" is intended to mean: a cyclic group with 3 to 7 ring members containing 1 or 2 heteroatoms chosen from O, S or N;
- "a cycloalk-1,1-diyl" or "a heterocycloalk-1,1-diyl" is intended to mean: a group of the type



where D is a cycloalkyl or heterocycloalkyl group;

- "a fluoroalkyl" is intended to mean: an alkyl group in which one or more hydrogen atoms have been substituted with a fluorine atom;
- "an alkoxyl" is intended to mean: an -O-alkyl radical where the alkyl group is as defined above;
- "a cycloalkoxyl" is intended to mean: an -O-cycloalkyl radical where the cycloalkyl group is as defined above;
- "a fluoroalkoxyl" is intended to mean: an alkoxyl group in which one or more hydrogen atoms have been substituted with a fluorine atom;
- "a thioalkyl" is intended to mean: an -S-alkyl radical where the alkyl group is as defined above;
- "an aryl" is intended to mean: a cyclic aromatic group containing between 6 and 10 carbon atoms. By way of examples of aryl groups, mention may be made of phenyl or naphthyl groups;
- "a heteroaryl" is intended to mean: an aromatic cyclic group with from 5 to 10 ring members containing from 1 to 4 heteroatoms chosen from O, S or N. By way of example, mention may be made of imidazolyl, thiazolyl, oxazolyl, furanyl, thiophenyl, oxadiazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, benzofuranyl, benzothiophenyl, benzoxazolyl, benzimidazolyl, indazolyl, benzothiazolyl, isobenzothiazolyl, benzotriazolyl, quinolinyl, isoquinolinyl and quinoxalinyl groups;
- "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine or an iodine;
- "oxo" signifies "= O";
- "thio" signifies "= S".

The compounds of formula (I) can contain one or more asymmetrical carbon atoms. They can therefore exist in the form of enantiomers or of diastereoisomers. These enantiomers

and diastereoisomers, and also mixtures thereof, including racemic mixtures, are part of the invention.

The compounds of formula (I) can exist in the form of bases or of addition salts with acids. Such addition salts are part of the invention.
These salts are advantageously prepared with pharmaceutically acceptable acids, but the salts of other acids useful, for example, for the purification or the isolation of the compounds of formula (I) are also part of the invention.
The compounds of formula (I) can be in the form of hydrates or of solvates, i.e. in the form of associations or of combinations with one or more molecules of water or with a solvent. Such hydrates and solvates are also part of the invention.

In the text which follows, the term "leaving group" is intended to mean a group that can be readily cleaved from a molecule by cleavage of a heterolytic bond, with the departure of a pair of electrons. This group can thus be readily replaced with another group during a substitution reaction, for example. Such leaving groups are, for example, halogens or an activated hydroxyl group, such as a methanesulphonate, benzenesulphonate, p-toluenesulphonate, triflate, acetate, etc. Examples of leaving groups and also references for the preparation thereof are given in "Advances in Organic Chemistry", J. March, 5th Edition, Wiley Interscience, 2001.

In accordance with the invention, the compounds of formula (I) can be prepared according to the process illustrated by scheme 1 which follows.

According to scheme 1, the compounds of formula (IV) can be obtained by reaction of a compound of formula (II) in which X_1, X_2, X_3 and X_4 are as defined in formula (I) and B is a C_1-C_6-alkoxyl group, with a compound of formula (III), in which Y and n are as defined in formula (I) and GP is a leaving group where GP is a hydroxyl group.

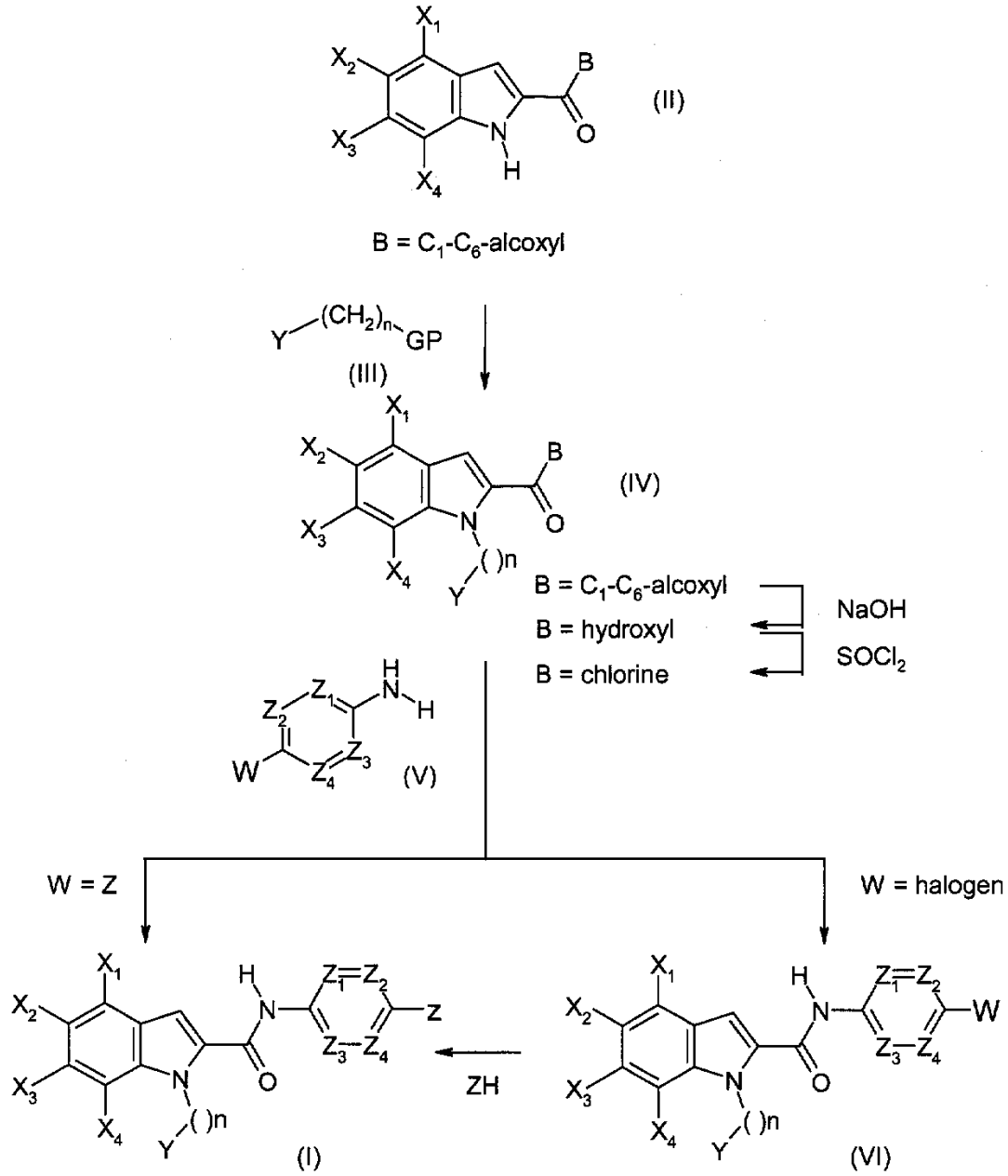
The compounds of formula (II) are commercially available or prepared according to many processes described in the literature (D. Knittel *Synthesis* **1985**, *2*, 186; T.M. Williams *J.Med.Chem.* **1993**, *36* (9), 1291; JP2001151771A2, for example).

When the compound of formula (III) is defined such that n is equal to 1, 2 or 3 and GP is a leaving group such as a chlorine, bromine or iodine atom, the reaction can be carried out in the presence of a base such as sodium hydride or potassium carbonate, in a polar solvent such as dimethylformamide, dimethyl sulphoxide or acetone (n = 1: Kolasa T.,

Bioorg.Med.Chem. **1997**, *5* (3) 507, n = 2: Abramovitch R., *Synth. Commun.*, **1995**, *25* (1), 1).

When the compound of formula (III) is defined such that n is equal to 1, 2 or 3 and GP is a hydroxyl group, the compounds of formula (IV) can be obtained by reaction of the compound of formula (II) with a compound of formula (III) in the presence of a phosphine such as, for example, triphenylphosphine, and of a reactant such as, for example, diethyl azodicarboxylate in solution in a solvent such as dichloromethane or tetrahydrofuran (O. Mitsonobu, *Synthesis,* **1981**, 1-28).

Scheme 1



When the compound of formula (III) is defined such that n is equal to 0, GP is a leaving group such as a chlorine, bromine or iodine atom and the reaction can be carried out at a temperature of between 80°C and 250°C, in the presence of a copper-based catalyst such as copper bromide or copper oxide, and also of a base such as potassium carbonate (Murakami Y., *Chem.Pharm.Bull.*, **1995**, *43* (8), 1281). The milder conditions described in S.L. Buchwald, *J.Am.Chem.Soc.* **2002**, *124*, 11 684 can also be used.

The compound of formula (IV), for which B is a C_1-C_6-alkoxyl group, can be converted to a compound of formula (IV) where B is a hydroxyl group, by the action of a base such as sodium hydroxide or potassium hydroxide in solution in a solvent such as ethanol. The compound of formula (IV) where B is a hydroxyl group can, subsequently, be converted to a compound of formula (IV) where B is a chlorine atom, by the action of a chlorinating agent such as thionyl chloride in a solvent such as dichloromethane.

The compounds of formulae (I) and (VI) can subsequently be obtained, for example, by reaction of a compound of formula (IV) where B is a chlorine atom, as obtained above, with an amine of formula (V), in which Z_1, Z_2, Z_3 and Z_4 are as defined in formula (I), and W is a halogen atom, such as a chlorine, a bromine or an iodine, or with a cyclic amine Z as defined in formula (I), in a solvent such as dichloroethane, toluene or tetrahydrofuran.
The compounds of formulae (I) and (VI) can also be obtained by reaction of a compound of formula (IV) where B is a hydroxyl group, as obtained above, with an amine of formula (V), in which Z_1, Z_2, Z_3 and Z_4 are as defined in formula (I) and W is a halogen atom, such as a chlorine, a bromine or an iodine, or with a cyclic amine Z as defined in formula (I), in the presence of a coupling agent such as diethylcyanophosphonate, in the presence of a base such as triethylamine, in a solvent such as dimethylformamide, or in the presence of a coupling agent such as *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, in the presence of *N*-1-hydroxybenzotriazole, in a solvent such as dimethylformamide. When W is a halogen atom, a compound of (VI) is obtained. When W is a cyclic amine Z as defined in the formula of (I), a compound of formula (I) is obtained.
The compound of formula (I) can also be obtained by reaction of a compound of formula (VI) where W is a halogen atom, in the presence of an amine of formula ZH in which Z is a cyclic amine as defined in general formula (I), without solvent or in a solvent such as N-methylpyrrolidinone, or else by application of a catalysed N-arylation method such as that described by J. Hartwig (J.F. Hartwig, *Angew Chem. Int. Ed.* **2005**, *44*, 1371-1375), preferably under an inert atmosphere, in the presence of a base such as lithium bistrimethylsilylamide in the presence of a source of palladium in catalytic amount, such

as palladium diacetate, and of a catalytic amount of a palladium ligand, such as a phosphine, the whole in solution in a solvent such as dimethoxyethane (DME).

