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Derivatives of indole 2-carboxamides and azaindole 2-carboxamides substituted by a silanyle group, preparation thereof and therapeutic use thereof

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(71) Applicant(s)
SANOFI-AVENTIS

(72) Inventor(s)
Malanda, Andre;Evanno, Yannick;Dubois, Laurent

(74) Agent / Attorney
A J PARK, L 11 60 Marcus Clarke St, Canberra, ACT, 2601

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(71) Déposant (pour tous les États désignés sauf US) :
SANOFI-AVENTIS [FR/FR]; 174, avenue de France,
F-75013 Paris (FR).

(72) Inventeurs; et

(75) Inventeurs/Déposants (pour US seulement) : DUBOIS,
Laurent [FR/FR]; c/o Sanofi-Aventis, Département
Brevets, 174, avenue de France, F-75013 Paris (FR).

EVANNO, Yannick [FR/FR]; c/o Sanofi-Aventis,
Département Brevets, 174, avenue de France, F-75013
Paris (FR). MALANDA, André [FR/FR]; c/o Sanofi-
Aventis, Département Brevets, 174, avenue de France,
F-75013 Paris (FR).

(74) Mandataire : MOREL-PECHEUX, Muriel; Sanofi-
Aventis, Département Brevets, 174, avenue de France,
F-75013 Paris (FR).

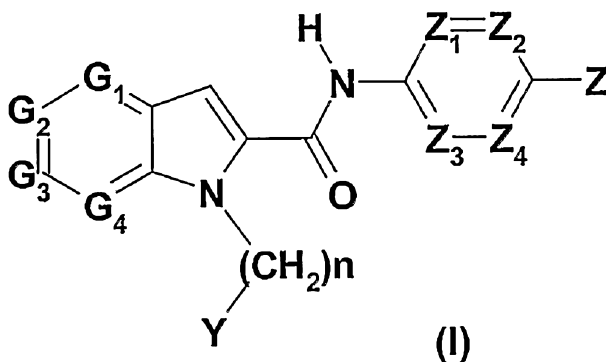
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[Suite sur la page suivante]

(54) Title : DERIVATIVES OF INDOLE 2-CARBOXAMIDES AND AZAINDOLE 2-CARBOXAMIDES SUBSTITUTED BY A SILANYLE GROUP, PREPARATION THEREOF AND THERAPEUTIC USE THEREOF

(54) Titre : DERIVES D'INDOLE 2-CARBOXAMIDES ET D'AZAINDOLE 2-CARBOXAMIDES SUBSTITUES PAR UN GROUPE SILANYLE, LEUR PREPARATION ET LEUR APPLICATION EN THERAPEUTIQUE



(57) Abstract : The invention relates to compounds of the general formula (I) in which: G₁, G₂, G₃ et G₄ are independent from one another, a C-X group or a nitrogen atom; one of G₁, G₂, G₃ and G₄ and at most one of G₁, G₂, G₃ and G₄ is a C-X group In which X is a -Si(X₁)(X₂)(X₃) group; n is 0, 1, 2 or 3; Y is an optionally substituted aryl or heteroaryl; Z₁, Z₂, Z₃, Z₄ are independent from one another, a nitrogen atom or a C(R₆) group, at least one being a nitrogen atom and at least one being a C(R₆) group; Z is cyclic amino or acyclic amino; said compounds can be in the state of a base or an addition salt to an acid, as well as in the hydrate or solvate state. The invention also relates to a method for preparing the same and to the therapeutic use thereof.

(57) Abrégé :

[Suite sur la page suivante]

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L'invention concerne les composés de formule générale (I) dans laquelle G_1 , G_2 , G_3 et G_4 représentent, indépendamment l'un de l'autre, un groupe C-X ou un atome d'azote; l'un des G_1 , G_2 , G_3 et G_4 et au maximum l'un des G_1 , G_2 , G_3 et G_4 représente un groupe C-X où X est un groupe $-\text{Si}(\text{X}_1)(\text{X}_2)(\text{X}_3)$; n est égal à 0, 1, 2 ou 3; Y représente un aryle ou un hétéroaryle éventuellement substitué; Z1, Z2, Z3, Z4 représentent, indépendamment l'un de l'autre, un atome d'azote ou un groupe $\text{C}(\text{R}_6)$, l'un au moins correspondant à un atome d'azote et l'un au moins correspondant à un groupe $\text{C}(\text{R}_6)$; Z représente soit un aminé cyclique, soit un aminé acyclique; à l'état de base ou de sel d'addition à un acide, ainsi qu'à l'état d'hydrate ou de solvate. Procédé de préparation et application en thérapeutique.

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DERIVATIVES OF INDOLE-2-CARBOXAMIDES AND AZAINDOLE-2-CARBOXAMIDES
SUBSTITUTED BY A SILANYL GROUP, PREPARATION THEREOF AND
THERAPEUTIC USE THEREOF

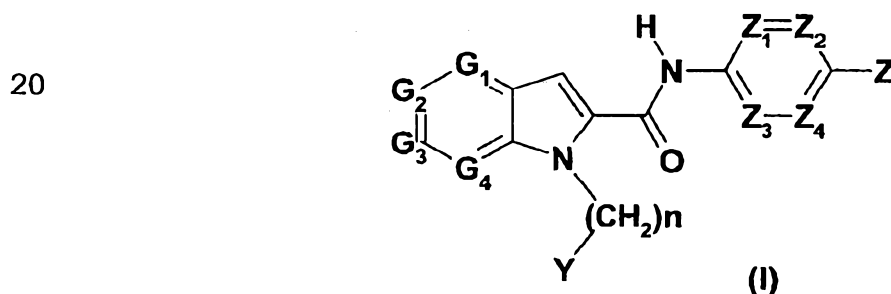
5 The subject of the invention is compounds derived from indole-2-carboxamides and from azaindole-2-carboxamides substituted with a silanyl group, which exhibit an antagonistic or agonistic activity, *in vitro* and *in vivo*, with respect to TRPV1 (or VR1) receptors.

10 A first subject of the invention concerns the compounds corresponding to general formula (I) below.

Another subject of the invention concerns processes for preparing the compounds of general formula (I).

15 Another subject of the invention concerns the use of the compounds of general formula (I), in particular in medicaments or in pharmaceutical compositions.

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



25 in which:

G_1 , G_2 , G_3 and G_4 are, independently of one another, a C-X group or a nitrogen atom; X is chosen from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, cyano, C₁-C₆-thioalkyl, NR₁R₂, aryl-C₁-C₆-alkylene-O-, aryl, heteroaryl or -Si(X₁)(X₂)(X₃) group; the C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl and C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O- groups being optionally substituted with a hydroxyl, C₁-C₆-alkoxyl or NR₄R₅ group; the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

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one of G_1 , G_2 , G_3 and G_4 and at most one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an -Si(X_1)(X_2)(X_3) group;

X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkyl, hydroxyl, aryl or heteroaryl group;

the aryl or heteroaryl groups of X_1 , X_2 , X_3 being optionally substituted with one or more substituents chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, C_1 - C_6 -fluoroalkoxyl, nitro or cyano group;

the C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl and C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkyl groups of X_1 , X_2 , X_3 being optionally substituted with one or more substituents chosen from a hydroxyl, C_1 - C_6 -alkoxyl, aryl-O-, NR_1R_2 , aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, C_1 - C_6 -fluoroalkoxyl, nitro or cyano group;

it also being possible for X_1 and X_2 to form, together with the silicon atom which bears them, a 4- to 7-membered ring optionally containing a heteroatom chosen from O, S and N;

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

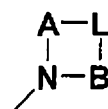
Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more substituents chosen from a halogen atom or a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, hydroxyl, C_1 - C_6 -alkoxyl, C_3 - C_7 -cycloalkoxyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene-O-, C_1 - C_6 -fluoroalkoxyl, cyano, C_1 - C_6 -thioalkyl, thiol, -S(O)- C_1 - C_6 -alkyl, -S(O)₂- C_1 - C_6 -alkyl, C(O)NR₁R₂, SO₂NR₁R₂, SF₅, nitro, OCONR₁R₂, NR₃COR₄, NR₃CONR₁R₂, NR₁R₂, NR₃SO₂NR₁R₂, NR₃COR₄, NR₃SO₂R₅, 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 chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -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 , 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 of position 1, being optionally substituted with R_7 when the carbon atom at position 2 or 4 relative to this reference nitrogen is substituted with an oxo or thio

group;

Z is

- 5 either a cyclic amine linked via the nitrogen atom, of formula:



- 10 in which:

A is a C₁-C₇-alkylene group optionally substituted with one or two R₈ groups;

B is a C₁-C₇-alkylene group optionally substituted with one or two R₉ groups;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with an R₁₀ or R₁₁;

- 15 the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;

or an acyclic amine, linked via the nitrogen atom, of formula NRaRb in which Ra and Rb are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, C₁-C₆-alkyl-C(O)-, HO-C(O)-C₁-C₆-alkylene, C₁-C₆-alkyl-O-C(O)-C₁-C₆-alkylene, aryl or heteroaryl group, it being possible for Ra and Rb to be optionally substituted with one or more R_c groups which may be identical to or different from one another;

- 20 R_c is a halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, C₁-C₆-thioalkyl, -S(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, cyano, C(O)NR₁R₂, NR₁R₂, SO₂NR₁R₂, NR₃COR₄, NR₃SO₂R₅, OC(O)NR₁R₂, NR₃COOR₅, NR₃CONR₁R₂, NR₃SO₂NR₁R₂, hydroxyl, thiol, oxo, thio, aryl-C₁-C₆-alkylene, aryl or heteroaryl group,
- 30 the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

- R₁ and R₂ are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, aryl-C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-
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- cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group; or R₁ and R₂ form, together with the nitrogen atom which bears them, an azetidiny, pyrrolidiny, piperidiny, azepiny, morpholiny, thiomorpholiny, piperaziny or homopiperaziny group, this group being optionally substituted with a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, aryl-C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;
- R₃ and R₄ are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, aryl-C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group; or R₃ and R₄ together form a (C₂-C₅)alkylene group; or R₁ and R₃ together form a (C₂-C₅)alkylene group;
- R₅ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, aryl-C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group; or R₃ and R₅ together form a (C₂-C₅)alkylene group;
- R₆ is a hydrogen or halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, C₁-C₆-thioalkyl, -S(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, hydroxyl, thiol, oxo, thio, aryl, aryl-C₁-C₆-alkylene or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;
- R₇ is a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, aryl, aryl-C₁-C₆-alkylene or heteroaryl group, the aryl

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and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

5 R₈, R₉ and R₁₀ are defined such that:

two R₈ groups may together form a bond or a C₁-C₆-alkylene group;

two R₉ groups may together form a bond or a C₁-C₆-alkylene group;

R₈ and R₉ may together form a bond or a C₁-C₆-alkylene group;

R₈ and R₁₀ may together form a bond or a C₁-C₆-alkylene group;

10 R₉ and R₁₀ may together form a bond or a C₁-C₆-alkylene group;

R₁₁ is a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, hydroxyl, C₁-C₆-alkyl-CO-, COOR₅, C(O)NR₁R₂, aryl-
15 C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

20 R₁₂ is a fluorine atom, a C₁-C₆-alkyl group optionally substituted with an R₁₃ group; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-cycloalk-1,1-diyl, C₃-C₇-heterocycloalk-1,1-diyl optionally substituted on a nitrogen atom with an R₁₁ group; C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, CO₂H, C(O)O-C₁-C₆-alkyl, C(O)NR₁R₂, NR₁R₂, NR₃COR₄, OC(O)NR₁R₂,
25 NR₃COOR₅, NR₃CONR₁R₂, hydroxyl, thiol, oxo, thio, aryl-C₁-C₆-alkylene or aryl; the aryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

30 R₁₃ is a C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C(O)NR₁R₂, NR₁R₂, NR₃COR₄, OC(O)NR₁R₂, NR₃COOR₅ or hydroxyl group;

it being possible for the nitrogen atom(s) of the compounds of general formula (I) to be in oxidized form (N-oxide);

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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.

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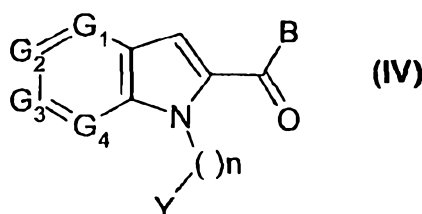
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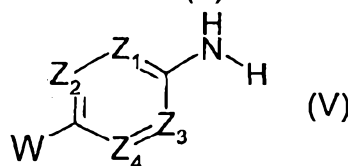
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By way of nonlimiting examples of substituted or unsubstituted amines Z, mention may be made of methylamine, ethylamine, 2-methoxyethylamine, 2-hydroxyethylamine, cyclopropylamine, hydroxylamine, 2-(*N,N*-dimethylamino)ethylamine, dimethylamine, isopropylamine, *N*-ethylmethylamine, 2,5-dimethylpyrrolidine, 3-hydroxypyrrolidine, 3-ethoxypyrrolidine, 3,3-difluoropyrrolidine, 3,3-difluoroazetidine, 3-hydroxyazetidine, proline, aziridine, azetidine, pyrrolidine, piperidine, azepine, morpholine, thiomorpholine, piperazine, homopiperazine, azabicyclo[3.1.0]hexanes, azabicyclo[3.2.0]heptanes, azabicyclo[3.3.0]octanes, octahydrofuropyrroles, octahydro-pyrrolopyrroles, octahydroindole, octahydroisoindole, octahydropyrrolopyridines, decahydroquinoline, decahydroisoquinoline, decahydronaphthyridines, octahydro-pyridopyrazine, azabicyclo[3.1.1]heptanes, diazabicyclo[2.2.1]heptanes, azabicyclo[3.2.1]octanes, diazabicyclo[3.2.1]octanes and azabicyclo[3.3.1]nonanes.

The invention also provides a process for preparing a compound of formula (I) of the invention, wherein a compound of general formula (IV)



in which G_1 , G_2 , G_3 and G_4 , Y and n are as defined in general formula (I) of the invention and B is a chlorine atom, is reacted with an amine of general formula (V)



in which $W = Z$ and Z, Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) of the invention, in a solvent.

The invention also provides a process for preparing a compound of formula (I) of the invention,

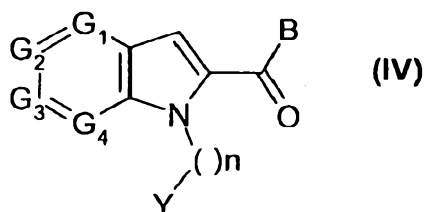
wherein a compound of general formula (IV)

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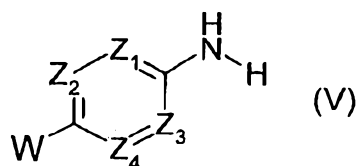
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in which G_1 , G_2 , G_3 and G_4 , Y and n are as defined in general formula (I) of the invention and B is a hydroxyl group,

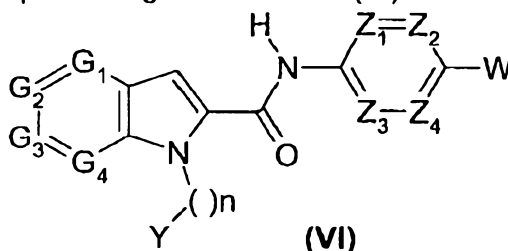
5 is reacted with an amine of general formula (V)



in which $W = Z$ and Z , Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) of the invention, in the presence of a coupling agent, and optionally of a base, in a solvent.

10

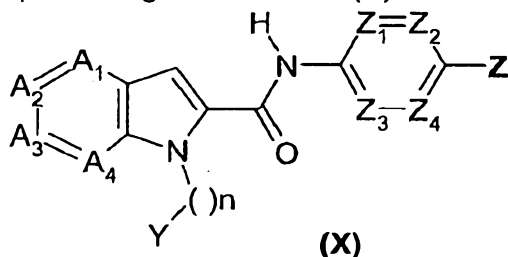
The invention also provides a process for preparing a compound of formula (I) of the invention, wherein a compound of general formula (VI)



15 in which G_1 , G_2 , G_3 and G_4 , Y , n , Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) of the invention and W is a halogen atom,

is reacted with an amine of formula $Z-H$, in which Z is as defined in general formula (I) of the invention.

20 The invention also provides a process for preparing a compound of formula (I) of the invention, wherein a compound of general formula (X)



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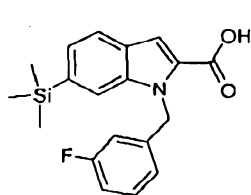
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in which Y, n, Z, Z₁, Z₂, Z₃ and Z₄ are as defined in general formula (I) of the invention and A₁, A₂, A₃ and A₄ are, independently of one another, a C-X group or a nitrogen atom; X being as defined in general formula (I); one of A₁, A₂, A₃ and A₄ and at most one of A₁, A₂, A₃ and A₄ is a C-q group where q is a halogen atom in the position where the silanyl group should be introduced,

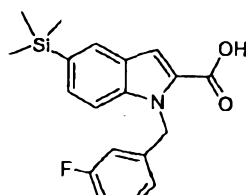
is reacted with a silane of formula SiH(X₁)(X₂)(X₃) in which X₁, X₂ and X₃ are as defined in general formula (I) of the invention,

in the presence of a catalytic amount of a metal complex and of a base in a solvent.

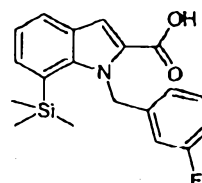
The invention also provides a compound (IVa), (IVb), (IVc), (IVd), (IVe) or (IVf):



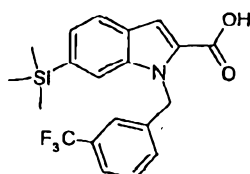
(IVa)



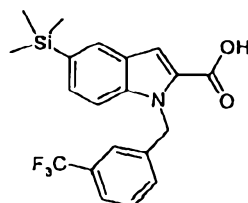
(IVb)



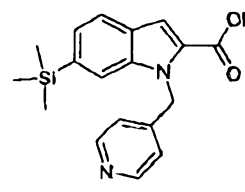
(IVc)



(IVd)



(IVe)



(IVf)

The invention also provides a medicament, comprising a compound of formula (I) of the invention, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I).

The invention also provides a pharmaceutical composition, comprising a compound of formula (I) of the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also at least one pharmaceutically acceptable excipient.

The invention also relates to a use of a compound of formula (I) of the invention, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I) for the preparation of a medicament for preventing and treating pathologies in which TRPV1-type receptors are involved.

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The invention also relates to a use of a compound of formula (I) of the invention, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I) for the preparation of a medicament for preventing or treating pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritus, dermal, ocular or mucosal irritations, herpes, shingles, multiple sclerosis, depression or cancers.

The invention also relates to a method of preventing or treating pathologies in which receptors of TRPV1 type are involved, pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritus, dermal, ocular or mucous irritations, herpes, zona, multiple sclerosis, depression and cancers, the method comprising administering to a patient an effective dose of a compound of the invention, or a pharmaceutically acceptable salt, or hydrate or solvate thereof.

In the context of the present invention:

- The term "comprising" as used in this specification means "consisting at least in part of". When interpreting each statement in this specification that includes the term "comprising", features other than that or those prefaced by the term may also be present. Related terms such as "comprise" and "comprises" are to be interpreted in the same manner.
- the expression " C_t-C_z where t and z may have the values of 1 to 7" is intended to mean a carbon-based chain that may contain from t to z carbon atoms; for example, " C_1-C_3 " is intended to mean a carbon-based chain that may contain from 1 to 3 carbon atoms;
- the term "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;
- the term "an alkylene" is intended to mean: a linear or branched, saturated divalent alkyl group, for example a C_{1-3} -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;
- the term "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;

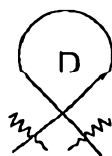
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- the term "a heterocycloalkyl" is intended to mean: a 3- to 7-membered cyclic group containing from 1 to 2 heteroatoms chosen from O, S or N;
- the term "a cycloalk-1,1-diyl" or "a heterocycloalk-1,1-diyl" is intended to mean: a group of the type:



5

where D is a cycloalkyl or heterocycloalkyl group;

- the term "a fluoroalkyl" is intended to mean: an alkyl group of which one or more hydrogen atoms has (have) been substituted with a fluorine atom;

- the term "an alkoxy" is intended to mean: an -O-alkyl radical where the alkyl group is as defined above;
- the term "a cycloalkoxy" is intended to mean: an -O-cycloalkyl radical where the cycloalkyl group is as defined above;
- 5 - the term "a fluoroalkoxy" is intended to mean: an alkoxy group of which one or more hydrogen atoms has (have) been substituted with a fluorine atom;
- the term "a thioalkyl" is intended to mean: an -S-alkyl radical where the alkyl group is as defined above;
- the term "an aryl" is intended to mean: a cyclic aromatic group comprising between
10 6 and 10 carbon atoms. By way of examples of aryl groups, mention may be made of phenyl or naphthyl groups;
- the term "a heteroaryl" is intended to mean: a 5- to 14-membered aromatic monocyclic, bicyclic or tricyclic group containing from 1 to 8 heteroatoms chosen from O, S or N.
- 15 By way of examples of a monocyclic heteroaryl, mention may be made of imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, furanyl, thiophenyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyridinyl, pyrazinyl, pyrimidinyl, pyridazinyl or triazinyl groups;
- by way of examples of a bicyclic heteroaryl, mention may be made of indolyl, isoindolyl,
20 benzofuranyl, benzothiophenyl, benzoxazolyl, benzimidazolyl, indazolyl, benzothiazolyl, isobenzofuranyl, isobenzothiazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, pyrrolo[3,2-c]pyridinyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl or quinoxalinyl groups;
- by way of examples of a tricyclic heteroaryl, mention may be made of pyrido[1,2-
25 a]benzimidazolyl, thiazolo[1,2-a]benzimidazolyl, imidazo[1,2-a]benzimidazolyl, pyrimido[1,2-a]benzimidazolyl or pyrazino[1,2-a]benzimidazolyl groups;
- the term "a silanyl" is intended to mean: an -Si(X₁)(X₂)(X₃) group where X₁, X₂ and X₃ are as defined in general formula (I);
- the term "a halogen atom" is intended to mean: a fluorine, a chlorine, a bromine or
30 an iodine;
- "oxo" means "=O";
- "thio" means "=S".

The compounds of formula (I) may comprise one or more asymmetrical carbon atoms.
35 They may therefore exist in the form of enantiomers or of diastereoisomers. These enantiomers and diastereoisomers, and also mixtures thereof, including racemic mixtures, form part of the invention.

The compounds of formula (I) may exist in the form of bases or of addition salts with acids. Such addition salts form part of the invention.

These salts are advantageously prepared with pharmaceutically acceptable acids, but
5 the salts of other acids that are useful, for example, for purifying or isolating the compounds of formula (I) also form part of the invention.

The compounds of general formula (I) may be in the form of hydrates or of solvates, i.e. in the form of associations or combinations with one or more molecules of water or with
10 a solvent. Such hydrates and solvates also form part of the invention.

Among the compounds of general formula (I) which are subjects of the invention, a first subgroup of compounds is constituted by the compounds for which:

one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an $-\text{Si}(X_1)(X_2)(X_3)$ group; the others of G_1 , G_2 , G_3 and G_4 being a CH group;
15 X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl group.

Among the compounds of general formula (I) which are subjects of the invention, a second subgroup of compounds is constituted by the compounds for which:

20 one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an $-\text{Si}(X_1)(X_2)(X_3)$ group; the others of G_1 , G_2 , G_3 and G_4 being a CH group;
 X_1 , X_2 and X_3 are, independently of one another, a methyl, ethyl, isopropyl, tert-butyl, cyclohexyl or phenyl group.

25 Among the compounds of general formula (I) which are subjects of the invention, a third subgroup of compounds is constituted by the compounds for which:
n is equal to 1.

Among the compounds of general formula (I) which are subjects of the invention, a
30 fourth subgroup of compounds is constituted by the compounds for which:

Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more groups chosen from a halogen atom or a C_1 - C_6 -fluoroalkyl group.

Among the compounds of general formula (I) which are subjects of the invention, a fifth
35 subgroup of compounds is constituted by the compounds for which:

Y is a phenyl or a pyridinyl; the phenyl being optionally substituted with one or more

groups chosen from a fluorine atom or a CF₃ group.

Among the compounds of general formula (I) which are subjects of the invention, a sixth subgroup of compounds is constituted by the compounds for which:

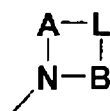
- 5 Z₁, Z₂, Z₃ and Z₄ are, independently of one another, a nitrogen atom or a C(R₆) group, one corresponding to a nitrogen atom and the others corresponding to a C(R₆) group; R₆ is a hydrogen atom.

- 10 Among the compounds of general formula (I) which are subjects of the invention, a seventh subgroup of compounds is constituted by the compounds for which:

Z₄ is a nitrogen atom and Z₁, Z₂ and Z₃ are a CH group.

Among the compounds of the general formula (I) which are subjects of the invention, an eighth subgroup of compounds is constituted by the compounds for which:

- 15 Z is a cyclic amine linked via the nitrogen atom, of formula:



- 20 in which:

A is a C₁-C₇-alkylene group optionally substituted with one or two R₈ groups;

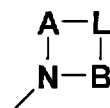
B is a C₁-C₇-alkylene group optionally substituted with one or two R₉ groups;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with an R₁₀ or R₁₁ group;

- 25 the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;
R₈, R₉, R₁₀, R₁₁ and R₁₂ being as defined in general formula (I).

- 30 Among the compounds of general formula (I) which are subjects of the invention, a ninth subgroup of compounds is substituted by the compounds for which:

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



- 35

in which:

A is a C₁-C₇-alkylene group;

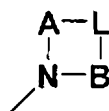
B is a C₁-C₇-alkylene group;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with an R₁₁ group;

- 5 the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;
R₁₁ and R₁₂ being as defined in general formula (I).

10 Among the compounds of general formula (I) which are subjects of the invention, a tenth subgroup of compounds is constituted by the compounds for which:

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



15

in which:

A is a C₁-C₇-alkylene group;

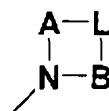
B is a C₁-C₇-alkylene group;

L is a bond;

- 20 the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;
R₁₂ being as defined in general formula (I).

25 Among the compounds of general formula (I) which are subjects of the invention, an eleventh subgroup of compounds is constituted by the compounds for which:

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



30

in which:

A is a C₁-C₃-alkylene group;

B is a C₁-C₃-alkylene group;

L is a bond;

- 35 the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;

R₁₂ is a hydroxyl group.

Among the compounds of general formula (I) which are subjects of the invention, a twelfth subgroup of compounds is constituted by the compounds for which:

- 5 Z is an azetidinyI or pyrrolidinyl group;
the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;
R₁₂ is a hydroxyl group.
- 10 Among the compounds of general formula (I) which are subjects of the invention, a thirteenth subgroup of compounds is constituted by the compounds for which:
Z is an acyclic amine, linked via the nitrogen atom, of formula NRaRb in which Ra and Rb are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl group.
- 15 Among the compounds of general formula (I) which are subjects of the invention, a fourteenth subgroup of compounds is constituted by the compounds for which:
Z is an acyclic amine, linked via the nitrogen atom, of formula NRaRb in which Ra and Rb are, independently of one another, a C₁-C₆-alkyl group, more particularly methyl.
- 20 Among the compounds of general formula (I) which are subjects of the invention, a fifteenth subgroup of compounds is constituted by the compounds for which the definitions of G₁, G₂, G₃ and G₄, n, Y, Z₁, Z₂, Z₃, Z₄ and Z given above are combined.

- 25 Among the compounds of general formula (I) which are subjects of the invention, a sixteenth subgroup of compounds is constituted by the compounds for which:

- one of G₁, G₂, G₃ and G₄ is a C-X group where X is an -Si(X₁)(X₂)(X₃) group; the others of G₁, G₂, G₃ and G₄ being a CH group;
X₁, X₂ and X₃ are, independently of one another, a C₁-C₆-alkyl, C₃-C₇-cycloalkyl or aryl
30 group;
n is equal to 1;
Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more groups chosen from a halogen atom or a C₁-C₆-fluoroalkyl group;
Z₁, Z₂, Z₃ and Z₄ are, independently of one another, a nitrogen atom or a C(R₆) group,
35 one corresponding to a nitrogen atom and the others corresponding to a C(R₆) group;
R₆ is a hydrogen atom;

Z is:

either a cyclic amine linked via the nitrogen atom, of formula:



in which:

A is a C₁-C₃-alkylene group;

B is a C₁-C₃-alkylene group;

10 L is a bond;

the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;

R₁₂ is a hydroxyl group;

or an acyclic amine, linked via the nitrogen atom, of formula NRaRb in which Ra and
15 Rb are, independently of one another, a hydrogen atom or a C₁-C₆-alkyl group.