The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3 and/or X_4 are a cyano group or an aryl, can be obtained by a coupling reaction, catalysed by a metal such as palladium, carried out on the corresponding compounds of formulae (I), (II) and (IV) in which X_1, X_2, X_3 and/or X_4 are a leaving group, for example a bromine, according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3 and/or X_4 are a $C(O)NR_1R_2$ group, can be obtained from the corresponding compounds of formulae (I), (II) and (IV) in which X_1, X_2, X_3 and/or X_4 are a cyano group, according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3, X_4 and/or R_6 are an -S(O)-alkyl or $-S(O)_2$-alkyl group, can be obtained by oxidation of the corresponding compounds of formulae (I), (II) and (IV) in which X_1, X_2, X_3, X_4 and/or R_6 are a C_1-C_6-thioalkyl group, according to methods which are described in the literature or which are known to those skilled in the art.

Similarly, the compounds of formulae (I) and (IV), in which Y is substituted with an -S(O)-alkyl or $-S(O)_2$-alkyl group, can be obtained by oxidation of the corresponding compounds of formulae (I) and (IV) in which Y is substituted with a C_1-C_6-thioalkyl group, according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formula (I) in which Z_1, Z_2, Z_3 and/or Z_4 are a C-R_6 group corresponding to a C-OH group, can be obtained starting from the corresponding compounds of formula (I) in which Z_1, Z_2, Z_3 and/or Z_4 are a C-R_6 group corresponding to a C_1-C_6-alkoxyl group, according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3 and/or X_4 are an NR_1R_2, NR_3COR_4 or $NR_3SO_2R_5$ group, can be obtained from the corresponding compounds of formulae (I), (II) and (IV) in which X_1, X_2, X_3 and/or X_4 are a nitro group, for example by reduction, and then acylation or sulphonylation, according to methods which are described in the literature or which are known to those skilled in the art.

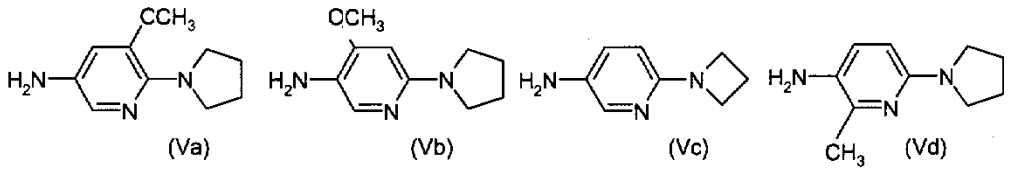
The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3 and/or X_4 are an NR_1R_2, NR_3COR_4 or $NR_3SO_2R_5$ group, can be obtained from the corresponding compounds of formulae (I), (II) and (IV) in which X_1, X_2, X_3 and/or X_4 are, for example, a bromine atom, by coupling reaction respectively with an amine, an amide or a sulphonamide in the

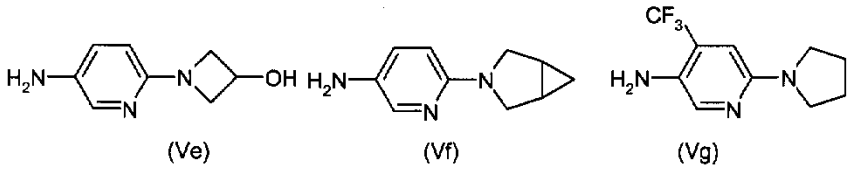
presence of a base, of a phosphine and of a palladium-based catalyst, according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formulae (I), (II) and (IV), in which X_1, X_2, X_3 and/or X_4 are an $SO_2NR_1R_2$ group, can be obtained by a method similar to that described in *Pharmazie* **1990**, *45*, 346, or according to methods which are described in the literature or which are known to those skilled in the art.

The compounds of formula (III) are commercially available, described in the literature (Carling R.W. et al *J.Med.Chem.* **2004** (47), 1807 – 1822 or Russel M.G.N. et al. *J.Med.Chem.* **2005** (48), 1367 – 1383) or accessible using methods known to those skilled in the art. Certain compounds of formula (IV) are described in the literature (WO 07/010144, for example). The compounds (V) and the other reactants, when the method for preparing them is not described, are commercially available or described in the literature (WO 05/028452, WO 02/048152, WO 06/040522, WO 04/052869, *Heterocycles* **1977**, 6(12), 1999 - 2004, *J.Chem.Soc. Perkin trans 1*, **1973** (*1*) 68-69, JP07/051121, WO 05/035526, WO 07/011284, WO 04/062665, GB 870027, US 4 104 385).

According to another of its aspects, a subject of the invention is also the compounds of formulae (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg). These compounds are useful as intermediates for the synthesis of the compounds of formula (I).





The amines of formulae (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg) can be prepared, for example, according to the process described in example no. 5, by aromatic nucleophilic substitution of a 6-chloropyridine precursor which is optionally substituted (Va: with a 5-methoxy group, Vb: with a 4-methoxy group, Vd: with a 2-methyl group, Vg: with a 4-trifluoromethyl group), with an amine, such as pyrrolidine, for example in a solvent such as ethanol. Access to the amines Va-g can subsequently require the reduction of a nitro group, for example, by catalytic hydrogenation in the presence of a catalyst such as palladium-on-charcoal, or by any other methods known to those skilled in the art, for the

reduction of a nitro group to an amine. The amines of formulae (Va), (Vb), (Vc), (Vd), (Ve), (Vf), (Vg) were prepared in the form of a powder or of an oil, in the form of a base or of an addition salt with an acid. Table 1 gives the ^{1}H NMR data for these amines.

Table 1

No.	^{1}H NMR, δ (ppm):
Va	In $CDCl_3$, δ (ppm): 2.5 (m, 4H); 3.23 (broad peak, 2H); 3.49 (m, 4H); 3.91 (s, 3H); 5.90 (s, 1H); 7.71 (s, 1H).
Vb	In DMSO D_6, δ (ppm): 1.81 (m, 4H); 3.29 (m, 4H); 3.71 (s, 3H); 4.52 (broad peak, 2H); 6.61 (s, 1H); 7.16 (s, 1H).
Vc	In DMSO D_6, δ (ppm): 2.21 (m, 2H); 3.78 (m, 4H); 4.42 (broad peak, 2H); 6.20 (d, 1H); 6.89 (d, 1H); 7.58 (s, 1H).
Vd	In $CDCl_3$, δ (ppm): 1.89 (m, 4H); 2.23 (s, 3H); 2.98 (broad peak, 2H); 3.31 (m, 4H); 6.03 (d, 1H); 6.82 (d, 1H).
Ve	In DMSO D_6, δ (ppm): 3.49 (m, 2H); 3.98 (m, 2H); 4.48 (broad peak, 3H); 5.48 (broad peak, 1H); 6.22 (d, 1H); 6.91 (d, 1H); 7.58 (s, 1H).
Vf	In DMSO D_6, δ (ppm): 0.2 (m, 1H); 0.66 (m, 1H); 1.6 (m, 2H); 3.11 (m, 2H); 3.51 (d, 2H); 4.32 (broad peak, 2H); 6.25 (d, 1H); 6.99 (d,1H); 7.55 (s, 1H).
Vg	In DMSO D_6, δ (ppm): 2 (m, 4H); 3.52 (m, 4H); 7.1 (s, 1H); 7.49 (broad peak, 2H); 7.92 (s, 1H); hydrochloride form 1:1

The following examples describe the preparation of certain compounds in accordance with the invention. These examples are not limiting and merely illustrate the present invention. The numbers of the compounds exemplified refer to those given in Table 2. The elemental microanalyses, the LC-MS (liquid chromatography coupled to mass spectrometry) analyses, the IR spectra or the NMR spectra confirm the structures of the compounds obtained.

Example 1 (Compound No. 1)

N-{6-[((*R*)-3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]pyridin-3-yl}-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

1.1. 5-Fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid

An aqueous solution of sodium hydroxide, prepared from 1.15 g (28.92 mmol) of sodium hydroxide pellets in 50 ml of water, is added to a solution of 7.6 g (24.10 mmol) of ethyl 5-

fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylate (WO 2006/024776) in 241 ml of ethanol. The mixture is heated for two hours and then concentrated under reduced pressure. The resulting solid is taken up in 200 ml of water. The solution is washed with twice 100 ml of ethyl ether, acidified by successive additions of small amounts of concentrated hydrochloric acid, and then extracted with 200 ml of ethyl acetate. The organic phase is finally washed twice with 100 ml of water and once with 50 ml of a saturated sodium chloride solution, dried over magnesium sulphate, and concentrated under reduced pressure. After drying at 50°C under reduced pressure, 6.4 g of the expected product are obtained in the form of a solid, which will be used as it is in the next step.

1.2 *N*-{6-[((*R*)-3-tert-Butoxycarbonylamino)pyrrolidin-1-yl]pyridin-3-yl}-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (compound no. 1)

0.85 ml (4.91 mmol) of diisopropylethylamine is added, dropwise, at 20°C under argon, to a solution of 0.47 g (1.64 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (obtained in step 1.1), of 0.5 g (1.8 mmol) of 3-amino-6-[((*R*)-3-tert-butoxycarbonylamino)pyrrolidin-1-yl]pyridine (JP2004175739) and of 0.85 g (1.64 mmol) of trispyrrolidinophosphonium hexafluorophosphate (PYBOP) in 20 ml of dichloromethane. The mixture is stirred at ambient temperature for 12 hours, concentrated under reduced pressure, and then taken up with 50 ml of ethyl acetate. This solution is then successively washed with three times 15 ml of a saturated sodium hydrogen carbonate solution and 20 ml of a saturated sodium chloride solution and then dried over sodium sulphate, filtered and concentrated under reduced pressure. The product obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. The resulting solid is then triturated in ethyl ether. 0.788 g of a solid is obtained, which solid is dried under reduced pressure.

Melting point: 207 – 209°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.49 (s, 9H); 1.85 (sext, 1H); 2.1 (sext, 1H); 3.2 (m, 4H); 4.09 (m, 1H); 5.88 (s, 2H); 6.41 (d, 1H); 7.04 (m, 7H); 7.61 (m, 2H); 7.8 (dxd, 1H); 8.31 (d, 1H); 10.19 (s, 1H).