Among the compounds of general formula (I) which are subjects of the invention, mention may in particular be made of the following compounds:

- 20 1. N-[6-(azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
2. N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
3. N-[6-(azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-
25 indole-2-carboxamide
4. N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
5. N-[6-(azetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
- 30 6. N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
7. N-[6-(Dimethylamino)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide
8. N-[6-(azetidin-1-yl)pyridin-3-yl]-5-(ethyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-
35 1H-indole-2-carboxamide
9. N-[6-(azetidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-

fluorophenyl)methyl]-1*H*-indole-2-carboxamide

10. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[[3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide

11. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[[3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide

12. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-(diphenyl)methylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

13. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide

10 14. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide

15. *N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

15 16. *N*-[6-(azetidin-1-yl)pyridin-3-yl]pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

17. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-triethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

18. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-tert-butyl(dimethyl)silyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

20 19. *N*-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

20. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-phenyldimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

21. *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-(isopropyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

22. *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(methyl)diethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide.

Among the compounds of general formula (I) which are subjects of the invention, a seventeenth subgroup of compounds is constituted by the compounds for which:

G_1 , G_2 , G_3 and G_4 are, independently of one another, a C-X group;

X is chosen from a hydrogen atom or an -Si(X_1)(X_2)(X_3) group;

one of G_1 , G_2 , G_3 and G_4 and at most one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an -Si(X_1)(X_2)(X_3) group;

X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl group.

Among the compounds of general formula (I) which are subjects of the invention, an eighteenth subgroup of compounds is constituted by the compounds for which n is equal to 1 and Y is an aryl, more particularly a phenyl, optionally substituted with one or more halogen atoms, more particularly fluorine atoms.

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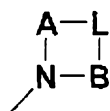
Among the compounds of general formula (I) which are subjects of the invention, a nineteenth subgroup of compounds is constituted by the compounds for which Z_1 , Z_2 , Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $C(R_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $C(R_6)$ group; where R_6 is a hydrogen atom.

10

Among the compounds of general formula (I) which are subjects of the invention, a twentieth subgroup of compounds is constituted by the compounds for which:

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

15



in which:

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

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

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

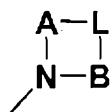
the carbon atoms of the cyclic amine Z being optionally substituted with one or more R_{12} groups which may be identical to or different from one another.

25

Among the compounds of general formula (I) which are subjects of the invention, a twenty-first subgroup of compounds is constituted by the compounds for which:

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

30



this cyclic amine being an azetidiny group;

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

R_{12} is a hydroxyl group.

35

Among the compounds of general formula (I) which are subjects of the invention, a twenty-second subgroup of compounds is constituted by the compounds for which:

G_1 , G_2 , G_3 and G_4 are, independently of one another, a C-X group;

X is chosen from a hydrogen atom or an $-\text{Si}(\text{X}_1)(\text{X}_2)(\text{X}_3)$ group;

- 5 one of G_1 , G_2 , G_3 and G_4 and at most one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an $-\text{Si}(\text{X}_1)(\text{X}_2)(\text{X}_3)$ group;

X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl group;

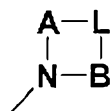
n is equal to 1;

- 10 Y is an aryl, more particularly a phenyl, optionally substituted with one or more halogen atoms, more particularly fluorine atoms;

Z_1 , Z_2 , Z_3 and Z_4 are, independently of one another, a hydrogen atom or a $\text{C}(\text{R}_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $\text{C}(\text{R}_6)$ group; where R_6 is a hydrogen atom;

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

15



this cyclic amine being an azetidinyl group;

- 20 the carbon atoms of the cyclic amine Z being optionally substituted with an R_{12} group; where R_{12} is a hydroxyl group.

- 25 In the subsequent text, the term "leaving group" is intended to mean a group that can be readily cleaved from a molecule by heterolytic bond breaking, with the departure of a pair of electrons. This group can thus be readily replaced with another group in 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",
30 J. March, 5th Edition, Wiley Interscience, 2001.

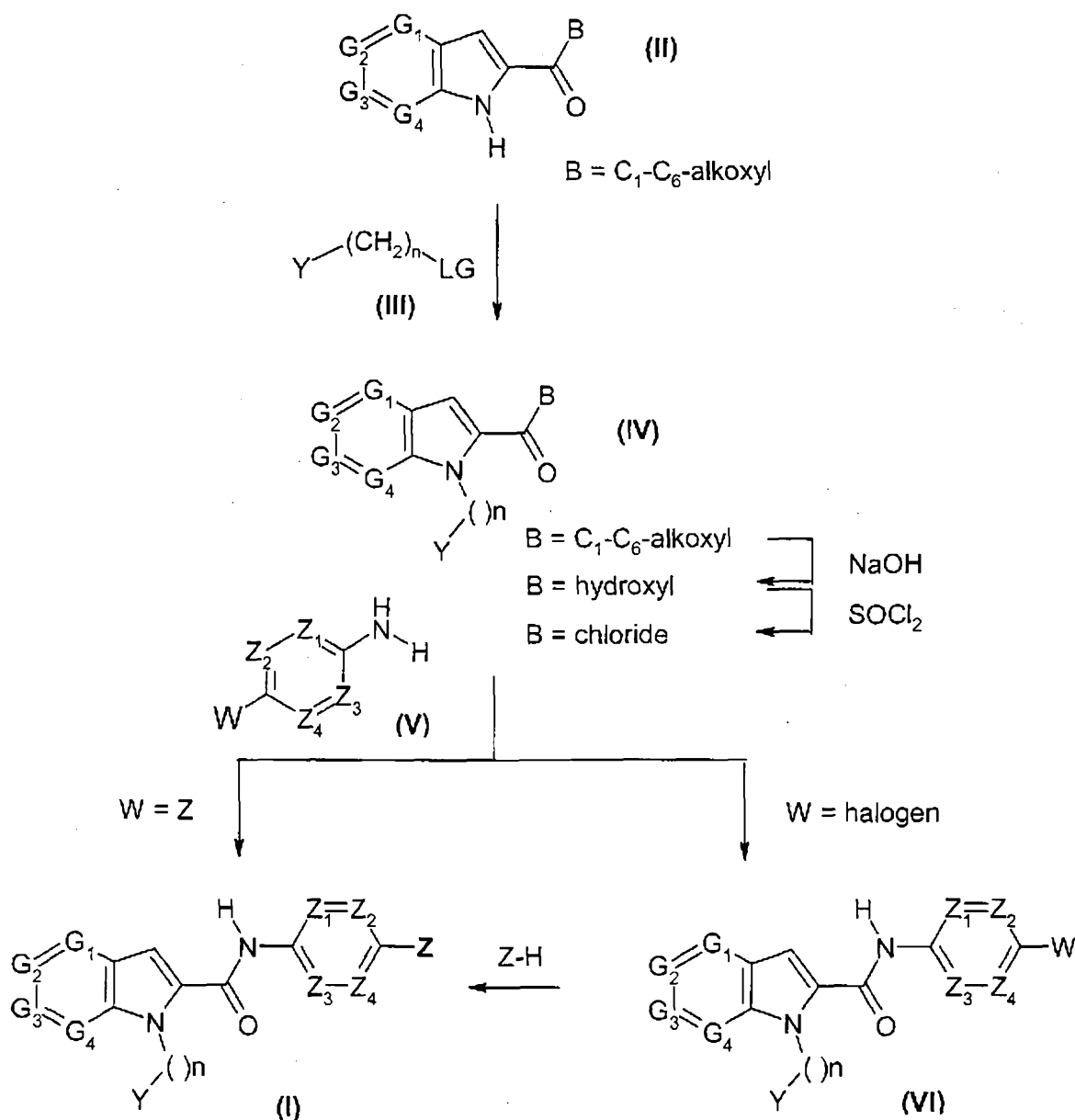
In accordance with the invention, the compounds of general formula (I) can be prepared according to the process illustrated by scheme 1 which follows.

- 35 According to scheme 1, the compounds of general formula (IV) can be obtained by reacting a compound of general formula (II), in which G_1 , G_2 , G_3 and G_4 are as defined in general formula (I) and B is a C_1 - C_6 -alkoxyl group, with a compound of general formula (III), in which Y and n are as defined in general formula (I) and LG is a leaving

group or LG is a hydroxyl group.

In scheme 1, when the compound of general formula (III) is defined such that n is equal to 1, 2 or 3 and LG is a leaving group such as a chlorine, bromine or iodine atom, the reaction for formation of the compounds of general formula (IV) 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 general formula (III) is defined such that n is equal to 1, 2 or 3 and LG is a hydroxyl group, the compounds of general formula (IV) can be obtained by reacting the compound of general formula (II) with a compound of general formula (III) in the presence of a phosphine such as, for example, triphenylphosphine, and a reactant such as, for example, diethyl azodicarboxylate in solution in a solvent such as dichloromethane or tetrahydrofuran (O. Mitsunobu, *Synthesis*, **1981**, 1-28).

Scheme 1

5

Similarly, the compounds of general formula (IV) can be obtained by reacting the compound of general formula (II) with a compound of general formula (III), in the presence of a phosphine supported on a resin, and a reactant such as, for example, diisopropyl azodicarboxylate in solution in a solvent such as dichloromethane or tetrahydrofuran.

10

When the compound of general formula (III) is defined such that n is equal to 0 and LG is a leaving group such as a chlorine, bromine or iodine atom, the reaction for formation

of compounds of general formula (IV) can be carried out by application and adaptation of the methods described by S. L. Buchwald et al. (*J. Am. Chem. Soc.*, **2001**, 123, 7727 and **2002**, 124, 11684), preferably under an inert atmosphere in a basic medium, for example in the presence of potassium triphosphate, in the presence of a copper salt
5 such as copper iodide, optionally in the presence of an additive such as *N,N'*-dimethylcyclohexane-1,2-diamine, the whole in an organic solvent such as toluene.

The compound of general formula (IV), for which B is a C₁-C₆-alkoxyl group, can be converted to a compound of general formula (IV), where B is a hydroxyl group, by the
10 action of a base such as sodium hydroxide or potassium hydroxide in solution in a solvent such as ethanol. The compound of general formula (IV), where B is a hydroxyl group, can subsequently be converted to a compound of general 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.

15 The compound of general formula (VI) can subsequently be obtained, for example, by reacting a compound of general formula (IV), where B is a chlorine atom, as obtained above, with an amine of general formula (V), in which Z₁, Z₂, Z₃ and Z₄ are as defined in general formula (I) and W is a halogen such as a chlorine atom, in a solvent such as
20 dichloroethane, toluene or tetrahydrofuran.

The compound of general formula (VI) can also be obtained by reacting a compound of general formula (IV), where B is a hydroxyl group, as obtained above, with an amine of general formula (V), in which Z₁, Z₂, Z₃ and Z₄ are as defined in general formula (I) and W is a halogen atom such as a chlorine atom, in the presence of a coupling agent such
25 as diethyl cyanophosphonate or *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, optionally in the presence of a base such as triethylamine, in a solvent such as dimethylformamide.

The compound of general formula (I) can be obtained, for example, by reacting a
30 compound of general formula (IV), where B is a chlorine atom, as obtained above, with an amine of general formula (V), in which W = Z and Z, Z₁, Z₂, Z₃ and Z₄ are as defined in general formula (I), in a solvent such as dichloroethane, toluene or tetrahydrofuran.

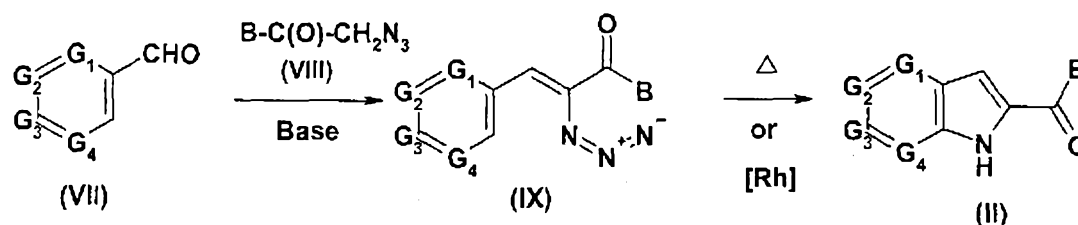
The compound of general formula (I) can also be obtained by reacting a compound of
35 general formula (IV), where B is a hydroxyl group, as obtained above, with an amine of general formula (V), in which W = Z and Z, Z₁, Z₂, Z₃ and Z₄ are as defined in general

formula (I), in the presence of a coupling agent such as diethyl cyanophosphonate or *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide, and optionally in the presence of a base such as triethylamine, in a solvent such as dimethylformamide.

- 5 The compound of general formula (I) can also be obtained by reacting a compound of general formula (VI) in the presence of an amine of formula Z-H, in which Z is as defined in general formula (I), without solvent or in a solvent such as *N*-methylpyrrolidone, or else by application and adaptation of the methods described by S. L. Buchwald et al. (*J. Am. Chem. Soc.*, **2001**, 123, 7727 and **2002**, 124, 11684),
10 preferably under an inert atmosphere in a basic medium, for example in the presence of potassium triphosphate, in the presence of a copper salt such as copper iodide, optionally in the presence of an additive such as *N,N'*-dimethylcyclohexane-1,2-diamine, the whole in an organic solvent such as toluene, or else by application and adaptation of the methods described by Hartwig et al. (*Angewandte Chemie*, **2005**, 44,
15 1371-1375), for example in the presence of a base and of catalytic amounts of a palladium-based catalyst, such as palladium diacetate, and of a phosphine.

The compounds of general formula (II) of scheme 1, in which G₁, G₂, G₃ and G₄ are as defined in general formula (I) and B is a C₁-C₆-alkoxyl group, can, when their method of
20 preparation is not described, be obtained, for example, according to the method illustrated in scheme 2.

Scheme 2



The compounds of general formula (II) are prepared starting from aromatic or heteroaromatic aldehydes substituted with a silanyl group of general formula (VII) in which G₁, G₂, G₃ and G₄ are as defined in general formula (I), by reaction with an alkyl
30 azidoacetate of general formula (VIII) in which B is a C₁-C₆-alkoxyl group, such as ethyl azidoacetate for example, in the presence of a base such as sodium ethoxide, in a solvent such as ethanol or methanol, so as to give the alkyl azido-2-cinnamates of

general formula (IX). The latter are subsequently converted to indole or azaindole esters at the reflux of a solvent, for example in xylene or toluene, by adaptation of protocols described in the literature (Hemetsberger et al *Monatsh. Chem.*, **1969**, 100, 1599 and **1970**, 101, 161; P. Roy et al *Synthesis.*, **2005**, 16, 2751-2757; R. Guillard et al *J. Heterocyclic. Chem.*, **1981**, 18, 1365-1377; W. Rees et al *J. Chem. Soc., perkin trans 1* **1984**, 2189-2196; P. Molina et al *J. org. Chem.*, **2003**, 68(2), 489-499; C. Moody et al *J. Chem. Soc., Perkin Trans. 1* **1984**, 2189-2196; J. Sawyer et al *J. Med. Chem.*, **2005**, 48, 893-896; D. Tanner *Synlett* **2006**, 18, 3140-3144).