Example 2 (Compound No. 2)

N-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

0.28 ml (1.68 mmol) of diethyl cyanophosphonate is added, dropwise, at 20°C under argon, to a solution of 0.402 g (1.4 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1) and of 0.274 g (1.68 mmol) of 3-amino-6-(pyrrolidin-1-yl)pyridine (WO 02/48152) in 10 ml of dry dimethylformamide. The mixture is stirred for ten minutes and then 0.43 ml (3.08 mmol) of triethylamine is added dropwise. The mixture is stirred at ambient temperature for 18 hours, concentrated under reduced pressure, and then taken up with 50 ml of ethyl acetate. This solution is then successfully washed with three times 20 ml of a saturated sodium hydrogen carbonate solution, 50 ml of water and 20 ml of a saturated sodium chloride solution, and then dried over sodium sulphate, filtered, and concentrated under reduced pressure. The solid obtained is triturated in isopropylether under hot conditions. 0.527 g of a solid is obtained, which solid is dried under reduced pressure.

Melting point: 199 – 201°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.9 (m, 4H); 3.3 (m, 4H); 5.82 (s, 2H); 6.4 (d, 1H); 7.04 (m, 6H); 7.51 (m, 2H); 7.77 (dxd, 1H); 8.3 (d, 1H); 10.25 (s, 1H)

Example 3 (Compound No. 4)

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

3.1 N-[6-chloropyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

23.8 ml (47.57 mmol) of a 2M solution of trimethylaluminium in toluene are added to a solution, stirred at 20°C under an argon atmosphere, of 4.48 g (34.89 mmol) of 6-chloro-3-aminopyridine in 317 ml of toluene. The solution is then brought to 120°C and 10 g (31.71 mmol) of ethyl 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylate are added in several steps (WO 2006/024776). The reaction mixture is refluxed for 4 hours and is then cooled to 0°C. 15 ml of water are added to the reaction medium, which is then extracted with twice 200 ml of ethyl acetate. The organic phases are combined and washed twice with 50 ml of water and once with 50 ml of a saturated sodium chloride solution, and then dried over magnesium sulphate and concentrated under reduced pressure. The residue obtained is triturated in 100 ml of ethyl ether, the product is filtered, and 10 g of expected product are recovered in the form of a powder.

^{1}H NMR (DMSO D_6), δ (ppm): 5.9 (s, 2H); 6.9 (m, 2H); 7.05 (txd, 1H); 7,2 (txd, 1H); 7.32 (m, 1H); 7.58 (m, 4H); 8.25 (d, 1H); 8.79 (s, 1H); 10.79 (s, 1H)

3.2 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (Compound no. 4)

4.2 ml (4.2 mmol) of a 1M solution of lithium bistrimethylsilylamide in tetrahydrofuran are added to a mixture, stirred to 0°C under an argon atmosphere, of 0.7 g (1.76 mmol) of *N*-[6-chloropyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide, prepared in step 3.1, of 0.123 g (2.11 mmol) of azetidine, of 8 mg (0.04 mmol) of palladium diacetate and of 19.5 mg (0.04 mmol) of (*R*)-(-)-1-[(*S*)-2-(dicyclohexylphosphino)ferrocenyl]ethyldi-tert-butylphosphine in 1.8 ml of dry and degassed dimethoxyethane. The reactor is closed and then heated at 100°C for 16 hours. The reaction mixture is then poured into 50 ml of water. 5 ml of a molar solution of hydrochloric acid and then 50 ml of a saturated sodium hydrogencarbonate solution are added slowly. The mixture is extracted twice with 50 ml of ethyl acetate. The organic phases are combined and then washed twice with 50 ml of a saturated sodium hydrogen carbonate solution, dried over magnesium sulphate and then concentrated under reduced pressure. The product obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and acetone. The resulting solid is then triturated in 20 ml of hot isopropanol, recovered by filtration, and then recrystallized from a mixture of ethanol and methanol. 0.31 g of a solid is recovered by filtration, and dried under reduced pressure.

Melting point: 227 – 228°C

^{1}H NMR (DMSO D_6), δ (ppm): 2.25 (pent, 2H); 3.9 (t, 4H); 6.01 (s, 2H); 6.35 (d, 1H); 6.89 (m, 2H); 7.01 (txd, 1H); 7.12 (txd, 1H); 7.19 (q,1H); 7.34 (s, 1H);7.52 (m, 2H); 7.82 (dxd, 1H); 8.31 (s, 1H); 10.28 (s, 1H).

Example 4 (Compound No. 7)

N-[6-(3-Hydroxypyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

A mixture of 0.4 g (1.01 mmol) of *N*-[6-chloropyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide, prepared in step 3.1, and 0.81 ml (10.06 mmol) of 3-hydroxypyrrolidine in 1.2 ml of N-methylpyrrolidinone is heated for 20 minutes in a microwave oven regulated at 200°C under 300 watts. The reaction mixture is then poured into 50 ml of water. A solid is recovered by filtration and purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. The resulting solid is then recrystallized from a mixture of methanol and dichloromethane. 0.22 g of a solid is recovered by filtration and dried under reduced pressure.

Melting point: 229 – 230°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.9 (m, 1H); 2.04 (m, 1H); 3.3-3.47 (m, 4H); 4.49 (s, 1H); 4.92 (s, 1H); 5.9 (s, 2H); 6.47 (d, 1H); 6.91 (m, 2H); 7.05 (txd, 1H); 7.12 (txd, 1H); 7.31 (q,1H); 7.39 (s, 1H); 7.55 (m, 2H); 7.82 (dxd, 1H); 8.37 (s, 1H); 10.22 (s, 1H).

Example 5 (Compound No. 8)

N-[5-Methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

5.1 3-Methoxy-5-nitro-2-(pyrrolidin-1-yl)pyridine

A solution of 3 g (15.91 mmol) of 2-chloro-3-methoxy-5-nitropyridine and 2 ml (23.86 mmol) of pyrrolidine in 30 ml of dimethylformamide is heated at 100°C for 4 hours. The reaction mixture is subsequently concentrated under reduced pressure and then taken up in 100 ml of water and extracted three times with 100 ml of ethyl acetate. The organic phases are combined, then washed twice with 50 ml of water then once with 50 ml of a saturated sodium chloride solution, dried over sodium sulphate and then concentrated under reduced pressure. 3.47 g of the expected compound are thus isolated in the form of an orangey powder.

^{1}H NMR (DMSO D_6), δ (ppm): 1.9 (m, 4H); 3.79 (m, 4H); 3.88 (s, 3H); 7.62 (s, 1H); 8.69 (s, 1H).

5.2 3-Methoxy-2-(pyrrolidin-1-yl)-4-aminopyridine (compound Va)

A suspension of 3.4 g (15.54 mmol) of 3-methoxy-5-nitro-2-(pyrrolidin-1-yl)pyridine, obtained in step 5.1, and of 0.33 g of 10% palladium-on-charcoal in 40 ml of ethanol is stirred at 20°C for 5 hours under 5.6 bar of hydrogen. The reaction mixture is subsequently filtered through a celite pad, concentrated under reduced pressure, and then purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. 0.9 g of the expected compound is thus isolated, which compound will be used as it is in the rest of the synthesis.

^{1}H NMR ($CDCl_3$), δ (ppm): 2.5 (m, 4H); 3.23 (broad peak, 2H); 3.49 (m, 4H); 3.91 (s, 3H); 5.90 (s, 1H); 7.71 (s, 1H).

5.3 *N*-[5-Methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (Compound no. 8)

A solution of 0.5 g (1.74 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid, prepared in step 1.1, of 0.33 g (1.74 mmol) of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide and of 0.23 g (1.74 mmol) of *N*-1-hydroxybenzotriazole in 10 ml of dimethylformamide is stirred for 15 minutes at 20°C. 0.43 g (2.26 mmol) of the compound (Va) prepared in step 5.2 is then added to the reaction medium. The reaction mixture is subsequently stirred for 12 hours at 20°C and then concentrated under reduced pressure, poured into 100 ml of water and extracted twice with 100 ml of ethyl acetate. The organic phases are combined, then washed twice with 50 ml of water and then once with 50 ml of a saturated sodium chloride solution, dried over sodium sulphate, and then concentrated under reduced pressure. The product obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. 0.3 g of the expect compound is thus isolated.

Melting point: 172 – 174°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.85 (m, 4H); 3.61 (m, 4H); 3.78 (s, 3H); 5.91 (s, 2H); 6.91 (m, 2H); 7.07 (txd, 1H); 7.15 (txd, 1H);7.31 (q, 1H); 7.4 (s, 1H); 7.58 (m, 3H); 8.08 (s, 1H); 10.3 (s, 1H).

Example 6 (Compound No. 16)

N-[4-Methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

6.1 4-Methoxy-5-nitro-2-(pyrrolidin-1-yl)pyridine

The process is carried out according to the method described in step 5.1, using 5.4 g (28.64 mmol) of 2-chloro-4-methoxy-5-nitropyridine (WO 03/080610) and 4.53 g (63 mmol) of pyrrolidine. The product obtained is, in this case, purified by silica column chromatography, elution being carried out with a mixture of heptane and ethyl acetate. 3 g of the expected product are thus isolated.

^{1}H NMR (DMSO D_6), δ (ppm): 2.17 (m, 4H); 3.65 (m, 4H); 4.07 (s, 3H); 5.79 (s, 1H); 8.98 (s, 1H).

6.2 4-Methoxy-2-(pyrrolidin-1-yl)-5-aminopyridine (Compound Vb)

The process is carried out according to the method described in 5.2, using 1.5 g (6.72 mmol) of 4-methoxy-5-nitro-2-(pyrrolidin-1-yl)pyridine, obtained in step 6.1, and 0.15 g of 10% palladium-on-charcoal. 1.25 g of the expected product are thus obtained.

^{1}H NMR (DMSO D_6), δ (ppm): 1.81 (m, 4H); 3.29 (m, 4H); 3.71 (s, 3H); 4.52 (broad peak, 2H); 6.61 (s, 1H); 7.16 (s, 1H).

6.3 *N*-[4-Methoxy-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (Compound no. 16)

The process is carried out according to the method described in example 2, using 0.5 g (1.74 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1) and 0.424 g (2.09 mmol) of 4-methoxy-2-(pyrrolidin-1-yl)-5-aminopyridine, obtained in step 6.1 (Compound Vb). 0.59 g of the expected product is thus isolated.

Melting point: 196 – 198°C

^{1}H NMR ($CDCl_3$), δ (ppm): 2.01 (m, 4H); 3.49 (m, 4H); 3.91 (s, 3H); 5.86 (m, 3H); 6.79 (dxd 1H); 6.9 (m, 2H);7.02 (m, 2H); 7.23 (m, 2H);7.34 (dxd, 1H); 7.9 (m, 1H); 8.85 (s, 1H).

Example 7 (Compound No. 20)

N-[6-(1-Oxypyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

A solution of 0.5 g (1.16 mmol) of *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (compound no. 2 prepared according to the method described in example 2) and of 0.31 g (1.27 mmol) of metachloroperbenzoic acid (70%) in 20 ml of dichloromethane is stirred at 20°C for 24 hours. 100 ml of dichloromethane are added to the reaction mixture, which is then washed successively with 20 ml of a saturated sodium carbonate solution and then 3 times with 20 ml of water, dried over magnesium sulphate, and then concentrated under reduced pressure. The product obtained is then purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. 0.23 g of the expected product is thus isolated.