- 10 Alternatively, according to scheme 2, the formation of the compounds of general formula (II) can be obtained by decomposition of the alkyl azido-2-cinnamate of general formula (IX), in the presence of a rhodium dimer complex, in a solvent such as toluene at a temperature of between 25°C and 60°C, according to an adaptation of protocols described in the literature (Tom G. Drivers et al *J. Am. Chem. Soc.*, **2007**, 129, 7500-
15 7501; J. Sawyer et al *J. Med. Chem.*, **2005**, 48, 893-896).

The silanyl group of the compounds of general formula (II) can also be introduced by reacting the corresponding indole or azaindole ester substituted with a halogen, such as a bromine or an iodine, in the position where the silanyl group should be introduced,
20 in the presence of a disilane, such as hexamethyldisilane, of a catalytic amount of a metal complex, preferably a palladium complex, for example tetrakis(triphenylphosphine)palladium, and of a base, in a solvent such as toluene, at a temperature of between 20°C and the boiling point of the solvent.

- 25 The silanyl group of the compounds of the general formula (II) can also be introduced by reacting the corresponding indole or azaindole ester substituted with a halogen, such as an iodine, in the position where the silanyl group should be introduced, in the presence of a silane, such as triethylsilane, of a catalytic amount of a metal complex, preferably a palladium complex, for instance bis(tri-tert-butylphosphine)palladium, and
30 of a base such as potassium triphosphate, in a solvent such as N-methyl-2-pyrrolidinone, at a temperature close to 20°C (adaptation of the protocols described in the literature: Yoshinori Yamanoi et al *J. org. Chem.*, **2005**, 70 (23), 9607-9609 and cited references).

- 35 The aromatic or heteroaromatic aldehydes substituted with a silanyl group of general

formula (VII) can, when they are not commercially available, be obtained starting from the corresponding aromatic or heteroaromatic aldehydes, preferably masked in the form of an acetal, for example, substituted with a halogen atom, such as a bromine or an iodine, in the position where the silanyl group should be introduced:

- 5 - for example by reaction with a disilane such as hexamethyldisilane, in the presence of a catalytic amount of a metal complex, preferably a palladium complex, for instance tetrakis(triphenylphosphine)palladium, without solvent or in a solvent, preferably a polar solvent, for instance hexamethylphosphoramide, in the presence of a base such as potassium carbonate, at a temperature of between 20°C and the boiling point of the
- 10 solvent (adaptation of the protocols described in the literature: J. Babin et al *J. organometal. Chem.*, **1993**, 446 (1-2), 135-138; E. Shirakawa et al *Chem. Commun.*, **2000**, 1895-1896; L. Goossen et al *Synlett*, **2000**, 1801-1803; H. Matsumoto et al *J. organometal. Chem.*, **1975**, 85, C1; FR2677358);
- for example by reaction with a disilane such as hexamethyldisilane, in the presence of
- 15 a strong base, for instance potassium methoxide or sodium methoxide, in a polar solvent, for instance hexamethylphosphoric triamide (HMPT), at a temperature close to 20°C (adaptation of the protocols described in the literature: A.I Meyers et al *J. org. Chem.*, **1977**, 42 (15), 2654-2655; K. Ishimaru et al *Heterocycles*, **2001**, 55 (8), 1591-1597);
- 20 - for example by reaction with a silane such as triethylsilane, in the presence of a catalytic amount of a metal complex, preferably a palladium complex, for instance bis(tri-tert-butylphosphine)palladium, and of a base such as potassium triphosphate, in a solvent such as N-methyl-2-pyrrolidinone, at a temperature close to 20°C (adaptation of the protocols described in the literature: Yoshinori Yamanoi et al *J. org. Chem.*,
- 25 **2005**, 70 (23), 9607-9609 and cited references).

The aromatic or heteroaromatic aldehydes substituted with a silanyl group of general formula (VII) according to scheme 2 can, when they are not commercially available, also be obtained starting from the corresponding dihalogenated aromatics or

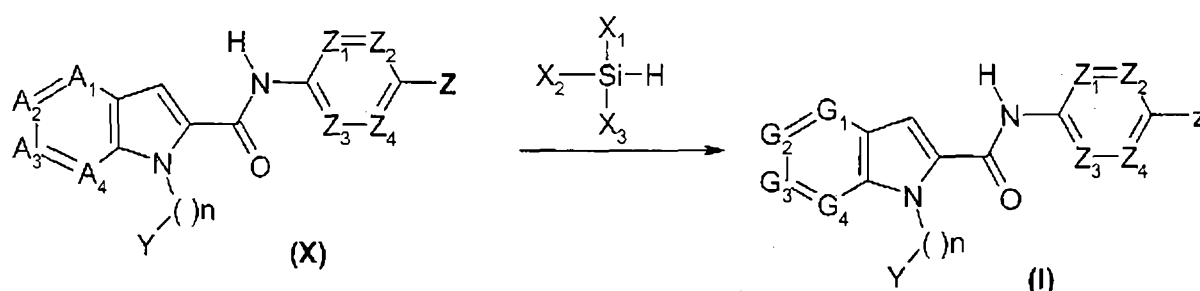
30 heteroaromatics, such as a derivative which is dibrominated, in the position where the silanyl group should be introduced, by exchange with an organometallic compound, for instance n-butyllithium. The metal aromatics or heteroaromatics thus formed can subsequently react with organohalosilanes or be converted to formylated derivatives by adaptation of the methods described in the literature. The reaction is preferably carried

35 out at low temperatures of between -110°C and ambient temperature, in a solvent such

as ether or THF (adaptation of the protocols described in the literature: Bao-Hui Ye et al *Tetrahedron.*, **2003**, 59, 3593-3601; P. Pierrat et al *Synlett* **2004**, 13, 2319-2322; K.T.Warner et al *Heterocycles* **2002**, 58, 383; D. Deffieux et al *J. organometal. Chem.*, **1994**, 13 (6), 2415-2422; WO2005080328; S.G.Davies et al *J. Chem. Soc, perkin trans*
 5 *1* **1991**, 501; G. Queguiner et al *J. Org. Chem.*, **1981**, 46, 4494-4497; G. Breton et al. *Tetrahedron* **2000**, 56 (10), 1349-1360; S. De Montis et al. *Tetrahedron* **2004**, 60 (17), 3915-3920; L. Buchwald et al *J. Am. Chem. Soc.*, **1998**, 120, 4960-4976).

According to scheme 3, the silanyl group of G₁, G₂, G₃ or G₄ of the compounds of
 10 general formula (I) can also be introduced by starting from the compounds of general formula (X), in which A₁, A₂, A₃ and A₄ are, independently of one another, a C-X group or a nitrogen atom; X being as defined in general formula (I); one of A₁, A₂, A₃ and A₄ and at most one of A₁, A₂, A₃ and A₄ is a C-q group where q is a halogen atom, such as an iodine or a bromine, in the position where the silanyl group should be introduced.
 15 For example, the reaction can be carried out in the presence of a silane, such as triethylsilane, of a catalytic amount of a metal complex, preferably a palladium complex, for instance bis(tri-tert-butylphosphine)palladium, and of a base such as potassium triphosphate, preferably under an inert atmosphere, in a solvent such as N-methyl-2-pyrrolidinone, at a temperature close to 20°C, or else by application and adaptation of
 20 the methods described by Yoshinori Yamanoi et al. *J. org. Chem.*, **2005**, 70 (23), 9607-9609 and cited references.

Scheme 3



25

30

The compounds of general formula (X) as defined above can be obtained, for example, by analogy with the preparation of the compounds of general formula (I) described above or by adaptation of the protocols described in the literature (WO2007010138) and known to those skilled in the art.

The compounds of general formula (I), in which Z is an acyclic amine NRaRb corresponding to an NH₂ group, can be obtained, according to conditions known to those skilled in the art and described in the literature (Greene, Wuts, *Protective groups in organic synthesis*, Wiley-Interscience), from precursors of general formula (I) where
5 NRaRb = NH-GP, GP corresponding to a protective group such as an acetyl or tert-butoxycarbonyl group.

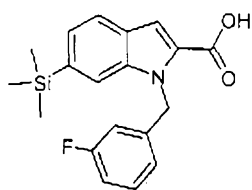
The compounds of general formula (I) comprising a CO₂H group can be obtained, according to conditions known to those skilled in the art and described in the literature
10 (Greene, Wuts, *Protective groups in organic synthesis*, Wiley-Interscience), from precursors of general formula (I) comprising a CO₂GP group, GP corresponding to a carboxylic acid-protecting group, such as a methyl or tert-butyl group.

The compounds of general formula (I) comprising a CH₂OH group can be obtained, according to conditions known to those skilled in the art, from compounds of general
15 formula (I) comprising a CO₂alkyl group, for example, by reaction in the presence of a reducing agent such as sodium borohydride in a solvent such as tetrahydrofuran.

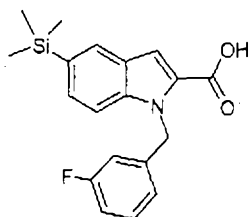
The compounds of general formula (III) are commercially available, described in the literature (Carling R.W. et al *J.Med.Chem.* **2004** (47), 1807 – 1822 or Russel M.G.N. et
20 al. *J.Med.Chem.* **2005** (48), 1367 – 1383) or accessible using methods known to those skilled in the art.

The compounds of general formula (V) and the other reactants, when the method for preparing them is not described, are commercially available or described in the
25 literature (WO2005028452, WO2002048152, WO2006040522, WO2004052869, WO2004062665, WO2005035526, WO2004110986, *Heterocycles* **1977**, 6(12), 1999 - 2004, for example).

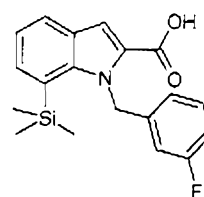
According to another of its aspects, a subject of the invention is also the compounds of
30 general formulae (IVa), (IVb), (IVc), (IVd), (IVe) and (IVf). These compounds are of use as intermediates for the synthesis of the compounds of formula (I).



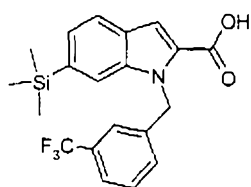
(IVa)



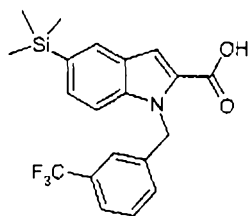
(IVb)



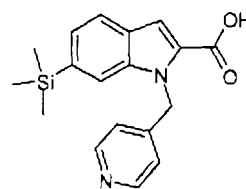
(IVc)



(IVd)



(IVe)



(IVf)

The acids (IVa), (IVb), (IVc), (IVd), (IVe) and (IVf) are prepared according to the processes described in examples No. 1, 3, 5, 10, 13 and 15.

The following examples describe the preparation of a number of compounds in accordance with the invention. These examples are not limiting and merely illustrate the present invention. The numbers of the compounds exemplified refer back to those given in table 1. The elemental microanalyses, the LC-MS (liquid chromatography-mass spectroscopy) analyses, the IR spectra or the NMR spectra confirm the structures of the compounds obtained.

Example 1 (Compound No. 1)

N-[6-(azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

1.1. Ethyl 2-azido-3-(4-trimethylsilylphenyl)propenoate

1.26 g (54.96 mmol) of sodium and 30 ml of anhydrous ethanol are introduced into a 100 ml round-bottomed flask equipped with a magnetic stirrer and maintained under a nitrogen atmosphere. The reaction mixture is stirred at ambient temperature until a homogeneous solution is obtained. A solution containing 16.83 ml (54.96 mmol) of ethyl azidoacetate (34% in CH_2Cl_2) and 5 g (27.48 mmol) of 4-trimethylsilylbenzaldehyde in 5 ml of ethanol is added dropwise to this solution, cooled to -10°C . The reaction mixture is subsequently stirred at 0°C for 4 hours. The reaction medium is hydrolysed by adding 100 ml of an ammonium chloride solution (30%

aqueous) with vigorous stirring. The product is extracted with three times 50 ml of ethyl acetate. The combined organic phases are washed with twice 20 ml of water, dried over sodium sulphate and concentrated under reduced pressure. The resulting oil is purified by silica gel column chromatography, elution being carried out with a mixture of heptane and dichloromethane. 4.96 g of the expected product are isolated in the form of a yellow oil.

¹H NMR (DMSO D₆), δ (ppm): 7.6 (d, 2H); 7.35 (d, 2H); 6.7 (s, 1H); 4.1 (q, 2H); 1.1 (t, 3H); 0 (s, 9H).

1.2 Ethyl 6-trimethylsilyl-1*H*-indole-2-carboxylate

0.17 g (0.16 mmol) of the dirhodium heptafluorobutyrate dimer complex is added to a solution of 1.0 g (3.14 mmol) of ethyl 2-azido-3-(4-trimethylsilylphenyl)propenoate obtained in stage 1.1, in 20 ml of dry toluene, maintained under an inert atmosphere. The reaction mixture is then stirred for 12 h at 70°C. After a return to ambient temperature, the reaction mixture is filtered through silica gel, elution being carried out with ethyl acetate. The filtrate is subsequently concentrated under reduced pressure. The residue is purified by silica gel column chromatography, elution being carried out with a mixture of heptane and dichloromethane. 0.61 g of the expected product is isolated in the form of a beige powder.

Mp = 127-129°C

¹H NMR (DMSO D₆), δ (ppm): 11.7 (s, 1H); 7.41 (dd, 1H); 7.39 (d, 1H); 6.97 (dd, 1H); 6.88 (d, 1H); 4.1 (q, 2H); 1.1 (t, 3H); 0.0 (s, 9H).

1.3. Ethyl 6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate

A solution of 0.9 g (3.44 mmol) of ethyl 6-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 1.2, in 5 ml of dry DMF is added dropwise to a suspension of 0.15 g (3.79 mmol) of sodium hydride (60%) in 5 ml of dry DMF, maintained under an inert atmosphere. The reaction mixture is stirred at ambient temperature for 2 hours. 0.82 g (4.13 mmol) of 3-fluorobenzyl bromide is subsequently added, dropwise, at ambient temperature. The reaction mixture is then stirred for 20 h at ambient temperature and then diluted with 100 ml of a mixture of water and ether (1/1). The resulting mixture is separated by settling out and the aqueous phase is extracted with 30 ml of ether. The combined organic phases are washed three times with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting oil is purified by silica gel column chromatography, elution

being carried out with a mixture of heptane and ethyl acetate. 0.89 g of the expected product is isolated.

Mp = 87-88°C

¹H NMR (DMSO D₆), δ (ppm): 7.65 (m, 1H); 7.35 (s, 1H); 7.32-7.1 (m, 3H); 6.9-6.6 (m, 3H); 5.80 (s, 2H); 4.25 (q, 2H); 1.3 (t, 3H); 0.2 (s, 9H).

1.4 6-Trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid
(Compound No. IVa)

A solution of 0.85 g (2.30 mmol) of ethyl 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate, obtained in stage 1.3, in 15 ml of ethanol and 5 ml of 1N sodium hydroxide is stirred at reflux for 4 hours. After this period of time, the reaction mixture is concentrated under reduced pressure and then taken up in 50 ml of water. The medium is acidified at pH 1 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water, and then dried under reduced pressure. 0.65 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

Mp = 189-191°C

¹H NMR (DMSO D₆), δ (ppm): 13.1 (broad peak, 1H); 7.7 (m, 2H); 7.3 (m, 3H); 7.1 (m, 1H); 6.9 (m, 2H); 5.9 (s, 2H); 0.35 (s, 9H).

20

1.5 2-(Azetidin-1-yl)-5-nitropyridine

4.7 g (80.76 mmol) of azetidine are added dropwise to a suspension, stirred at 20°C, of 27.9 g (0.201 mol) of potassium carbonate and of 11 g (67.3 mmol) of 2-chloro-5-nitropyridine in 100 ml of dimethylformamide. The mixture is stirred for 5 minutes at 20°C and then for 6 hours at 70°C. After this period of time, the suspension is poured into a mixture of 300 ml of water and 300 ml of ethyl acetate. The aqueous phase is separated and then extracted with 200 ml of ethyl acetate. The organic phases are combined, washed three times with 250 ml of water and then dried over sodium sulphate and concentrated under reduced pressure. 11.7 g of the expected product are thus obtained in the form of a solid.

30

Mp = 132-134°C

¹H NMR (CDCl₃), δ (ppm): 8.92 (d, 1H); 8.09 (dxd, 1H); 6.07 (d, 1H); 4.12 (m, 4H); 2.46 (quint., 2H).

35 1.6 3-Amino-6-(azetidin-1-yl)pyridine

A suspension of 11.5 g (64.18 mmol) of 2-(azetidin-1-yl)-5-nitropyridine, prepared in the previous stage, and of 1 g of Pd/C at 10% in 400 ml of ethanol is stirred vigorously at 20°C under 5 atmospheres of hydrogen for 4 hours. After this period of time, the mixture is filtered through a celite buffer and then concentrated under reduced pressure. 9.3 g of the expected product are thus obtained, which product is used as it is in the subsequent synthesis.

¹H NMR (DMSO D₆), δ (ppm): 7.57 (d, 1H); 6.92 (dxd, 1H); 6.2 (d, 1H); 4.46 (broad peak, 2H); 3.78 (m, 4H); 2.25 (quint., 2H).

- 10 1.7 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 1)
- 114 mg (0.59 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 81 mg (0.59 mmol) of 1-hydroxybenzotriazole (HOBT) are added to a solution, stirred at 20°C under an inert atmosphere, of 0.2 g (0.59 mmol) of 6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared in stage 1.4, in 5 ml of DMF. The reaction mixture is stirred at ambient temperature for 15 minutes. 131 mg (0.88 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared in stage 1.6, are subsequently added to the reaction mixture. After stirring for 16 hours at 20°C, the reaction mixture is poured into a mixture of 30 ml of a saturated aqueous solution of NaHCO₃ and 30 ml of ethyl acetate. The resulting mixture is separated by settling out and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are washed three times with 30 ml of water, 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. The solid obtained after evaporation of the solvent under reduced pressure is washed with isopropyl ether at reflux, filtered under hot conditions and then dried under reduced pressure. 170 mg of the expected product are thus isolated.

Mp = 208-210°C

- 30 ¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.28 (d, 1H); 7.75 (dd, 1H); 7.6 (d, 1H); 7.58 (s, 1H); 7.2 (m, 3H); 7.0-6.8 (m, 3H); 6.3 (d, 1H); 5.8 (s, 2H); 3.8 (t, 4H); 2.2 (m, 2H); 0.15 (s, 9H).

Example 2 (Compound No. 2)

- 35 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-

indole-2-carboxamide

2.1 2-(3-Hydroxyazetidin-1-yl)-5-nitropyridine

A mixture of 0.311 g (2.84 mmol) of 3-hydroxyazetidine hydrochloride, 0.3 g
5 (1.89 mmol) of 2-chloro-5-nitropyridine and 0.41 ml (2.84 mmol) of triethylamine in
10 ml of dimethylformamide is heated overnight at 100°C. After this period of time, the
suspension is poured into a mixture of 30 ml of water and 30 ml of ethyl acetate. The
aqueous phase is separated and then extracted with 20 ml of ethyl acetate. The
organic phases are combined, washed three times with 25 ml of water and then dried
10 over sodium sulphate and concentrated under reduced pressure. 0.34 g of the
expected product is thus obtained in the form of a solid which will be used as it is in the
subsequent synthesis.

¹H NMR (DMSO D₆), δ (ppm): 8.95 (s, 1H); 8.21 (dxd, 1H); 6.41 (d, 1H); 5.85 (d, 1H);
4.62 (m, 1H); 4.37 (m, 2H); 3.9 (m, 2H).

15

2.2 3-Amino-6-(3-hydroxyazetidin-1-yl)pyridine

A suspension of 0.34 g (1.74 mmol) of 2-(3-hydroxyazetidin-1-yl)-5-nitropyridine,
prepared in the preceding stage, and of 9 mg of Pd/C at 10% in 10 ml of ethanol is
stirred vigorously at 20°C under 5 atmospheres of hydrogen for 4 hours. After this
20 period of time, the mixture is filtered through a celite buffer and then concentrated
under reduced pressure. The resulting product is purified by silica column
chromatography, elution being carried out with a mixture of dichloromethane and
methanol. 0.1 g of the expected product is thus obtained, which product will be used as
it is in the subsequent synthesis.

25 ¹H NMR (DMSO D₆), δ (ppm): 7.58 (s, 1H); 6.91 (d, 1H); 6.22 (d, 1H); 5.48 (broad
peak, 1H); 4.48 (broad peak, 3H); 3.98 (m, 2H); 3.49 (m, 2H).

2.3 N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxamide (Compound No. 2)

30 114 mg (0.59 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
(EDAC) and 81 mg (0.59 mmol) of 1-hydroxybenzotriazole (HOBT) are added to a
solution, stirred at 20°C under an inert atmosphere, of 0.2 g (0.59 mmol) of
6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1H-indole-2-carboxylic acid, prepared in
stage 1.4, in 5 ml of DMF. The reaction mixture is stirred at ambient temperature for 15
35 minutes. 145 mg (0.88 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared

in stage 2.2, are subsequently added to the reaction mixture. After stirring at 20°C for 20 hours, the reaction mixture is poured into a mixture of 30 ml of a saturated aqueous solution of NaHCO₃ and 30 ml of ethyl acetate. The resulting mixture is separated by settling out and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are washed three times with 30 ml of water, 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. The solid obtained after evaporation of the solvent under reduced pressure is recrystallized from isopropyl ether. 175 mg of the expected product are thus isolated.

Mp = 188-189°C

¹H NMR (DMSO D₆), δ (ppm): 10.15 (s, 1H); 8.25 (d, 1H); 7.7 (dd, 1H); 7.6 (d, 1H); 7.55 (s, 1H); 7.3-7.18 (m, 3H); 7.0-6.75 (m, 3H); 6.3 (d, 1H); 5.85 (s, 2H); 5.5 (d, 1H); 4.45 (m, 1H); 4.0 (m, 2H); 3.5 (m, 2H); 0.15 (s, 9H).

Example 3 (Compound No. 3)

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

3.1 1-Bromo-3-trimethylsilylbenzene

26.49 ml (42.39 mmol) of a solution of BuLi (1.5M/hexane) are added dropwise, with stirring, over 30 min, to a solution of 10 g (42.39 mmol) of 1,3-dibromobenzene in 80 ml of anhydrous Et₂O, cooled to -78°C and maintained under a nitrogen atmosphere. After stirring for a further 30 min at -78°C, 5.96 ml (46.63 mmol) of TMSCl are introduced dropwise into the reaction mixture. The stirring is maintained at this temperature for 90 min and the reaction mixture is subsequently hydrolysed by adding 15 ml of water. The product is extracted with ethyl acetate (3 x 50 ml). The combined organic phases are washed with a saturated aqueous solution of NaCl (2 x 25 ml), dried over Na₂SO₄, filtered and evaporated under reduced pressure. The reaction crude is purified by silica gel column chromatography, elution being carried out with heptane, so as to isolate 9.3 g of the expected 1-bromo-3-trimethylsilylbenzene, in the form of a colourless oil.

¹H NMR (DMSO D₆), δ (ppm): 5.75 (s, 1H), 7.46 (m, 1H), 7.4 (m, 1H), 7.22 (t, 1H), 0.2 (s, 9H).

3.2 3-Trimethylsilylbenzaldehyde

16.36 ml (26.18 mmol) of BuLi (1.6N/hexane) are added dropwise, with stirring and over 30 min, to a solution of 5 g (21.89 mmol) of 1-bromo-3-trimethylsilylbenzene prepared according to the protocol described in stage 3.1, in 40 ml of anhydrous Et₂O, cooled to 0°C and maintained under a nitrogen atmosphere. The stirring is continued at 0°C for a further 30 min, and then maintained at ambient temperature for 90 min. 2.69 ml (34.91 mmol) of DMF, diluted in 17 ml of anhydrous Et₂O, are subsequently introduced into the reaction mixture. After stirring for 3 h at ambient temperature, the reaction mixture is hydrolysed at 0°C by successive additions of 10 ml of a concentrated HCl solution and 100 ml of water. The product is extracted with 3 x 50 ml of CH₂Cl₂. The combined organic phases are washed with 100 ml of water, dried over Na₂SO₄, filtered and evaporated under reduced pressure. The reaction crude is purified by flash chromatography on a silica gel column, elution being carried out with a gradient of 10 to 20% of CH₂Cl₂ in heptane, to give 1.82 g of expected 3-trimethylsilylbenzaldehyde in the form of a yellow oil.

¹H NMR (DMSO D₆), δ (ppm): 10.01 (s, 1H); 8.0 (s, 1H); 7.85 (d, 1H); 7.8 (d, 1H); 7.5 (dd, 1H) 0.3 (s, 9H)

3.3 Ethyl 2-azido-3-(3-trimethylsilylphenyl)propenoate

A mixture of 31.4 ml (87.5 mmol) of ethyl azidoacetate (at 34% in CH₂Cl₂) and 3.9 g (21.87 mmol) of 3-trimethylsilylbenzaldehyde prepared according to the procedure described in stage 3.2, diluted in 3 ml of EtOH, is added dropwise to a solution of 2 g (87.5 mmol) of sodium in 30 ml of anhydrous EtOH, maintained under a nitrogen atmosphere and cooled to -10°C. The reaction mixture is stirred at 0°C for 4 h. It is subsequently hydrolysed by adding, with vigorous stirring, 100 ml of an aqueous solution of NH₄Cl (30%). The aqueous phase is extracted with 3 x 50 ml of EtOAc. The combined organic phases are washed with water, dried over Na₂SO₄ and concentrated under reduced pressure. The reaction crude is purified by silica gel column chromatography, elution being carried out with an isocratic mixture of heptane and CH₂Cl₂ (80/20). 1.7 g of the expected ethyl 2-azido-3-(3-trimethylsilylphenyl)propenoate are thus isolated in the form of a yellow oil.

¹H NMR (DMSO D₆), δ (ppm): 7.9 (d, 1H); 7.8 (s, 1H); 7.4 (d, 1H); 7.3 (dd, 1H); 6.9 (s, 1H); 4.2 (q, 2H); 1.2 (t, 3H); 0.15 (s, 9H).

MS: [MH]⁺ = 289.

3.4 Ethyl 5-trimethylsilyl-1*H*-indole-2-carboxylate

0.62 g (0.59 mmol) of the dirhodium(II) heptafluorobutyrate dimer complex is added to a solution of 1.7 g (5.90 mmol) of ethyl 2-azido-3-(3-trimethylsilylphenyl)propenoate prepared according to the procedure described in stage 3.3, in 25 ml of dry toluene, maintained under an inert atmosphere. The reaction mixture is stirred for 7 h at 40°C. A second portion of 0.62 g (0.59 mmol) of the dirhodium(II) heptafluorobutyrate dimer complex is added to the reaction mixture while maintaining the stirring and the heating at 40°C for a further 1 h. After a return to ambient temperature, the reaction mixture is filtered over silica gel, elution being carried out with toluene. The filtrate is subsequently concentrated under reduced pressure. The greenish solid obtained is triturated several times in a minimum amount of heptane, until a white powder is obtained. The latter is dried under reduced pressure to give 0.87 g of the expected ethyl 5-trimethylsilyl-1*H*-indole-2-carboxylate in the form of a white powder.

Mp = 114-115°C

¹H NMR (DMSO D₆), δ (ppm): 11.7 (s, 1H); 7.7 (s, 1H); 7.35 (d, 1H); 7.25 (d, 1H); 7.0 (s, 1H); 4.2 (q, 2H); 1.2 (t, 3H); 0.15 (s, 9H).

LC-MS: 260 ([M-H]⁻, Rt= 5.05 min.).

3.5 Ethyl 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate

0.32 g (1.68 mmol) of 3-fluorobenzyl bromide and 100 mg (0.31 mmol) of tetrabutylammonium bromide are added, slowly at ambient temperature, to a suspension of 0.4 g (1.53 mmol) of ethyl 5-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 3.4, and of 0.64 g (4.59 mmol) of potassium carbonate in 15 ml of dry acetonitrile, maintained under an inert atmosphere. The reaction mixture is stirred at reflux for 2 h. After this period of time, the cooled suspension is filtered through a frit and rinsed with acetonitrile. The reaction crude obtained after evaporation of the filtrate under reduced pressure is purified by flash chromatography on a silica gel column, elution being carried out with a gradient of 5 to 15% of ether in heptane. 0.5 g of the expected ethyl 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate is thus isolated.

Mp = 80-82°C

¹H NMR (CDCl₃), δ (ppm): 7.9 (s, 1H); 7.5-7.1 (m, 4H); 6.9 (m, 2H); 6.75 (m, 1H); 5.8 (s, 2H); 4.3 (q, 2H); 1.35 (t, 3H); 0.3 (s, 9H).

LC-MS: 370 ([M+H]⁺, Rt= 6.22 min.).

3.6 5-Trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid
(Compound No. IVb)

A solution of 0.6 g (1.62 mmol) of ethyl 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate, obtained in stage 3.5, in 10 ml of absolute ethanol and 2.44 ml of
5 1N sodium hydroxide, is stirred at reflux for 4 hours. After this period of time, the reaction mixture is concentrated under reduced pressure and then taken up in 50 ml of water. The medium is acidified at pH 1 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 0.53 g of the expected product is thus obtained, which product is
10 used as it is in the subsequent stage.