Melting point: 140 – 143°C

^{1}H NMR (DMSO D_6), δ (ppm): 2.1 (m, 2H); 2.35 (m, 2H); 3.31 (m, 2H); 4.08 (m, 2H); 5.91 (s, 2H); 6.9 (m, 2H); 7.04 (txd, 1H); 7.2 (txd, 1H); 7.32 (m, 1H); 7.51 (s, 1H); 7.62 (m, 2H); 8.41 (m, 2H); 8.8 (s, 1H); 10.91 (s, 1H)

Example 8 (Compound No. 21)

N-[2-(Pyrrolidin-1-yl)pyrimidin-5-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

The process is carried out according to the method described in example 2, using 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1) and 2-(pyrrolidin-1-yl)-5-aminopyrimidine (US 20060281772).

Melting point: 220 – 222°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.97 (m, 4H); 3.51 (m, 4H); 5.89 (s, 2H); 6.91 (m, 2H); 7.05 (txd, 1H);7.16 (txd, 1H); 7.31 (m, 1H);7.40 (s, 1H); 7.57 (m, 2H); 8.61 (s, 2H); 10.32 (s, 1H).

Example 9 (Compound No. 27)

N-[2-Methyl-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

9.1 2-Methyl-6-(pyrrolidin-1-yl)-3-nitropyridine

A suspension of 0.5 g (2.9 mmol) of 6-chloro-3-nitro-2-picoline, of 0.73 ml (8.69 mmol) of pyrrolidine and of 0.8 g (5.79 mmol) of potassium carbonate is heated at 110°C for 2 hours. The reaction mixture is subsequently concentrated under reduced pressure and then poured into 100 ml of water. A solid is recovered by filtration and is dried so as to obtain 0.55 g of the expected product in the form of a yellow solid which will be used as it is in the rest of the synthesis.

9.2 2-Methyl-6-(pyrrolidin-1-yl)-3-aminopyridine (compound no. Vd)

The process is carried out according to the method described in step 5.2, using 0.55 g (2.65 mmol) of 2-methyl-6-(pyrrolidin-1-yl)-3-nitropyridine, prepared in step 9.1, and 0.1 g of 10% palladium-on-charcoal. 0.34 g of the expected product is thus obtained, which product will be used as it is in the rest of the synthesis.

^{1}H NMR ($CDCl_3$), δ (ppm): 1.89 (m, 4H); 2.23 (s, 3H); 2.98 (broad peak, 2H); 3.31 (m, 4H); 6.03 (d, 1H); 6.82 (d, 1H).

9.3 *N*-[2-Methyl-6-(pyrrolidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (Compound no. 27)

The process is carried out according to the method described in example 5.3, using 0.4 g (1.39 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1) and 0.32 g (1.81 mmol) of 2-methyl-6-(pyrrolidin-1-yl)-3-aminopyridine (compound no. Vd), described in step 9.2. 0.3 g of the expected product is thus isolated.

Melting point: 213 - 214°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.92 (m, 4H); 2.21 (s, 3H); 3.49 (m, 4H); 5.88 (s, 2H); 6.29 (d, 1H); 6.87 (d, 1H); 6.92 (d, 1H); 7.05 (txd, 1H); 7.15 (txd, 1H); 7.38 (m, 2H); 7.39 (s, 1H); 7.52 (d, 1H); 7.67 (m, 1H); 9.91 (s, 1H).

Example 10 (Compound No. 24)

N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

10.1 2-(3-Hydroxyazetidin-1-yl)-5-nitropyridine

The process is carried out according to the method described in step 5.1, using 7 g (42.83 mmol) of 2-chloro-5-nitropyridine and 5.75 g (51.4 mmol) of 3-azetidinol hydrochloride. In this case, 13 g (128.45 mmol) of triethylamine are also added. 8 g of the expected product are thus isolated.

Melting point: 175 - 176°C

^{1}H NMR (DMSO D_6), δ (ppm): 3.85 (m, 2H); 4.36 (m, 2H); 4.62 (m, 1H); 5.88 (d, 1H); 6.4 (d, 1H); 8.18 (dxd, 1H); 8.92 (s, 1H).

10.2 2-(3-Hydroxyazetidin-1-yl)-5-aminopyridine (Compound Ve)

The process is carried out according to the method described in step 5.2, using 5.5 g (28.18 mmol) of 2-(3-hydroxyazetidin-1-yl)-5-nitropyridine, prepared in step 10.1, and 0.5 g of 10% palladium-on-charcoal. 4.5 g of the expected product are thus obtained in the form of violet crystals.

Melting point: 148 - 150°C

^{1}H NMR (DMSO D_6), δ (ppm): 3.49 (m, 2H); 3.98 (m, 2H); 4.48 (broad peak, 3H); 5.48 (broad peak, 1H); 6.22 (d, 1H); 6.91 (d, 1H); 7.58 (s, 1H).

10.3 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (compound no. 24)

The process is carried out according to the method described in example 2, using 0.5 g (1.74 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1) and 0.35 g (2.09 mmol) of 2-(3-hydroxyazetidin-1-yl)-5-aminopyridine, obtained in step 10.2 (Compound Ve).

Melting point: 199 – 200°C

^{1}H NMR (DMSO D_6), δ (ppm): 3.67 (m, 2H); 4.13 (m, 2H); 4.58 (m, 1H); 5.61 (m, 1H); 5.91 (s, 2H); 6.42 (d, 1H); 6.91 (m, 2H);7.05 (m, 1H);7.18 (txd, 1H); 7.36 (m, 1H);7.42 (s, 1H); 7.58 (m, 2H); 7.88 (dxd, 1H); 8.39 (s, 1H); 10.35 (s, 1H).

Example 11 (Compound No. 53)

N-[6-(Pyrrolidin-1-yl)-4-(trifluoromethyl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

11.1 Methyl 6-(pyrrolidin-1-yl)-4-(trifluoromethyl)pyridine-3-carboxylate

A mixture of 2.5 g (10.43 mmol) of methyl 6-chloro-4-trifluoromethylnicotinate, of 2.88 g (20.87 mmol) of potassium carbonate and of 2.61 ml (31.3 mmol) of pyrrolidine in 90 ml of dimethylformamide is heated at 100°C for 3 hours. The reaction mixture is subsequently concentrated under reduced pressure and then taken up in 100 ml of water. A precipitate is recovered by filtration and is washed with 150 ml of water. After drying under reduced pressure, 2.5 g of the expected product are isolated.

^{1}H NMR ($CDCl_3$), δ (ppm): 2.11 (m, 4H); 3.61 (broad peak, 4H); 3.93 (s, 3H); 6.69 (s, 1H); 8.89 (s, 1H).

11.2 6-(Pyrrolidin-1-yl)-4-(trifluoromethyl)pyridine-3-carboxylic acid

A mixture of 2.5 g (9.12 mmol) of methyl 6-(pyrrolidin-1-yl)-4-(trifluoromethyl)pyridine-3-carboxylate, obtained in step 11.1, and of 0.76 g (13.67 mmol) of potassium hydroxide in 50 ml of methanol and 2 ml of water is stirred for 24 hours at 20°C. The mixture is subsequently concentrated under reduced pressure. 100 ml of water are subsequently added and the solution is washed with 100 ml of dichloromethane and then acidified to pH 4 by the addition of concentrated hydrochloric acid. A precipitate is recovered by filtration and is washed with 50 ml of water. After drying under reduced pressure, 2.2 g of the expected compound are isolated.

^{1}H NMR (DMSO D_6), δ (ppm): 1.99 (s, 4H); 3.51 (broad peak, 4H); 6.71 (s, 1H); 8.72 (s, 1H).

11.3 6-(Pyrrolidin-1-yl)-4-trifluoromethyl-3-(tert-butoxycarbonylamino)pyridine

A mixture of 2.2 g (8.45 mmol) of 6-(pyrrolidin-1-yl)-4-(trifluoromethyl)pyridine-3-carboxylic acid, obtained in step 11.2, of 2.37 ml (10.99 mmol) of diphenylphosphorylazide and of 2.95 ml (21.14 mmol) of triethylamine in 25 ml of tert-butanol is heated for 5 hours at 90°C. The reaction mixture is subsequently concentrated

under reduced pressure, taken up with 50 ml of water, and then extracted 3 times with 50 ml of dichloromethane. The organic phases are combined, washed with 50 ml of water, dried over sodium sulphate, and then concentrated under reduced pressure. The oil obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. 1.05 g of the expected product are thus isolated.

^{1}H NMR ($CDCl_3$), δ (ppm): 1.53 (s, 9H); 2.09 (m, 4H); 3.51 (m, 4H); 6.2 (broad peak, 1H); 6.52 (s, 1H); 8.39 (broad peak, 1H).

11.4 6-(Pyrrolidin-1-yl)-4-trifluoromethyl-3-aminopyridine hydrochloride (amine Vg)

A solution of 1 g (3.02 mmol) of 6-(pyrrolidin-1-yl)-4-trifluoromethyl-3-(tert-butoxycarbonylamino)pyridine, prepared in step 11.3, in 11 ml of 4N hydrochloric acid in dioxane is stirred for 5 hours at reflux. 200 ml of ethyl ether are subsequently added to the cooled reaction mixture. 0.8 g of a precipitate is recovered by filtration.

Melting point: 207 – 209°C;

^{1}H NMR (DMSO D_6), δ (ppm): 2 (m, 4H); 3.52 (m, 4H); 7.1 (s, 1H); 7.49 (broad peak, 2H); 7.92 (s, 1H).

11.5 *N*-[6-(Pyrrolidin-1-yl)-4-trifluoromethylpyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (compound no. 53)

The process is carried out according to the method described in step 5.3, using 0.3 g (1.04 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (example 1.1), and of 0.363 g (1.36 mmol) of 6-(pyrrolidin-1-yl)-4-trifluoromethyl-3-aminopyridine hydrochloride, prepared in step 11.4, in the presence of 0.22 ml (1.57 mmol) of triethylamine.

Melting point: 170 - 171°C;

^{1}H NMR (DMSO D_6), δ (ppm): 1.99 (m, 4H); 3.49 (m, 4H); 5.87 (s, 2H); 6.7 (s, 1H); 6.86 – 7.22 (m, 4H); 7.31 (m, 1H); 7.4 (s, 1H); 7.57 (dxd, 1H); 7.65 (m, 1H); 8.11 (s, 1H).