Mp = 177-178°C

¹H NMR (DMSO D₆), δ (ppm): 13.1 (broad peak, 1H); 7.9 (s, 1H); 7.4 (d, 1H); 7.4 (m, 3H); 7.1 (m, 1H); 6.85 (m, 2H); 5.9 (s, 2H); 0.3 (s, 9H).

15 3.7 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (compound No. 3)

98 mg (0.51 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) and 69 mg (0.51 mmol) of 1-hydroxybenzotriazole (HOBt) are added to a solution, stirred at 20°C under an inert atmosphere, of 0.16 g (0.47 mmol) of
20 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 3.6, in 10 ml of DMF. The reaction mixture is stirred at ambient temperature for 15 minutes. 84 mg (0.56 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, are subsequently added to the reaction mixture. After stirring at 20°C for 16 h, the reaction
25 mixture is poured into a mixture of 30 ml of a saturated aqueous solution of NaHCO₃ and 30 ml of EtOAc. The aqueous phase is extracted with 20 ml of EtOAc. The combined organic phases are washed with 3 x 30 ml of water, dried over Na₂SO₄, and then concentrated under reduced pressure. The solid obtained after evaporation of the solvent under reduced pressure is washed with isopropyl ether at reflux, filtered under
30 hot conditions and then dried under reduced pressure. 75 mg of the expected product are thus isolated.

Mp = 212-213°C

¹H NMR (DMSO D₆), δ (ppm): 10.1 (s, 1H); 8.2 (s, 1H); 7.75 (s, 1H); 7.7 (d, 1H); 7.4 (d, 1H); 7.3 (s, 1H); 7.35 (d, 1H); 7.2 (q, 1H); 6.9 (t, 1H); 6.8 (d, 1H); 6.75 (d, 1H); 6.25 (d, 1H); 5.8 (s, 2H); 3.8 (t, 4H); 2.2 (m, 2H); 0.15 (s, 9H)
35

LC-MS: 473 ([M+H]⁺, *R*_t= 1.28 min.).

Example 4 (Compound No. 4)

5 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

123 mg (0.64 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 87 mg (0.64 mmol) of 1-hydroxybenzotriazole (HOBT) are added to a solution, stirred at 20°C under an inert atmosphere, of 0.2 g (0.59 mmol) of 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 3.6, in 6 ml of DMF. The reaction mixture is stirred at ambient temperature for 15 minutes. 145 mg (0.88 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared in stage 2.2, are subsequently added to the reaction mixture. After stirring at 20°C for 16 hours, the reaction mixture is poured into a mixture of 30 ml of a saturated aqueous solution of NaHCO₃ and 30 ml of ethyl acetate. The resulting mixture is separated by settling out and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are washed three times with 30 ml of water, 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. The solid obtained after evaporation of the solvent under reduced pressure is recrystallized from isopropyl ether. 200 mg of the expected product are thus isolated.

Mp = 207-208°C

¹H NMR (DMSO D₆), δ (ppm): 10.1 (s, 1H); 8.2 (s, 1H); 7.72 (s, 1H); 7.7 (d, 1H); 7.4 (d, 1H); 7.25 (m, 2H); 7.2 (m, 1H); 6.9 (m, 1H); 6.8 (m, 2H); 6.3 (d, 1H); 5.8 (s, 2H); 5.5 (d, 1H); 4.4 (m, 1H); 4.0 (m, 2H); 3.5 (m, 2H); 0.2 (s, 9H)

LC-MS: 489 ([M+H]⁺, *R*_t= 1.25 min.).

Example 5 (Compound No. 5)

30 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

5.1 Ethyl 7-trimethylsilyl-1*H*-indole-2-carboxylate

35 70 ml of xylene are brought to reflux in a three-necked flask surmounted by a

condenser and a dropping funnel and maintained under an inert atmosphere. A solution of 0.7 g (2.42 mmol) of ethyl 2-azido-3-(3-trimethylsilylphenyl)propenoate prepared according to the procedure described in stage 3.3, in 1 ml of xylene, is subsequently added dropwise. The reaction mixture is refluxed for a further 1 h with stirring. After a return to ambient temperature, the reaction crude obtained after evaporation of the solvent under reduced pressure is purified by flash chromatography on a silica gel column, elution being carried out with a gradient of 0 to 20% of ethyl ether in heptane. Two regioisomeric products are thus isolated: 170 mg of ethyl 5-trimethylsilyl-1*H*-indole-2-carboxylate, in the form of a white powder, and 150 mg of the expected ethyl 7-trimethylsilyl-1*H*-indole-2-carboxylate in the form of an oil.

¹H NMR (DMSO *D*₆), δ (ppm): 10.8 (s, 1H); 7.7 (d, 1H); 7.4 (d, 1H); 7.2 (s, 1H); 7.1 (m, 1H); 4.3 (q, 2H); 1.3 (t, 3H); 0.4 (s, 9H).

LC-MS: 260 ([M-H]⁻, *R*_t = 5.48 min.).

5.2 Ethyl 7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate

0.42 ml (3.44 mmol) of 3-fluorobenzyl bromide is added, slowly at ambient temperature, to a suspension of 0.75 g (2.87 mmol) of ethyl 7-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 5.1, and of 1.18 g (8.61 mmol) of potassium carbonate in 50 ml of dry acetonitrile, maintained under an inert atmosphere. The reaction mixture is stirred at reflux for 18 h. After this period of time, the cooled suspension is filtered through a frit and then rinsed with acetonitrile. The reaction crude obtained after evaporation of the filtrate under reduced pressure is purified by flash chromatography on a silica gel column, elution being carried out with a gradient of 10 to 50% of dichloromethane in heptane. 0.67 g of the expected ethyl 7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate is thus isolated.

¹H NMR (DMSO *D*₆), δ (ppm): 7.8 (d, 1H); 7.5 (d, 1H); 7.2 (m, 2H); 6.95 (m, 2H); 6.35 (m, 2H); 5.9 (s, 2H); 4.1 (q, 2H); 1.1 (t, 3H); 0.2 (s, 9H).

LC-MS: 370 ([M+H]⁺, *R*_t = 6.15 min.).

5.3 7-Trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid
(Compound No. IVc)

0.23 g (4.06 mmol) of potassium hydroxide is added to a solution of 0.5 g (1.35 mmol) of ethyl 7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 5.2, in 30 ml of a mixture (v/v/v) of methanol, water and dioxane. After stirring at reflux for three hours, the reaction

mixture is one-third concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 1 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 0.37 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

¹H NMR (DMSO D₆), δ (ppm): 12.6 (broad peak, 1H); 7.6 (d, 1H); 7.3 (d, 1H); 7.2 (s, 1H); 7.0 (m, 2H); 6.75 (m, 1H); 6.2 (m, 1H); 6.1 (d, 1H); 5.8 (s, 2H); 0.05 (s, 9H).

LC-MS: 342 ([M+H]⁺, R_t = 1.48 min.).

5.4 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 5)

0.28 g (1.46 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC) and 0.2 g (1.46 mmol) of 1-hydroxybenzotriazole (HOBt) are added to a solution, stirred at 20°C under an inert atmosphere, of 0.5 g (1.46 mmol) of 7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 5.3, in 10 ml of DMF. The reaction mixture is stirred at ambient temperature for 20 minutes. 0.33 g (2.20 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, is subsequently added to the reaction mixture. After stirring at 20°C for 18 h, the reaction mixture is poured into a mixture of 30 ml of a saturated aqueous solution of NaHCO₃ and 30 ml of EtOAc. The aqueous phase is extracted with 20 ml of EtOAc. The combined organic phases are washed with 3 × 30 ml of water, dried over Na₂SO₄, then concentrated under reduced pressure. The solid obtained after evaporation of the solvent under reduced pressure is purified by flash chromatography on a silica gel column, elution being carried out with a gradient of 2 to 10% of MeOH in CH₂Cl₂. The isolated product is subsequently precipitated, then washed with a mixture of hexane and isopropyl ether at reflux, filtered under hot conditions, and then dried under reduced pressure. 147 mg of the expected product are thus isolated.

Mp = 160-162°C

¹H NMR (DMSO D₆), δ (ppm): 9.9 (s, 1H); 8.0 (s, 1H); 7.7 (d, 1H); 7.5 (d, 1H); 7.3 (d, 1H); 7.2 (s, 1H); 7.0 (m, 2H); 6.8 (m, 1H); 6.25 (d, 1H); 6.15 (m, 2H); 5.8 (s, 2H); 3.7 (t, 4H); 2.1 (m, 2H); 0.15 (s, 9H).

LC-MS: 473 ([M+H]⁺, R_t = 1.25 min.).

Example 6 (Compound No. 6)

N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 6)

Compound No. 6 was prepared according to a process similar to that described in stage 5.4, by reacting 0.15 g (0.44 mmol) of 7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 5.3, with 109 mg (0.66 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared according to the protocol described in stage 2.2, in the presence of 87 mg (0.44 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and of 61 mg (0.44 mmol) of 1-hydroxybenzotriazole (HOBT) in 5 ml of dimethylformamide. 27 mg of the expected product are obtained.

¹H NMR (DMSO D₆), δ (ppm): 9.9 (s, 1H); 8.0 (s, 1H); 7.7 (d, 1H); 7.5 (d, 1H); 7.3 (d, 1H); 7.2 (s, 1H); 7.0 (m, 2H); 6.8 (m, 1H); 6.25 (d, 1H); 6.15 (m, 2H); 5.8 (s, 2H); 5.5 (d, 1H); 4.4 (m, 1H); 4.0 (m, 2H); 3.5 (m, 2H); 0.15 (s, 9H).

LC-MS: 489 ([M+H]⁺, Rt= 1.3 min.).

Mp = 215-217°C.

Example 7 (Compound No. 7)

N-[6-(Dimethylamino)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

Compound No. 7 was prepared according to a process similar to that described in stage 5.4, by reacting 0.3 g (0.88 mmol) of 5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 3.6, with 181 mg (1.32 mmol) of 3-amino-6-(dimethylamino)pyridine in the presence of 185 mg (0.97 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and of 131 mg (0.97 mmol) of 1-hydroxybenzotriazole (HOBT) in 10 ml of dimethylformamide. The product obtained is purified by silica column chromatography, elution being carried out with a mixture of dichloromethane and acetone. The solid obtained after evaporation of the solvent under reduced pressure is recrystallized from isopropyl alcohol. 200 mg of the expected product are thus isolated.

Mp = 204-205°C

¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.4 (s, 1H); 7.9 (m, 2H); 7.55 (d, 1H); 7.4 (m, 2H); 7.3 (m, 1H); 7.0 (m, 1H); 6.9 (m, 2H); 6.65 (d, 1H); 5.9 (s, 2H); 3.0 (s, 6H); 0.25 (s, 9H).

LC-MS: 461 ([M-H]⁻, *R*_t = 1.3 min.).

Example 8 (Compound No. 8)

- 5 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(ethyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

8.1 Ethyl 5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate

A solution of 2.0 g (6.03 mmol) of ethyl 5-iodo-1*H*-indole-2-carboxylate (obtained according to the protocol described in the literature, Synthetic Communications (2003) 33(14), 2423-2427) in 10 ml of dry DMF is added dropwise, at 0°C, to a suspension of 0.26 g (6.63 mmol) of sodium hydride (60%) in 10 ml of dry DMF, maintained under an inert atmosphere. The reaction mixture is stirred at ambient temperature for one hour. 1.37 g (7.24 mmol) of 3-fluorobenzyl bromide are subsequently added, dropwise, at 15 0°C. The reaction mixture is then stirred at ambient temperature for 18 h and then diluted with 200 ml of a mixture of water and ethyl acetate (1/1). The resulting mixture is separated by settling out and the aqueous phase is extracted with 2 × 30 ml of ethyl acetate. The combined organic phases are washed three times with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting oil is purified by silica gel column chromatography, elution being carried out with a mixture of 20 heptane and ethyl acetate. 1.87 g of the expected product are isolated.

¹H NMR (DMSO *D*₆), δ (ppm): 8.15 (s, 1H); 7.6 (d, 1H); 7.5 (d, 1H); 7.35 (s, 1H); 7.3 (m, 1H); 7.1 (m, 1H); 6.85 (m, 2H); 5.9 (s, 2H); 4.3 (q, 2H); 1.3 (t, 3H).

LC-MS: 424 ([M+H]⁺, *R*_t = 1.65).

25

8.2 5-Iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid

A solution of 1.00 g (2.36 mmol) of ethyl 5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate, obtained in stage 8.1, and of 0.4 g (7.09 mmol) of potassium hydroxide, in 30 ml of a mixture (v/v/v) of methanol, dioxane and water, is stirred at reflux for 3 30 hours. After this period of time, the reaction mixture is concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 1 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 0.69 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

35 ¹H NMR (DMSO *D*₆), δ (ppm): 13.2 (broad peak, 1H); 8.1 (s, 1H); 7.5 (d, 1H); 7.4 (d,

1H); 7.25 (m, 2H); 7.0 (m, 1H); 6.8 (m, 2H); 5.8 (s, 2H).

LC-MS: 394 ([M-H]⁻, R_t = 3.5).

8.3 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

0.29 g (1.52 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 0.2 g (1.52 mmol) of 1-hydroxybenzotriazole (HOBT) are added to a solution, stirred at 20°C under an inert atmosphere, of 0.6 g (1.52 mmol) of 5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared in stage 8.2, in 15 ml of DMF. The reaction mixture is stirred at ambient temperature for 20 minutes. 0.25 g (1.67 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, is subsequently added to the reaction mixture. After stirring at 20°C for 18 hours, the reaction mixture is poured into a mixture of 50 ml of water and 50 ml of ethyl acetate. The resulting mixture is separated by settling out and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are washed three times with 30 ml of water, dried over sodium sulphate and then concentrated under reduced pressure. The isolated product is subsequently precipitated, then washed with isopropyl ether at reflux, filtered under hot conditions, and then dried under reduced pressure. 0.47 g of the expected product is thus isolated.

¹H NMR (DMSO D₆), δ (ppm): 10.3 (s, 1H); 8.35 (s, 1H); 8.2 (s, 1H); 7.85 (d, 1H); 7.55 (d, 1H); 7.45 (d, 1H); 7.3 (m, 2H); 7.05 (m, 1H); 6.9 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H).

LC-MS: 527 ([M+H]⁺, R_t = 5.07).