Example 12 (Compound No. 28)

N-[6-(3-Azabicyclo[3.1.0]hex-3-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

12.1 2-(3-Azabicyclo[3.1.0]hex-3-yl)-5-nitropyridine

A suspension of 0.2 g (1.26 mmol) of 2-chloro-5-nitropyridine, of 0.166 g (1.39 mmol) of 3-azabicyclo[3.1.0]hexane (*Bioorg.&Med.Chem. Lett.* **2005**, *15*(8) 2093) and of 0.52 g (3.78 mmol) of potassium carbonate in 5 ml of dimethylformamide is stirred at ambient temperature for 36 hours. The mixture is subsequently poured into 5 ml of water and then extracted 3 times with 20 ml of ethyl acetate. The organic phases are subsequently combined, dried over magnesium sulphate, and then concentrated under reduced pressure. 0.22 g of the expected product is thus obtained, which product is used as it is in the rest of the synthesis.

12.2 2-(3-Azabicyclo[3.1.0]hex-3-yl)-5-aminopyridine (Vf)

The process is carried out according to the method used in example 5.2, using 0.2 g (0.97 mol) of 2-(3-azabicyclo[3.1.0]hex-3-yl)-5-nitropyridine, described in step 12.1, and 0.5 g of 10% palladium-on-charcoal. 0.1 g of the expected product is thus isolated, which product will be used as it is in the next step.

^{1}H NMR (DMSO D_6), δ (ppm): 0.2 (m, 1H); 0.66 (m, 1H); 1.6 (m, 2H); 3.11 (m, 2H); 3.51 (d, 2H); 4.32 (broad peak, 2H); 6.25 (d, 1H); 6.99 (d,1H); 7.55 (s, 1H).

12.3 *N*-[6-(3-Azabicyclo[3.1.0]hex-3-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide (compound no. 28).

The process is carried out according to the method described in example 2, using 0.15 g (0.52 mmol) of 5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid and 0.1 g (0.57 mmol) of 2-(3-azabicyclo[3.1.0]hex-3-yl)-5-aminopyridine, prepared in step 12.2. 0.17 g of the expected product is thus isolated.

Melting point: 193 – 195°C

^{1}H NMR (DMSO D_6), δ (ppm): 0.02 (m, 1H); 0.51 (m, 1H); 1.47 (m, 2H); 3.41 (d, 2H); 5.67 (s, 2H); 6.25 (d, 1H); 6.69 (m, 2H);6.83 (m, 1H); 6.93 (m, 1H);7.1 (m, 1H); 7.15 (s, 1H); 7.31 (dxd, 1H); 7.39 (m, 1H); 7.6 (m, 1H); 8.11 (s, 1H); 10.03 (s, 1H).

Example 13 (Compound No. 29)

N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-1-(3-fluorobenzyl)-5-trifluoromethyl-1*H*-indole-2-carboxamide

The process is carried out according to the method described in example 2, using 5-trifluoromethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid (WO 2006/072736) and 2-(3-hydroxyazetidin-1-yl)-5-aminopyridine, prepared in step 10.2 of example 10 (Compound Ve).

Melting point: 194 – 196°C

^{1}H NMR (DMSO D_6), δ (ppm): 3.68 (m, 2H); 4.17 (m, 2H); 4.59 (m, 1H); 5.6 (d, 1H); 5.93 (s, 2H); 6.42 (d, 1H); 6.91 (m, 2H);7.09 (txd, 1H); 7.32 (m, 1H);7.55 (m, 2H); 7.79 (d, 1H); 7.88 (d, 1H); 8.2 (s, 1H); 8.38 (s, 1H); 10.41 (s, 1H).

Example 14 (Compound No. 30)

N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-1-(3-fluorobenzyl)-6-trifluoromethyl-1*H*-indole-2-carboxamide

The process is carried out according to the method described in example 2, using 6-trifluoromethyl-1-(3-fluorobenzyl)-1*H*-indole-2-carboxylic acid and 2-(3-hydroxyazetidin-1-yl)-5-aminopyridine, prepared in step 10.2 of example 10 (Compound Ve).

Melting point: 253 – 255°C

^{1}H NMR (DMSO D_6), δ (ppm): 3.67 (m, 2H); 4.17 (m, 2H); 4.59 (m, 1H); 5.6 (d, 1H); 6.0 (s, 2H); 6.42 (d, 1H); 6.91 (m, 2H);7.09 (txd, 1H); 7.36 (m, 1H);7.47 (d, 1H); 7.51 (s, 1H); 7.85 (d, 1H); 7.99 (d, 1H); 8.06 (s, 1H); 8.33 (s, 1H); 10.41 (s, 1H).

Example 15 (Compound No. 23)

N-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-fluoro-1*H*-indole-2-carboxamide

15.1 5-Fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylic acid

A solution of 2.1 g (7.04 mmol) of ethyl 5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylate (WO 2007/010144) and of 1.18 g (21.12 mmol) of potassium hydroxide in 80 ml of ethanol and 2 ml of water is refluxed for 2 hours. The reaction mixture is subsequently concentrated under reduced pressure. 100 ml of water are added and the pH of the solution is brought to pH 8 by the addition of a concentrated hydrochloric acid solution. A precipitate is recovered by filtration and is washed with water and then dried under reduced pressure. 1.5 g of the expected product are thus obtained.

Melting point: 282 – 283°C

15.2 *N*-[6-Chloropyridin-3-yl]-5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

The process is carried out according to the method described in example 2, using 0.7 g (2.59 mmol) of 5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylic acid, obtained in

step 15.1, and 0.4 g (3.11 mmol) of 2-chloro-5-aminopyridine. 0.41 g of expected product is isolated.

Melting point: 244 – 246°C

15.3 *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-fluoro-1*H*-indole-2-carboxamide (compound no. 23)

The process is carried out according to the method described in example 3.2, using 0.4 g (1.05 mmol) of *N*-[6-chloropyridin-3-yl]-5-fluoro-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide, obtained in step 15.2, and 2.63 ml (31.51 mmol) of pyrrolidine. 0.24 g of the expected product is isolated.

Melting point: 255 – 257°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.92 (m, 4H); 3.38 (m, 2H); 5.92 (s, 4H); 6.45 (d, 1H); 7.0 (d, 2H); 7.16 (txd, 1H); 7.43 (s, 1H);7.57 (m, 2H); 7.81 (m, 1H); 8.31 (s, 1H); 8.48 (d, 2H); 10.22 (s, 1H).

Example 16 (Compound No. 14)

N-[6-(pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-trifluoromethyl-1*H*-indole-2-carboxamide

16.1 5-Trifluoromethyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylic acid

The process is carried out according to the method described in example 15.1, using ethyl 5-trifluoromethyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylate (WO 07/010144). The product obtained is used as it is in the rest of the synthesis.

16.2 *N*-[6-Chloropyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-trifluoromethyl-1*H*-indole-2-carboxamide

The process is carried out according to the method described in example 3.1, using 0.5 g (1.56 mmol) of 5-trifluoromethyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylic acid, prepared in step 16.1, and 0.22 g (1.72 mmol) of 2-chloro-5-aminopyridine. 0.5 g of the expected product is isolated by this method, which product is used as it is in the rest of the synthesis.

16.3 *N*-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-trifluoromethyl-1*H*-indole-2-carboxamide (compound no. 14)

The process is carried out according to the method described in example 4, using 0.5 g (1.16 mmol) of *N*-[6-chloropyridin-3-yl]-1-[(pyridin-4-yl)methyl]-5-trifluoromethyl-1*H*-indole-2-carboxamide, obtained in step 16.2, and 2.91 ml (34.82 mmol) of pyrrolidine. The mixture is placed in a pressurized tube which is heated for 50 minutes at 170°C under 200 watts, by means of a microwave oven. The mixture is subsequently concentrated under reduced pressure, and taken up with 100 ml of ethyl acetate. The organic phase is subsequently washed twice with 30 ml of water and then once with a saturated sodium chloride solution, dried over magnesium sulphate, and then concentrated under reduced pressure. The product obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and methanol. 0.24 g of the expected product is thus isolated.

Melting point: 248 – 250°C

^{1}H NMR (DMSO D_6), δ (ppm): 1.95 (m, 4H); 3.41 (m, 4H); 5.98 (s, 2H); 6.45 (d, 1H); 7.03 (d, 2H); 7.59 (m, 2H); 7.73 (d, 1H);7.81 (d, 1H); 8.19 (s, 1H); 8.32 (s, 1H); 8.49 (d, 2H).

Example 17 (Compound No 22)

N-[6-(3-Azabicyclo[3.2.0]hept-3-yl)pyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide

A mixture of 0.2 g (0.5 mmol) of *N*-[6-chloropyridin-3-yl]-5-fluoro-1-(3-fluorobenzyl)-1*H*-indole-2-carboxamide, prepared in step 3.1, of 0.0806 g (0.6 mmol) of 3-azabicyclo[3.2.0]heptane (*J.Med.Chem.* 1967, 10(4), 621) and of 0.0564 g (1.01 mmol) of potassium hydroxide in 0.5 ml of N-methylpyrrolidinone is heated for 90 minutes in a microwave oven regulated at 150°C under 150 watts. The reaction mixture is subsequently poured into 20 ml of water. The mixture is extracted with three times 30 ml of ethyl acetate. The combined organic phases are washed with 30 ml of water, dried over sodium sulphate, and then concentrated under reduced pressure. The resulting solid is subsequently purified by silica column chromatography, elution being carried out with a mixture of n-heptane and ethyl acetate. 35 mg of the expected product are thus isolated.

Melting point: 163 – 165°C

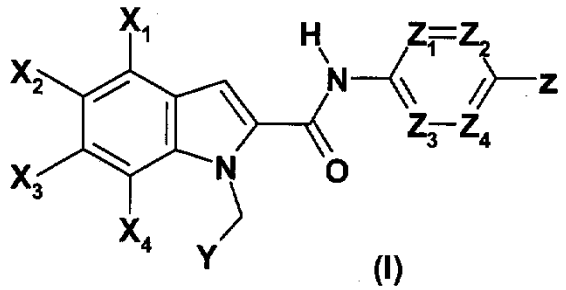
^{1}H NMR (DMSO D_6), δ (ppm): 1.71 (m, 2H); 2.23 (m, 2H); 3.02 (m, 2H); 3.2 (m, 2H); 3.63 (d, 2H); 5.9 (s, 2H); 6.62 (d, 1H); 6.91 (m, 2H); 7.05 (txd, 1H); 7.16 (txd, 1H); 7.33 (m,1H); 7.4 (s, 1H); 7.54 (dxd, 1H); 7.6 (m, 1H); 7.88 (dxd, 1H); 8.4 (s, 1H); 10.3 (s, 1H).

Table 2 which follows illustrates the chemical structures and the physical properties of some compounds of formula (I) according to the invention.

In this table:

- the "Mp" column gives the melting points of the products in degrees Celsius (°C);
- in the "salt/base" column, "-" represents a compound in the form of a free base, whereas "HCl" represents a compound in hydrochloride form and the ratio between parentheses is the (acid:base) ratio;
- "t-Bu" corresponds to a tert-butyl group, "iPr" to an isopropyl group, "et" to an ethyl group.

Table 2



(I)

No.	X_1, X_2, X_3, X_4	Y	Z_1, Z_2, Z_3, Z_4	Z	Salt / base	Mp (°C)
1	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	(*R*)-N-(3-tert-butoxy carbonylamino) pyrrolidinyl	-	207 - 209
2	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	pyrrolidinyl	-	199 - 201
3	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	(*R*)-3-amino-pyrrolidinyl	-	192 - 194
4	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	227 - 228
5	H, CF_3, H, H	3-fluorophenyl	CH, CH, CH, N	pyrrolidinyl	-	185 - 186
6	H, F, H, H	3-fluorophenyl	C-CH_3, CH, CH, N	pyrrolidinyl	-	176 - 178
7	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	3-hydroxypyrrolidinyl	-	229 - 230
8	H, F, H, H	3-fluorophenyl	CH, C-OCH_3, CH, N	pyrrolidinyl	-	172 - 174
9	H, H, CF_3, H	Pyridin-4-yl	CH, CH, CH, N	pyrrolidinyl	-	261 - 262
10	H, F, H, H	Pyridin-4-yl	C-CH_3, CH, CH, N	pyrrolidinyl	-	115 - 120
11	H, F, H, H	Pyridin-4-yl	CH, C-OCH_3, CH, N	pyrrolidinyl	-	213 - 215
12	H, F, H, H	3-(pyrrolidin-1yl)phenyl	CH, CH, CH, N	pyrrolidinyl	-	225 - 227
13	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	piperidinyl	-	190 - 192
14	H, CF_3, H, H	Pyridin-4-yl	CH, CH, CH, N	pyrrolidinyl	-	248 - 250

No.	X_1, X_2, X_3, X_4	Y	Z_1, Z_2, Z_3, Z_4	Z	Salt / base	Mp (°C)
15	H, F, H, H	6-methylpyridin-2-yl	CH, CH, CH, N	pyrrolidinyl	-	241 - 243
16	H, F, H, H	3-fluorophenyl	C-OCH_3, CH, CH, N	pyrrolidinyl	-	196 - 198
17	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	morpholinyl	HCl (1:1)	246 - 250
18	H, F, H, H	Pyridin-4-yl	C-OCH_3, CH, CH, N	pyrrolidinyl	-	225 - 226
19	H, F, H, H	2-methylpyridin-4-yl	CH, CH, CH, N	pyrrolidinyl	-	213 - 215
20	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	1-oxypyrrolidinyl	-	140 - 143
21	H, F, H, H	3-fluorophenyl	CH, N, CH, N	pyrrolidinyl	-	220 - 222
22	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	3-azabicyclo[3.2.0]heptyl	-	163 - 165
23	H, F, H, H	Pyridin-4-yl	CH, CH, CH, N	pyrrolidinyl	-	255 - 257
24	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	3-hydroxy-azetidinyl	-	199 - 200
25	H, CF_3, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	222 - 224
26	H, F, H, H	Pyridin-4-yl	CH, CH, CH, N	azetidinyl	-	212 - 214
27	H, F, H, H	3-fluorophenyl	CH, CH, C-CH_3, N	pyrrolidinyl	-	213 - 214
28	H, F, H, H	3-fluorophenyl	CH, CH, CH, N	3-azabicyclo[3.1.0]hexyl	-	193 - 195
29	H, CF_3, H, H	3-fluorophenyl	CH, CH, CH, N	3-hydroxy-azetidinyl	-	194 - 196
30	H, H, CF_3, H	3-fluorophenyl	CH, CH, CH, N	3-hydroxy-azetidinyl	-	253 - 255
31	H, F, H, H	phenyl	CH, CH, CH, N	azetidinyl	-	208 - 210
32	CH_3, H, CH_3, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	234 - 236
33	H, H, t-Bu, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	204 - 206
34	H, H, O-iPr, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	198 - 200
35	H, SO_2CH_3, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	258 - 260
36	H, H, $N(CH_3)_2$, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	256 - 258
37	H, H, SCH_3, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	206 - 208
38	F, H, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	214 - 216
39	H, H, H, F	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	244 - 246
40	H, H, F, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	210 - 212

No.	X_1, X_2, X_3, X_4	Y	Z_1, Z_2, Z_3, Z_4	Z	Salt / base	Mp (°C)
41	Cl, H, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	226 - 228
42	H, H, Cl, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	218 - 220
43	H, Cl, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	226 - 228
44	H, H, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	328 - 330
45	CH_3, H, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	246 - 248
46	H, H, CH_3, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	228 - 230
47	H, CH_3, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	236 - 238
48	H, iPr, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	204 - 206
49	H, t-Bu, H, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	212 - 214
50	H, H, Et, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	196 - 198
51	H, H, iPr, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	184 - 186
52	H, H, CF_3, H	3-fluorophenyl	CH, CH, CH, N	azetidinyl	-	220 - 222
53	H, F, H, H	3-fluorophenyl	C-CF_3, CH, CH, N	pyrrolidinyl	-	170 - 171

The NMR data of certain compounds of the table are subsequently described, by way of examples.

Compound no. 25:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 3.92 (t, 4H); 5.92 (s, 2H); 6.4 (d, 1H); 6.94 (m, 2H); 7.09 (txd, 1H); 7.37 (m, 1H);7.57 (m, 2H); 7.79 (d, 1H); 7.87 (dxd, 1H); 8.2 (s, 1H); 8.36 (d, 2H); 10.41 (s, 1H).

Compound no. 26:

^{1}H NMR (DMSO D_6), δ (ppm): 2.32 (m, 2H); 3.92 (t, 4H); 5.91 (s, 2H); 6.38 (d, 1H); 6.99 (d, 2H); 7.15 (txd, 1H); 7.41 (s, 1H);7.57 (m, 2H); 7.81 (m, 1H); 8.43 (m, 1H); 8.46 (d, 2H); 10.4 (s, 1H).

Compound no. 35:

^{1}H NMR (DMSO D_6), δ (ppm): 2.32 (m, 2H); 3.21 (s, 3H); 3.92 (t, 4H); 5.98 (s, 2H); 6.4 (d, 1H); 6.92 (d, 2H); 7.09 (txd, 1H); 7.35 (m, 1H); 7.6 (s, 1H); 7.81 (m, 3H); 8.39 (m, 2H); 10.42 (s, 1H).

Compound no. 38:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 3.92 (t, 4H); 5.92 (s, 2H); 6.4 (d, 1H); 6.93 (m, 3H); 7.08 (txd, 1H); 7.31 (m, 2H); 7.41 (m, 1H); 7.61 (s, 1H); 7.86 (dxd, 1H); 8.38 (s, 1H); 10.3 (s, 1H).

Compound no. 40:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 3.90 (t, 4H); 5.89 (s, 2H); 6.4 (d, 1H); 6.91 (m, 2H); 7.06 (m, 2H); 7.33 (m, 1H);7.41 (s, 1H); 7.47 (dxd, 1H); 7.78 (m, 1H); 7.86 (m, 1H); 8.35 (s, 1H); 10.23 (s, 1H).

Compound no. 45:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 2.56 (s, 3H); 3.91 (t, 4H); 5.9 (s, 2H); 6.4 (d, 1H); 6.91 (m, 3H); 7.04 (txd, 1H); 7.18 (m, 1H); 7.31 (m, 2H); 7.49 (s, 1H); 7.88 (m, 1H); 8.38 (s, 1H); 10.25 (s, 1H).

Compound no. 46:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 2.41 (s, 3H); 3.91 (t, 4H); 5.85 (s, 2H); 6.4 (d, 1H); 6.82-7.09 (m, 4H); 7.35 (m, 3H); 7.61 (d, 1H); 7.83 (dxd, 1H); 8.36 (s, 1H); 10.21 (s, 1H).

Compound no. 47:

^{1}H NMR (DMSO D_6), δ (ppm): 2.29 (m, 2H); 2.4 (s, 3H); 3.91 (t, 4H); 5.89 (s, 2H); 6.39 (d, 1H); 6.82-6.91 (m, 2H); 7.02 (txd, 1H); 7.12 (dxd, 1H); 7.31 (m, 2H); 7.41 (d, 1H); 7.51 (s, 1H); 7.87 (dxd, 1H); 8.34 (s, 1H); 10.23 (s, 1H).

Compound no. 49:

^{1}H NMR (DMSO D_6), δ (ppm): 1.32 (s, 9H); 2.3 (m, 2H); 3.91 (t, 4H); 5.85 (s, 2H); 6.38 (d, 1H); 6.92 (m, 2H); 7.03 (txd, 1H); 7.35 (m, 4H); 7.66 (s, 1H); 7.85 (dxd, 1H); 8.43 (s, 1H); 10.19 (s, 1H).

Compound no. 52:

^{1}H NMR (DMSO D_6), δ (ppm): 2.31 (m, 2H); 3.91 (t, 4H); 6 (s. 2H); 6.39 (d. 1H); 6.91 (m, 2H); 7.07 (txd, 1H); 7.32 (m, 1H); 7.45 (d, 1H); 7.49 (s, 1H); 7.82 (dxd, 1H); 7.92 (d, 1H); 8.02 (s, 1H); 8.34 (s, 1H); 10.41 (s, 1H).

The compounds of the invention were subjected to *in vitro* and *in vivo* pharmacological assays which demonstrated their advantage as substances with therapeutic activities.

The compounds of the invention also have characteristics of water-solubility which provides good activity *in vivo*.

Test for inhibition of the current induced by capsaicin on rat DRGs

- Primary culture of rat dorsal root ganglion (DRG) cells:

The neurons of the DRG naturally express the TRPV1 receptor.

Newborn rat DRG primary cultures are prepared from one-day-old rat pups. Briefly, after dissection, the ganglia are trypsinized and the cells are mechanically dissociated by controlled trituration. The cells are resuspended in an Eagle's basal culture medium containing 10% of foetal calf serum, 25 mM KCl, 2 mM glutamine, 100 µg/ml gentamycin and 50 ng/ml of NGF, and then deposited onto laminin-coated glass cover slips (0.25 x 10^6 cells per cover slip) which are then placed in 12-well Corning dishes. The cells are incubated at 37°C in a humidified atmosphere containing 5% CO_2 and 95% air. Cytosine β-D-arabinoside (1 µM) is added 48 h after placing in culture, in order to prevent the development of non-neuronal cells. The cover slips are transferred into the experimental chambers for the patch-clamp studies after 7-10 days of culture.

- Electrophysiology:

The measuring chambers (volume 800 µl) containing the cell preparation are placed on the platform of an inverted microscope (Olympus IMT2) equipped with Hoffman optics (Modulation Contrast, New York) and observed at the magnification of X400. The chambers are continually perfused by gravity (2.5 ml/min) by means of a solution distributing device with 8 inlets, and the sole outlet of which, consisting of a polyethylene tube (500 µm aperture), is placed at least 3 mm from the cell studied. The "whole cell" configuration of the patch-clamp technique was used. The borosilicate glass pipettes (resistance 5-10 MOhms) are moved close to the cell by means of a 3D piezoelectric micromanipulator (Burleigh, PC1000). The overall currents (membrane potential fixed at – 60 mV) are recorded with an Axopatch 1D amplifier (Axon Instruments, Foster city, California), connected to a PC control by Pclamp8 software (Axon Instrument). The current traces are recorded on paper and simultaneously digitized (sampling frequency

15 to 25 Hz) and acquired on the hard drive of the PC.