8.4 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(ethyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (compound No. 8)

27 mg (0.31 mmol) of (ethyl)dimethylsilane and 15 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium are added to a suspension of 0.15 g (0.28 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 8.3, and of 0.18 g (0.85 mmol) of potassium triphosphate in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP), maintained under an inert atmosphere. The reaction mixture is then stirred at ambient temperature under an inert atmosphere for 6 h and then diluted with 40 ml of a mixture of water and ethyl acetate (1/1). The resulting mixture is separated by settling out and the aqueous phase is extracted with 2 × 10 ml of ethyl acetate. The combined organic phases are

dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting oil is purified by silica gel column chromatography, elution being carried out with a mixture of heptane and ethyl acetate. 108 mg of the expected product are isolated.

5 Mp = 188-189°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.4 (s, 1H); 7.85 (m, 2H); 7.6 (d, 1H); 7.35 (m, 3H); 7.1 (m, 1H); 6.9 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H); 0.95 (t, 3H); 0.75 (q, 2H); 0.3 (s, 6H).

LC-MS: 487 ([M+H]⁺, R_t = 1.37).

10

Example 9 (Compound No. 9)

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 9)

15 Compound No. 9 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.28 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 8.3, with 44 mg (0.31 mmol) of (cyclohexyl)dimethylsilane in the presence of 0.18 g (0.85 mmol) of potassium triphosphate and of 15 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP).
20 93 mg of the expected product are obtained in the form of a white solid.

Mp = 202-203°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.4 (s, 1H); 7.8 (m, 2H); 7.5 (d, 1H); 7.35 (m, 3H); 7.0 (m, 1H); 6.9 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H);
25 1.65 (m, 5H); 1.3-0.7 (m, 6H); 0.25 (s, 6H).

LC-MS: 541 ([M+H]⁺, R_t = 1.56).

Example 10 (Compound No. 10)

30 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-trifluoromethyl)phenyl)methyl]-1*H*-indole-2-carboxamide

10.1 Ethyl 6-trimethylsilyl-1-[(3-trifluoromethyl)phenyl)methyl]-1*H*-indole-2-carboxylate

35 0.52 ml (3.83 mmol) of 3-(trifluoromethyl)phenylmethanol and 0.92 g (3.83 mmol) of

(cyanomethylene)tributylphosphorane (CMBP) are added, at ambient temperature, to a solution of 0.5 g (1.91 mmol) of ethyl 6-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 1.2, in 8 ml of dry toluene, maintained under an inert atmosphere. The reaction mixture is stirred at 110°C for 15 hours and then concentrated to dryness. The reaction crude is subsequently purified by successive rounds of flash chromatography on a silica gel column, to give 0.72 g of expected ethyl 6-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylate in the form of an oil.

¹H NMR (DMSO D₆), δ (ppm): 7.49-7.45 (m, 2H); 7.36-7.33 (m, 2H); 7.25 (t, 1H); 7.12 (s, 1H); 7.04-7.00 (m, 2H); 5.73 (s, 2H); 4.04 (q, 2H); 1.03 (t, 3H); 0.00 (s, 9H).

LC-MS: 420 ([M+H]⁺, Rt= 3.57).

10.2 6-Trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid (Compound No. IVd)

A solution of 0.125 g (2.18 mmol) of potassium hydroxide in 1 ml of water is added to a solution of 0.31 g (0.73 mmol) of ethyl 6-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylate, obtained in stage 10.1, in 10 ml of ethanol. After stirring at 85°C for two hours, the reaction mixture is concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 5 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 0.24 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

¹H NMR (DMSO D₆), δ (ppm): 13.2 (broad peak, 1H); 7.7 (m, 2H); 7.6 (m, 2H); 7.5 (m, 1H); 7.3 (m, 3H); 6.0 (s, 2H); 1.2 (s, 9H).

10.3 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide (Compound No. 10)

Compound No. 10 was prepared according to a process similar to that described in stage 8.3, by reacting 0.11 g (0.28 mmol) of 6-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 10.2, with 46 mg (0.31 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, in the presence of 59 mg (0.31 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 45 mg (0.31 mmol) of 1-hydroxybenzotriazole (HOBT) in 2 ml of

dimethylformamide. 200 mg of the expected product are obtained.

Mp = 167-168°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.35 (d, 1H); 7.85 (dd, 1H); 7.7 (m, 2H); 7.65 (s, 1H); 7.6 (m, 1H); 7.5 (t, 1H); 7.45 (m, 1H); 7.35 (s, 1H); 7.25 (d, 1H); 6.4 (d, 1H); 6.0 (s, 2H); 3.95 (t, 4H); 2.3 (m, 2H); 0.2 (s, 9H).

LC-MS: 523 ([M+H]⁺, Rt= 1.42 min.).

Example 11 (Compound No. 11)

10 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide (Compound No. 11)

Compound No. 11 was prepared according to a process similar to that described in stage 8.3, by reacting 0.11 g (0.28 mmol) of 6-trimethylsilyl-1-[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 10.2, with 51 mg (0.31 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared according to the protocol described in stage 2.2, in the presence of 59 mg (0.31 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide (EDAC) and 45 mg (0.31 mmol) of 1-hydroxybenzotriazole (HOBT) in 2 ml of dimethylformamide. 0.21 g of the expected product is obtained.

20 Mp = 183-184°C

¹H NMR (DMSO D₆), δ (ppm): 10.3 (s, 1H); 8.4 (d, 1H); 7.85 (m, 1H); 7.7 (m, 2H); 7.65 (s, 1H); 7.6 (m, 1H); 7.5 (t, 1H); 7.45 (m, 1H); 7.35 (s, 1H); 7.25 (d, 1H); 6.4 (d, 1H); 6.0 (s, 2H); 5.6 (d, 1H); 4.6 (m, 1H); 4.15 (m, 2H); 3.65 (m, 2H); 0.25 (s, 9H).

LC-MS: 539 ([M+H]⁺, Rt= 1.37min.).

25

Example 12 (Compound No. 12)

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(diphenyl)methylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

30 Compound No. 12 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.28 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 8.3, with 167 mg (0.84 mmol) of diphenylmethylsilane in the presence of 0.18 g (0.84 mmol) of potassium triphosphate and of 15 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP).

35

19 mg of the expected product are obtained.

Mp = 98-100°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.4 (s, 1H); 7.85 (m, 2H); 7.65-7.25 (m, 14H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.95 (m, 4H); 2.3 (m, 2H); 0.9 (s, 3H).

LC-MS: 597 ([M+H]⁺, Rt= 1.51).

Example 13 (Compound No. 13)

10 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide (compound No. 13)

13.1 Ethyl 5-trimethylsilyl-1-[[[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylate

15 0.51 ml (3.749 mmol) of 3-(trifluoromethyl)phenylmethanol and 0.9 g (3.749 mmol) of (cyanomethylene)tributylphosphorane (CMBP) are added, at ambient temperature, to a solution of 0.49 g (1.87 mmol) of ethyl 5-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 3.4, in 8 ml of dry toluene, maintained under an inert atmosphere. The reaction mixture is stirred at 110°C for 15
20 hours and then concentrated to dryness. The reaction crude is subsequently purified by flash chromatography on a silica gel column, elution being carried out with a mixture of hexane and ethyl acetate, to give 0.73 g of the expected ethyl 5-trimethylsilyl-1-[[[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylate.

25 ¹H NMR (DMSO D₆), δ (ppm): 7.90 (s, 1H); 7.62-7.57 (m, 2H); 7.51-7.43 (m, 3H); 7.40 (s, 1H); 7.17 (d, 1H); 5.92 (s, 2H); 4.28 (q, 2H); 1.26 (t, 3H); 0.27 (s, 9H).

LC-MS: 420 ([M+H]⁺, Rt= 3.62).

13.2 5-Trimethylsilyl-1-[[[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid (Compound No. IVe)

30 A solution of 0.125 g (2.18 mmol) of potassium hydroxide in 1 ml of water is added to a solution of 0.31 g (0.73 mmol) of ethyl 5-trimethylsilyl-1-[[[(3-trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylate, obtained in stage 13.1, in 10 ml of ethanol. After stirring at 85°C for two hours, the reaction mixture is concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 5
35 by successive additions of 1N hydrochloric acid. The precipitate is recovered by

filtration, washed with water and then dried under reduced pressure. 0.22 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

¹H NMR (DMSO D₆), δ (ppm): 12.9 (broad peak, 1H); 7.8 (s, 1H); 7.5 (m, 2H); 7.4 (m, 2H); 7.3 (d, 1H); 7.2 (s, 1H); 7.1 (d, 1H); 5.85 (s, 2H); 1.2 (s, 9H).

13.3 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide (Compound No. 13)

Compound No. 13 was prepared according to a process similar to that described in stage 8.3, by reacting 0.105 g (0.27 mmol) of 5-trimethylsilyl-1-[[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 13.2, with 44 mg (0.30 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, in the presence of 57 mg (0.30 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 43 mg (0.30 mmol) of 1-hydroxybenzotriazole (HOBT) in 6 ml of dimethylformamide. 95 mg of the expected product are obtained.

Mp = 199-200°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.3 (s, 1H); 7.9 (s, 1H); 7.8 (d, 1H); 7.55 (m, 3H); 7.5 (m, 1H); 7.4 (m, 2H); 7.3 (d, 1H); 6.3 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H); 0.25 (s, 9H).

LC-MS: 523 ([M+H]⁺, Rt= 1.50 min).

Example 14 (Compound No. 14)

25 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxamide (Compound No. 14)

Compound No. 14 was prepared according to a process similar to that described in stage 8.3, by reacting 0.1 g (0.26 mmol) of 5-trimethylsilyl-1-[[[3-(trifluoromethyl)phenyl]methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 13.2, with 46 mg (0.28 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared according to the protocol described in stage 2.2, in the presence of 54 mg (0.28 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 41 mg (0.28 mmol) of 1-hydroxybenzotriazole (HOBT) in 6 ml of dimethylformamide. 100 mg of the expected product are obtained.

35 Mp = 217-218°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.2 (d, 1H); 7.75 (s, 1H); 7.7 (dd, 1H); 7.45-7.35 (m, 4H); 7.5 (m, 1H); 7.3 (m, 2H); 7.2 (m, 1H); 6.3 (d, 1H); 5.85 (s, 2H); 5.45 (d, 1H); 4.4 (m, 1H); 4.0 (m, 2H); 3.55 (m, 2H); 0.0 (s, 9H).

LC-MS: 539 ([M+H]⁺, Rt= 1.40 min.).

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Example 15 (Compound No. 15)

N-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide (Compound No. 15)

10

15.1. Ethyl 6-trimethylsilyl-1-[(4-pyridinyl)methyl]-1*H*-indole-2-carboxylate

0.42 g (3.82 mmol) of 4-pyridinylmethanol and 0.92 g (3.826 mmol) of (cyanomethylene)tributylphosphorane (CMBP) are added, at ambient temperature, to a solution of 0.5 g (1.91 mmol) of ethyl 6-trimethylsilyl-1*H*-indole-2-carboxylate, obtained according to the protocol described in stage 1.2, in 8 ml of dry toluene, maintained under an inert atmosphere. The reaction mixture is stirred at 110°C for 15 hours and then concentrated to dryness. The reaction crude is subsequently purified by flash chromatography on a silica gel column, elution being carried out with a mixture of heptane and ethyl acetate, to give 0.644 g of the expected ethyl 6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxylate in the form of a yellow solid.

20

¹H NMR (DMSO D₆), δ (ppm): 8.2 (d, 2H); 7.49 (d, 1H); 7.42 (s, 1H); 7.15 (s, 1H); 7.05 (d, 1H); 6.70 (d, 2H); 5.68 (s, 2H); 4.01 (q, 2H); 1.01 (t, 3H); 0.00 (s, 9H).

LC-MS: 353 ([M+H]⁺, Rt= 2.63).

25 15.2 6-Trimethylsilyl-1-[(4-pyridinyl)methyl]-1*H*-indole-2-carboxylic acid (Compound No. IVf)

A solution of 0.11 g (1.87 mmol) of potassium hydroxide in 1 ml of water is added to a solution of 0.22 g (0.62 mmol) of ethyl 6-trimethylsilyl-1-[(4-pyridinyl)methyl]-1*H*-indole-2-carboxylate, obtained in stage 15.1, in 10 ml of ethanol. After stirring at 85°C for two hours, the reaction mixture is concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 5 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 0.19 g of the expected product is thus isolated, which product is used as it is in the subsequent stage.

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¹H NMR (DMSO D₆), δ (ppm): 8.2 (d, 2H); 7.4 (d, 1H); 7.3 (s, 1H); 7.0 (d, 1H); 6.9 (s,

1H); 6.8 (d, 2H); 5.8 (s, 2H); 0.95 (s, 9H).

15.3 *N*-[6-(3-Hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide (Compound No. 15)

- 5 Compound No. 15 was prepared according to a process similar to that described in stage 8.3, by reacting 94 mg (0.29 mmol) of 6-trimethylsilyl-1-[(4-pyridinyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 15.2, with 53 mg (0.32 mmol) of 3-amino-6-(3-hydroxyazetidin-1-yl)pyridine, prepared according to the protocol described in stage 2.2, in the presence of 61 mg (0.32 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 46 mg
10 (0.32 mmol) of 1-hydroxybenzotriazole (HOBT) in 2 ml of dimethylformamide. 80 mg of the expected product is obtained.

- ¹H NMR (DMSO *D*₆), δ (ppm): 10.2 (s, 1H); 8.45 (d, 2H); 8.35 (s, 1H); 7.85 (d, 1H); 7.75 (d, 1H); 7.6 (s, 1H); 7.45 (s, 1H); 7.3 (d, 1H); 7.0 (d, 2H); 6.4 (d, 1H); 5.95 (s, 2H); 5.6
15 (d, 1H); 4.6 (m, 1H); 4.15 (m, 2H); 3.65 (m, 2H); 0.25 (s, 9H).

LC-MS: 472 ([M+H]⁺, *R*_t = 0.91 min.).

Example 16 (Compound No. 16)

- 20 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-1*H*-indole-2-carboxamide

- Compound No. 16 was prepared according to a process similar to that described in stage 8.3, by reacting 95 mg (0.29 mmol) of 6-trimethylsilyl-1-[(4-pyridinyl)methyl]-1*H*-indole-2-carboxylic acid, prepared according to the protocol described in stage 15.2,
25 with 48 mg (0.32 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, in the presence of 62 mg (0.32 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 47 mg (0.32 mmol) of 1-hydroxybenzotriazole (HOBT) in 2 ml of dimethylformamide. 95 mg of the expected product are obtained.

- 30 ¹H NMR (DMSO *D*₆), δ (ppm): 10.25 (s, 1H); 8.5 (d, 2H); 8.35 (s, 1H); 7.85 (d, 1H); 7.75 (d, 1H); 7.6 (s, 1H); 7.45 (s, 1H); 7.3 (d, 1H); 7.0 (d, 2H); 6.4 (d, 1H); 5.95 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H); 0.25 (s, 9H).