The application of a micromolar solution of capsaicin causes, on the DRG cells (voltage fixed at –70 mV), an inward cationic current. In order to minimize the desensitization of the receptors, a minimum period of one minute is observed between two applications of capsaicin. After a controlled period (stabilization of the capsaicin response alone), the compounds to be tested are applied alone at a given concentration (concentration of 10 nM or of 0.1 nM) for a period of 4 to 5 minutes, during which several capsaicin + compound tests are carried out (obtaining of maximum inhibition). The results are expressed as % inhibition of the control capsaicin response.

The percentages of inhibition of the capsaicin response (1 microM) are between 20% and 100% for the most active compounds of the invention tested at concentrations of 10 nM to 0.1 nM (see examples in table 3).

The compounds of the invention are therefore effective antagonists, in vitro, of TRPV1-type receptors.

Table 3

Compound no.	% inhibition in DRG patch
2	46% (1 nM)
4	89% (1 nM)
7	85% (10 nM)
21	79% (10 nM)

Mouse corneal irritation test

The irritant nature of capsaicin can be readily assessed at the level of the cornea since this organ is one of the most innervated by C fibres. In this context, according to preliminary experiments, the application of a very small amount of capsaicin (2 µl at a concentration of 160 µM) to the surface of the cornea of an animal results in a certain number of stereotyped behaviours associated with the irritation and that can be readily listed. Among these are: blinking of the eye, rubbing of the instilled eye with the ipsilateral forelimb, rubbing of the face with both forelimbs, scratching of the ipsilateral face with the hind limb. The duration of these behaviours does not exceed the 2 minutes of observation and the animal then returns to its normal activity. Its appearance is, moreover, also normal. The mouse is not hidden away in a corner with its coat bristling and does not develop any observable signs of suffering. It can be concluded from this that the duration of action of capsaicin at these doses is less than 2 minutes.

Summary of the methodology:

The principle of the series of experiments is to determine whether the compounds of the invention can influence the behavioural response induced via a given amount of capsaicin. The capsaicin is initially diluted to 25 mM in DMSO and diluted, for its final use, in physiological saline with 10% Tween 80. It appears, based on control studies, that, under these conditions, the solvent has no effect.

In practice, the product to be tested, prepared at 25 mM in DMSO and diluted for its final use in physiological serum with 10% Tween 80, at the highest concentration of 500 µM, is administered by local application to the surface of the cornea in a volume of 2 µl, 10 minutes before the application of the capsaicin. The animal receives the ocular instillation of 2 µl of a solution of capsaicin at 160 µM prepared as indicated above. Over the course of a period of observation of 2 minutes following the instillation, the number of times the instilled eye is rubbed by the ipsilateral forelimb is counted for each animal.

For each given group, the percentage protection is calculated as follows:

P= 100 – ((average number of scratches of the group treated with the compound / average number of scratches of the group treated with the solvent) x 100)

This percentage protection is averaged for each group of animals (n = number of animals tested with the compound of the invention).

The protection percentages evaluated, in this model, for the most active compounds of the invention, used at the concentration of 500 µM, are between 20% and 100% (see example in table 4):

Table 4

Compound no.	% P 500 µM
2	72%

The results of these assays show that the most active compounds of the invention block the effects induced by the stimulation of the TRPV1 receptors.

The compounds of the invention can therefore be used for the preparation of medicaments, in particular for the preparation of a medicament for preventing or treating pathologies in which TRPV1-type receptors are involved.

Thus, according to another of its aspects, a subject of the invention is medicaments which comprise a compound of formula (I), or a pharmaceutically acceptable salt, or else a hydrate or a solvate of said compound.

These medicaments can be used in therapeutics, in particular in the prevention and/or treatment of pain and inflammation, chronic pain, neuropathic pain (trauma-related, diabetic, metabolic, infection-related or toxic pain, or pain induced by an anticancer or iatrogenic treatment), (osteo-)arthritic pain, rheumatic pain, fibromyalgia, back pain, cancer-related pain, facial neuralgia, headaches, migraine, dental pain, burns, sunburn, animal bites or insect bites, post-herpetic neuralgia, muscle pain, trapped nerves (central and/or peripheral), spinal column and/or brain trauma, ischaemia (of the spinal column and/or of the brain), neurodegeneration, haemorrhagic strokes (of the spinal column and/or of the brain) and post-stroke pain.

The compounds of the invention can also be used for the preparation of a medicament for preventing and/or treating urological disorders such as bladder hyperactivity, bladder hyperreflexia, bladder instability, incontinence, urgent urination, urinary incontinence, cystitis, nephritic colic, pelvic hypersensitivity and pelvic pain.

The compounds of the invention can be used for the preparation of a medicament for preventing and/or treating gynaecological disorders such as vulvodynia, pain associated with salpingitis or with dysmenorrhoea.

These products can also be used for the preparation of a medicament for preventing and/or treating gastrointestinal disorders such as gastro-oesophageal reflex disorder, stomach ulcers, duodenal ulcers, functional dyspepsia, colitis, IBS, Crohn's disease, pancreatitis, oesophagitis or biliary colic.

The compounds of the invention can also be used for the preparation of a medicament for treating diabetes.

Similarly, the products of the present invention can be used in the prevention and/or treatment of respiratory disorders such as asthma, coughing, chronic obstructive pulmonary disease (COPD), bronchoconstriction and inflammatory disorders. These products can also be used for preventing and/or treating psoriasis, pruritis, dermal, ocular or mucosal irritations, herpes and shingles.

The compounds of the invention can also be used for the preparation of a medicament for treating depression.

According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a compound according to the invention. These pharmaceutical compositions contain an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate of said compound, and also at least one pharmaceutically acceptable excipient.

Said excipients are selected according to the pharmaceutical form and the method of administration desired, from the usual excipients known to those skilled in the art.

In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, local, intratracheal, intranasal, transdermal or rectal administration, the active ingredient of formula (I) above, or its optional salt, solvate or hydrate, can be administered in unit administration form, as a mixture with conventional pharmaceutical excipients, to animals and to human beings for the prophylaxis or the treatment of the disorders or diseases mentioned above.

The appropriate unit administration forms include oral forms such as tablets, soft or hard gelatine capsules, powders, granules and oral solutions or suspensions, sublingual, buccal, intratracheal, intraocular and intranasal administration forms, forms for administration by inhalation, topical, transdermal, subcutaneous, intramuscular or intravenous administration forms, rectal administration forms, and implants. For topical application, the compounds according to the invention can be used in creams, gels, ointments or lotions.

By way of example, a unit administration form of a compound according to the invention in tablet form may comprise the following components:

Compound according to the invention	50.0 mg
Mannitol	223.75 mg
Sodium croscaramellose	6.0 mg
Maize starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

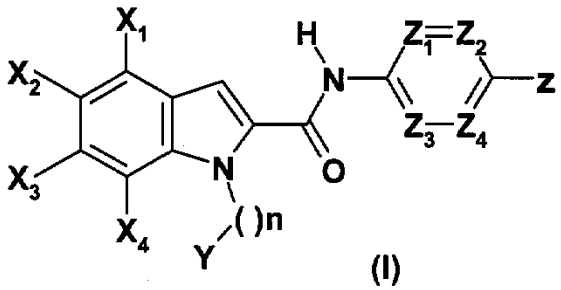
Said unit forms are dosed so as to allow a daily administration of from 0.001 to 30 mg of active ingredient per kg of body weight, according to the galenic form.

There may be specific cases where higher or lower dosages are appropriate: such dosages do not depart from the scope of the invention. According to the usual practice, the dosage appropriate for each patient is determined by the physician according to the method of administration and the weight and response of said patient.

According to another of its aspects, the present invention also relates to a method for treating the pathologies indicated above, which comprises the administration, to a patient, of an effective dose of at least one compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate thereof.

CLAIMS

1. Compound corresponding to formula (I)



(I)

in which

X_1 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, cyano, $C(O)NR_1R_2$, nitro, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

X_2 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

X_3 and X_4 are, independently of one another, a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, nitro, NR_1R_2, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, NR_3COR_4, $NR_3SO_2R_5$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, at least one corresponding to a nitrogen atom and at least one corresponding to a $C(R_6)$ group; the nitrogen atom or one of the nitrogen atoms present in the ring,

defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group;

n is equal to 0, 1, 2 or 3;

Y is an aryl or a heteroaryl optionally substituted with one or more groups selected from a halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, hydroxyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, cyano, $C(O)NR_1R_2$, nitro, NR_1R_2, C_1-C_6-thioalkyl, thiol, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, $SO_2NR_1R_2$, NR_3COR_4, $NR_3SO_2R_5$, aryl-C_1-C_6-alkylene or aryl group, the aryl and the aryl-C_1-C_6-alkylene being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

Z is a cyclic amine attached via the nitrogen atom, of formula:



in which A is a C_1-C_7-alkylene group optionally substituted with one or two groups R_8;

B is a C_1-C_7-alkylene group optionally substituted with one or two groups R_9;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with a group R_{10} or R_{11},

the carbon atoms of the cyclic amine Z being optionally substituted with one or more groups R_{12} which may be identical to or different from one another;

R_1 and R_2 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group; or R_1 and R_2 form, together with the nitrogen atom which bears them, an azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiomorpholinyl, piperazinyl or homopiperazinyl group, this group being optionally substituted with a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_3 and R_4 are, independently of one another, a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_5 is a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;

R_6 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-

C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, C_1-C_6-thioalkyl, -S(O)-C_1-C_6-alkyl, -$S(O)_2$-C_1-C_6-alkyl, aryl, aryl-C_1-C_6-alkylene, heteroaryl, hydroxyl, thiol, oxo or thio group;

R_7 is a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, aryl, aryl-C_1-C_6-alkylene or heteroaryl group;

R_8, R_9 and R_{10} are defined such that:

two groups R_8 can together form a bond or a C_1-C_6-alkylene group;

two groups R_9 can together form a bond or a C_1-C_6-alkylene group;

R_8 and R_9 can together form a bond or a C_1-C_6-alkylene group;

R_8 and R_{10} can together form a bond or a C_1-C_6-alkylene group;

R_9 and R_{10} can together form a bond or a C_1-C_6-alkylene group;

R_{11} is a hydrogen atom or a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, hydroxyl, $COOR_5$, $C(O)NR_1R_2$, aryl-C_1-C_6-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

R_{12} is a fluorine atom, a C_1-C_6-alkyl group optionally substituted with a group R_{13}, a C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl or C_1-C_6-cycloalk-1,1-diyl group, a C_3-C_7-heterocycloalk-1,1-diyl group optionally substituted on a nitrogen atom with a group R_{11}, or a C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, C_1-C_6-fluoroalkoxyl, $C(O)NR_1R_2$, NR_1R_2, NR_3COR_4, $OC(O)NR_1R_2$, NR_3COOR_5, $NR_3CONR_1R_2$, hydroxyl, thiol, oxo, thio, aryl-C_1-C_6-alkylene or aryl group, the aryl being optionally substituted with one or more substituents selected from a halogen, and a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_1-C_6-fluoroalkoxyl, nitro or cyano group;

R_{13} is a C_1-C_6-alkoxyl, C_3-C_7-cycloalkoxyl, C_3-C_7-cycloalkyl-C_1-C_6-alkylene-O-, $C(O)NR_1R_2$, NR_1R_2, NR_3COR_4, $OC(O)NR_1R_2$, NR_3COOR_5 or hydroxyl;

it being possible for the nitrogen atom(s) of the compound of formula (I) to be in oxidized form;

it being possible for the sulphur atom(s) of the compound of formula (I) to be in oxidized form;

in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

2. Compound of formula (I) according to Claim 1, characterized in that X_1, X_2, X_3 and X_4 are selected, independently of one another, from a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl, C_1-C_6-thioalkyl or -$S(O)_2$-C_1-C_6-alkyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

3. Compound of formula (I) according to Claim 1, characterized in that
X_1 is a hydrogen or halogen atom or a C_1-C_6-alkyl group;
X_2 is a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl or -$S(O)_2$-C_1-C_6-alkyl group;
X_3 and X_4 are, independently of one another, a hydrogen or halogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl, C_1-C_6-alkoxyl, NR_1R_2 or C_1-C_6-thioalkyl group;
R_1 and R_2 are, independently of one another, a C_1-C_6-alkyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

4. Compound of formula (I) according to any one of Claims 1 to 3, characterized in that Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, at least two of them corresponding to a $C(R_6)$ group; the nitrogen atom or one of the nitrogen atoms present in the ring, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I) according to Claim 1;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

5. Compound of formula (I) according to Claim 4, characterized in that Z_1 and Z_3 are a $C(R_6)$ group and Z_2 and Z_4 are a nitrogen atom; R_6 corresponding to a hydrogen atom; in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

6. Compound of formula (I) according to Claim 4, characterized in that Z_1, Z_2, Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $C(R_6)$ group; the nitrogen atom present in the cycle, defined as nitrogen in the 1-position, being optionally substituted with R_7 when the carbon atom in the 2- or 4-position with respect to this reference

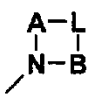
nitrogen is substituted with an oxo or thio group; R_6 and R_7 being as defined in formula (I) according to Claim 1;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

7. Compound of formula (I) according to Claim 6, characterized in that
Z_4 is a nitrogen atom and Z_1, Z_2 and Z_3 are, independently of one another, a $C(R_6)$ group;
R_6 is a hydrogen atom or a C_1-C_6-alkyl, C_1-C_6-fluoroalkyl or C_1-C_6-alkoxyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

8. Compound of formula (I) according to any one of Claims 1 to 7, characterized in that n is equal to 1;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

9. Compound of formula (I) according to any one of Claims 1 to 8, characterized in that Y is an aryl or a heteroaryl optionally substituted with one or more groups selected from a halogen atom or a C_1-C_6-alkyl or NR_1R_2 group;
R_1 and R_2 form, together with the nitrogen atom which bears them, an azetidinyl, pyrrolidinyl, piperidinyl, azepinyl, morpholinyl, thiomorpholinyl, piperazinyl or homopiperazinyl group, this group being optionally substituted with a C_1-C_6-alkyl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkyl-C_1-C_3-alkylene, aryl-C_1-C_6-alkylene, aryl or heteroaryl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

10. Compound of formula (I) according to any one of Claims 1 to 9, characterized in that Z is a cyclic amine attached via the nitrogen atom, of formula:



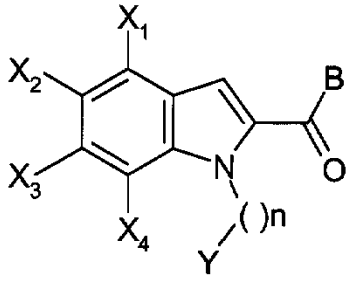
in which A is a C_1-C_4-alkylene group optionally substituted with one or two groups R_8;
B is a C_1-C_4-alkylene group optionally substituted with one or two groups R_9;
L is a bond or an oxygen atom;
it being possible for the nitrogen atom of the cyclic amine Z to be in N-oxide form;

the carbon atoms of the cyclic amine Z being optionally substituted with a group R_{12};
R_8 and R_9 are defined such that:
two groups R_8 can together form a bond; or
two groups R_9 can together form a bond; or
R_8 and R_9 can together form a bond;
R_{12} is an NR_1R_2, NR_3COOR_5 or hydroxyl group;
R_1 and R_2 are, independently of one another, a hydrogen atom;
R_3 is a hydrogen atom;
R_5 is a C_1-C_6-alkyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

11. Compound of formula (I) according to Claim 10, characterized in that
Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;
it being possible for the nitrogen atom of the cyclic amine Z to be in N-oxide form;
the carbon atoms of the cyclic amine Z being optionally substituted with a group R_{12};
R_{12} is an NR_1R_2, NR_3COOR_5 or hydroxyl group;
R_1 and R_2 are, independently of one another, a hydrogen atom;
R_3 is a hydrogen atom;
R_5 is a C_1-C_6-alkyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

12. Compound of formula (I) according to Claim 11, characterized in that
Z is a cyclic amine selected from azetidine, pyrrolidine, piperidine, morpholine, azabicylo[3.1.0]hexane and azabicylo[3.2.0]heptane;
the carbon atoms of the azetidine being optionally substituted with a hydroxyl group;
the carbon atoms of the pyrrolidine being optionally substituted with an NR_1R_2, NR_3COOR_5 or hydroxyl group; it being possible for the nitrogen atom of the pyrrolidine to be in N-oxide form;
R_1 and R_2 are, independently of one another, a hydrogen atom;
R_3 is a hydrogen atom;
R_5 is a C_1-C_6-alkyl group;
in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

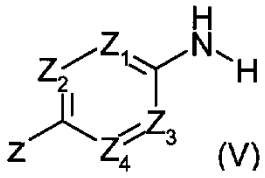
13. Process for preparing a compound of formula (I) according to any one of Claims 1 to 12, characterized in that a compound of formula (IV)



(IV)

in which X_1, X_2, X_3, X_4, Y and n are as defined in formula (I) according to Claim 1 and B is a chlorine atom,

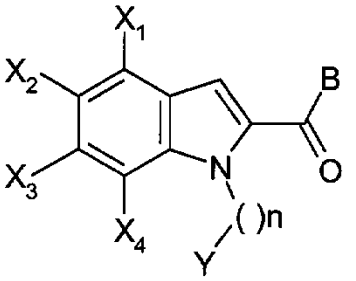
is reacted with an amine of formula (V)



(V)

in which Z_1, Z_2, Z_3, Z_4 and Z are as defined in formula (I) according to Claim 1, in a solvent.

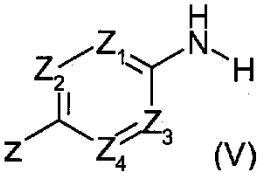
14. Process for preparing a compound of formula (I) according to any one of Claims 1 to 12, characterized in that a compound of formula (IV)



(IV)

in which X_1, X_2, X_3, X_4, Y and n are as defined in formula (I) according to Claim 1 and B is a hydroxyl group,

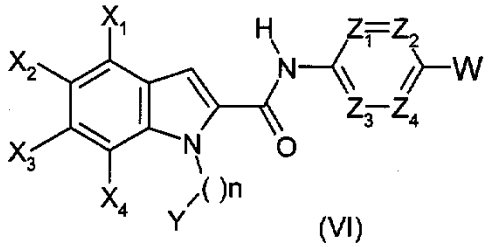
is reacted with an amine of formula (V)



(V)

in which Z_1, Z_2, Z_3, Z_4 and Z are as defined in formula (I) according to Claim 1, in the presence of a coupling agent and of a base in a solvent.

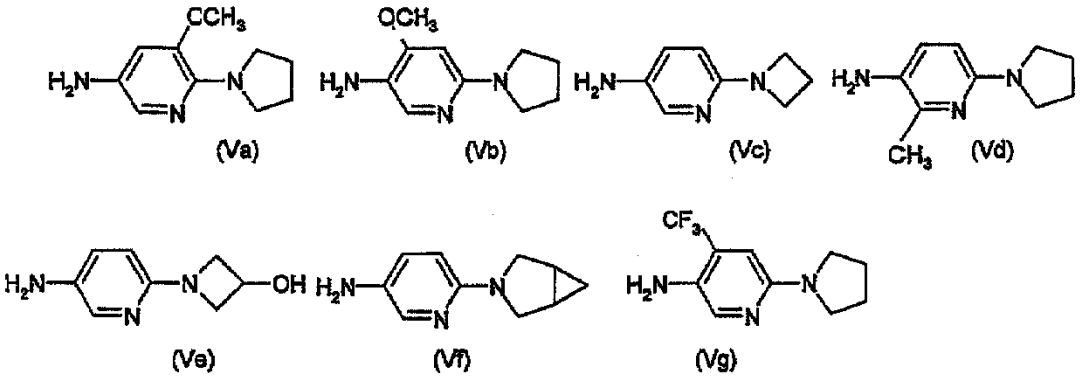
15. Process for preparing a compound of formula (I) according to any one of Claims 1 to 12, characterized in that a compound of formula (VI)



(VI)

in which X_1, X_2, X_3, X_4, Z_1, Z_2, Z_3, Z_4, Y and n are as defined in formula (I) according to Claim 1 and W is a halogen atom, is reacted in the presence of an amine of formula ZH in which Z is a cyclic amine as defined in formula (I) according to Claim 1.

16. Amine of formula (V) selected from the following amines:



(Va) (Vb) (Vc) (Vd)

(Ve) (Vf) (Vg)

in the form of a base or of an addition salt with an acid.

17. Medicament, characterized in that it comprises a compound of formula (I) according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt, or else a hydrate or a solvate of the compound of formula (I).

18. Pharmaceutical composition, characterized in that it comprises a compound of formula (I) according to any one of Claims 1 to 12, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also at least one pharmaceutically acceptable excipient.

19. Use of a compound of formula (I) according to any one of Claims 1 to 12, for the preparation of a medicament for preventing or treating pathologies in which TRPV1-type receptors are involved.

20. Use of a compound of formula (I) according to any one of Claims 1 to 12, for the preparation of a medicament for preventing or treating pain, inflammation, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritis, dermal, ocular or mucosal irritations, herpes or shingles, or for treating depression or diabetes.