LC-MS: 456 ([M+H]⁺, *R*_t = 0.95 min.).

- 35 **Example 17 (Compound No. 17)**

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-triethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

5 17.1 Ethyl 5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate

A solution of 5.0 g (18.65 mmol) of ethyl 5-bromo-1*H*-indole-2-carboxylate in 25 ml of dry DMF is added dropwise, at 0°C, to a suspension of 0.96 g (24.24 mmol) of sodium hydride (60%) in 15 ml of dry DMF, maintained under an inert atmosphere. The reaction mixture is stirred at ambient temperature for 1 hour. 4.23 g (2.75 mmol) of 3-fluorobenzyl bromide are subsequently added dropwise, at 0°C. The reaction mixture is then stirred for 18 h at ambient temperature and then diluted with 200 ml of a mixture of water and ethyl acetate (1/1). The resulting mixture is separated by settling out and the aqueous phase is extracted with 2 × 30 ml of ethyl acetate. The combined organic phases are washed three times with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The resulting oil is purified by silica gel column chromatography, elution being carried out with a mixture of heptane and ethyl acetate. 5.76 g of the expected product are isolated.

¹H NMR (DMSO D₆), δ (ppm): 8.0 (s, 1H); 7.6 (d, 1H); 7.45 (d, 1H); 7.35 (s, 1H); 7.3 (m, 1H); 7.05 (m, 1H); 6.85 (m, 2H); 5.9 (s, 2H); 4.3 (q, 2H); 1.3 (t, 3H).

20 LC-MS: 376 ([M+H]⁺, R_t= 11.8).

17.2 5-Bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid

A solution of 1.5 g (3.99 mmol) of ethyl 5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylate, obtained in stage 17.1, and 0.67 g (11.96 mmol) of potassium hydroxide, in 45 ml of a mixture (v/v/v) of methanol, dioxane and water, is stirred at reflux for three hours. After this period of time, the reaction mixture is concentrated under reduced pressure and then taken up in 10 ml of water. The medium is acidified at pH 1 by successive additions of 1N hydrochloric acid. The precipitate is recovered by filtration, washed with water and then dried under reduced pressure. 1.17 g of the expected product are thus isolated, which product is used as it is in the subsequent stage.

LC-MS: 346 ([M-H]⁻, R_t= 3.37 min.).

17.3 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

0.77 g (4.02 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and 0.54 g (4.02 mmol) of 1-hydroxybenzotriazole (HOBT) are added to a solution, stirred at 20°C under an inert atmosphere, of 1.4 g (4.02 mmol) of 5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxylic acid, prepared in stage 17.2, in 20 ml of DMF. The reaction mixture is stirred at ambient temperature for 20 minutes. 0.66 g (4.42 mmol) of 3-amino-6-(azetidin-1-yl)pyridine, prepared according to the protocol described in stage 1.6, is subsequently added to the reaction mixture. After stirring at 20°C for 18 hours, the reaction mixture is poured into a mixture of 50 ml of water and 50 ml of ethyl acetate. The resulting mixture is separated by settling out and the aqueous phase is extracted with 20 ml of ethyl acetate. The combined organic phases are washed three times with 30 ml of water, dried over sodium sulphate and then concentrated under reduced pressure. The isolated product is subsequently precipitated, then washed with isopropyl ether at reflux, filtered under hot conditions, and then dried under reduced pressure. 11.46 g of the expected product are thus isolated.

¹H NMR (DMSO D₆), δ (ppm): 10.4 (s, 1H); 8.38 (d, 1H); 8.0 (d, 1H); 7.85 (dd, 1H); 7.6 (d, 1H); 7.45-7.25 (m, 3H); 7.05 (dt, 1H); 6.9 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H).

LC-MS: 479 ([M+H]⁺, R_t = 1.39 min.).

17.4 *N*-[6-(Azetidin-1-yl)pyridin-3-yl]-5-triethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 17)

Compound No. 17 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.31 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 17.3, with 110 mg (0.93 mmol) of triethylsilane in the presence of 0.2 g (0.94 mmol) of potassium triphosphate and of 16 mg (0.03 mmol) of bis(*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP). 26 mg of the expected product are obtained.

Mp = 166-168°C

¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.4 (d, 1H); 7.85 (m, 2H); 7.55 (d, 1H); 7.35 (m, 3H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H);

1.65 (m, 5H); 0.95 (m, 9H); 0.8(m, 6H).

LC-MS: 515 ([M+H]⁺, R_t= 1.55).

Example 18 (Compound No. 18)

5

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-tert-butyl(dimethyl)silyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

Compound No. 18 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.31 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-bromo-1-
10 [(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 17.3, with 108 mg (0.93 mmol) of tert-butyldimethylsilane in the presence of 0.2 g (0.94 mmol) of potassium triphosphate and of 16 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP). 28 mg of the expected product are obtained.

15 Mp = 110-112°C

¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.4 (d, 1H); 7.85 (m, 2H); 7.55 (d, 1H); 7.4-7.3 (m, 3H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (t, 4H); 2.3 (quint., 2H); 0.9 (s, 9H); 0.3(s, 6H).

LC-MS: 515 ([M+H]⁺, R_t= 1.53).

20

Example 19 (Compound No. 19)

N-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

25

19.1 *N*-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

The compound was prepared according to a process similar to that described in stage 5.4, by reacting 0.3 g (0.76 mmol) of 5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-
30 carboxylic acid, prepared according to the protocol described in stage 8.2, with 148 mg (0.91 mmol) of 3-amino-6-(pyrrolidin-1-yl)pyridine in the presence of 145 mg (0.76 mmol) of *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDAC) and of 105 mg (0.76 mmol) of 1-hydroxybenzotriazole (HOBT) in 5 ml of dimethylformamide. 290 mg of the expected product are obtained.

35 ¹H NMR (DMSO D₆), δ (ppm): 10.3 (s, 1H); 8.4 (d, 1H); 8.15 (s, 1H); 7.85 (dd, 1H); 7.55

(d, 1H); 7.45 (d, 1H); 7.3 (m, 2H); 7.05 (m, 1H); 6.95 (m, 2H); 6.45 (d, 1H); 5.9 (s, 2H); 3.4 (m, 4H); 1.9 (m, 4H).

LC-MS: 541 ([M+H]⁺, R_t= 1.25).

5 19.2 *N*-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound 19)

Compound No. 19 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.28 mmol) of *N*-[6-(pyrrolidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol
10 described in stage 19.1, with 120 mg (0.83 mmol) of cyclohexyldimethylsilane in the presence of 0.18 g (0.83 mmol) of potassium triphosphate and of 14 mg (0.027 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP). 41 mg of the expected product are obtained.

Mp = 192-194°C

15 ¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.4 (d, 1H); 7.85 (m, 2H); 7.55 (d, 1H); 7.4-7.3 (m, 3H); 7.05 (m, 1H); 6.95 (m, 2H); 6.45 (d, 1H); 5.9 (s, 2H); 3.4 (m, 4H); 2.0 (m, 4H); 1.7 (m, 4H); 1.15 (m, 6H); 0.8 (m, 1H); 0.3 (s, 6H).

LC-MS: 555 ([M+H]⁺, R_t= 1.64).

20 **Example 20 (Compound No. 20)**

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(phenyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide (Compound No. 20)

Compound No. 20 was prepared according to a process similar to that described in
25 stage 8.4, by reacting 0.25 g (0.28 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-iodo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 8.3, with 71 mg (0.52 mmol) of phenyldimethylsilane in the presence of 0.30 g (1.42 mmol) of potassium triphosphate and of 24 mg (0.05 mmol) of bis(tri-*tert*-butylphosphine)palladium in 3 ml of dry 1-methyl-2-pyrrolidinone (NMP). 140 mg of
30 the expected product are obtained in the form of a white solid.

Mp = 200-202°C

¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.4 (s, 1H); 7.85 (m, 2H); 7.55 (m, 3H); 7.45-7.25 (m, 6H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.95 (t, 4H); 2.3 (quint., 2H); 0.6 (s, 6H).

35 LC-MS: 535 ([M+H]⁺, R_t= 1.44).

Example 21 (Compound No. 21)

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(isopropyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-
5 indole-2-carboxamide

Compound No. 21 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.31 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 17.3, with 95 mg (0.93 mmol) of dimethyl(isopropyl)silane in the
10 presence of 0.2 g (0.94 mmol) of potassium triphosphate and of 16 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP). 23 mg of the expected product are obtained.

Mp = 179-180°C

¹H NMR (DMSO D₆), δ (ppm): 10.25 (s, 1H); 8.35 (s, 1H); 7.85 (m, 2H); 7.55 (m, 1H);
15 7.3 (m, 3H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (m, 4H); 2.3 (m, 2H); 0.9 (m, 7H); 0.3(s, 6H).

LC-MS: 501 ([M+H]⁺, Rt= 1.49).

Example 22 (Compound No. 22)

20

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(methyl)diethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-
indole-2-carboxamide

Compound No. 22 was prepared according to a process similar to that described in stage 8.4, by reacting 0.15 g (0.31 mmol) of *N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-bromo-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide, prepared according to the protocol described in stage 17.3, with 95 mg (0.93 mmol) of diethyl(methyl)silane in the
25 presence of 0.2 g (0.94 mmol) of potassium triphosphate and of 16 mg (0.03 mmol) of bis(tri-*tert*-butylphosphine)palladium in 2 ml of dry 1-methyl-2-pyrrolidinone (NMP). 13 mg of the expected product are obtained.

30 Mp = 171-173°C

¹H NMR (DMSO D₆), δ (ppm): 10.2 (s, 1H); 8.35 (s, 1H); 7.85 (m, 2H); 7.55 (m, 1H);
7.35 (m, 3H); 7.05 (m, 1H); 6.95 (m, 2H); 6.4 (d, 1H); 5.9 (s, 2H); 3.9 (m, 4H); 2.3 (m, 2H); 0.95 (m, 6H); 0.8(m, 4H); 0.25 (s, 3H).

LC-MS: 501 ([M+H]⁺, Rt= 1.50).

35

Table 1 which follows illustrates the chemical structures and the physical properties of some compounds of general formula (I) according to the invention.

In this table:

- 5 - the compounds of general formula (I) are defined with n equal to 1;
 - the column "Mp (°C) or [MH]⁺" gives, respectively, either the melting points of the products in degrees Celsius (°C), or their mass peak in LC-MS; the liquid chromatography (LC) method used to determine the mass peaks of compounds No. 15 and 16 of Table 1 is the following:

10 Apparatus: UPLC / TOF

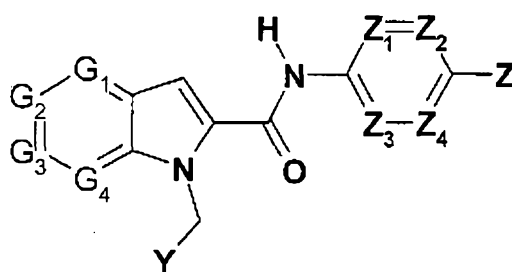
Mobile phases: A = H₂O + 0.05% TFA and B = ACN + 0.035% TFA

Gradient 3 min: T0: 98%A T1.6 to T2.1min: 100%B T2.5 to T3min: 98%A

Flow rate: 1.0ml/min - T° column = 40°C - Injection 2μL

Column Acquity BEH C18 (50×2.1mm; 1.7μm)

- 15 - the compounds are in the form of a free base;
 - "CH₃" corresponds to a methyl group, "Et" corresponds to an ethyl group,
 "cHex" corresponds to a cyclohexyl group, "tertBu" corresponds to a *tert*-butyl group, "Ph" corresponds to a phenyl group, "iPr" corresponds to an isopropyl group.

Table 1

N°	G ₁ , G ₂ , G ₃ , G ₄	Y	Z ₁ , Z ₂ , Z ₃ , Z ₄	Z	Mp (°C) (or [MH] ⁺)
1	CH, CH, -Si(CH ₃) ₃ , CH	3-fluorophenyl	CH,CH,CH,N	AzetidinyI	208 - 210
2	CH, CH, -Si(CH ₃) ₃ , CH	3-fluorophenyl	CH,CH,CH,N	3-Hydroxy-azetidinyI	188 - 189
3	CH, -Si(CH ₃) ₃ , CH, CH	3-fluorophenyl	CH,CH,CH,N	azetidinyI	212 - 213
4	CH, -Si(CH ₃) ₃ , CH, CH	3-fluorophenyl	CH,CH,CH,N	3-Hydroxy-azetidinyI	207-208
5	CH, CH, CH, -Si(CH ₃) ₃	3-fluorophenyl	CH,CH,CH,N	AzetidinyI	160-162
6	CH, CH, CH, -Si(CH ₃) ₃	3-fluorophenyl	CH,CH,CH,N	3-Hydroxy-azetidinyI	215-217
7	CH, -Si(CH ₃) ₃ , CH, CH	3-fluorophenyl	CH,CH,CH,N	Dimethyl-amino	204-205
8	CH, -Si(Me ₂)Et, CH, CH	3-fluorophenyl	CH,CH,CH,N	AzetidinyI	188-189
9	CH, -Si(cHex)(Me ₂), CH, CH	3-fluorophenyl	CH,CH,CH,N	AzetidinyI	202-203
10	CH, CH, -Si(CH ₃) ₃ , CH	3-(trifluoromethyl)-phenyl	CH,CH,CH,N	AzetidinyI	167-168
11	CH, CH, -Si(CH ₃) ₃ , CH	3-(trifluoromethyl)-phenyl	CH,CH,CH,N	3-Hydroxy-azetidinyI	183-184
12	CH, -SiCH ₃ (Ph) ₂ , CH, CH	3-fluorophenyl	CH,CH,CH,N	AzetidinyI	98-100
13	CH, -Si(CH ₃) ₃ , CH, CH	3-(trifluoromethyl)-phenyl	CH,CH,CH,N	AzetidinyI	199-200
14	CH, -Si(CH ₃) ₃ , CH, CH	3-(trifluoromethyl)-phenyl	CH,CH,CH,N	3-Hydroxy-azetidinyI	217-218

N°	G ₁ , G ₂ , G ₃ , G ₄	Y	Z ₁ , Z ₂ , Z ₃ , Z ₄	Z	Mp (°C) (or [MH] ⁺)
15	CH, CH, -Si(CH ₃) ₃ , CH	pyridin-4-yl	CH,CH,CH,N	3-Hydroxy-azetidiny	(472)
16	CH, CH, -Si(CH ₃) ₃ , CH	pyridin-4-yl	CH,CH,CH,N	Azetidiny	(456)
17	CH, -Si(Et) ₃ , CH, CH	3-fluorophenyl	CH,CH,CH,N	Azetidiny	166-168
18	CH, -Si(<i>tert</i> Bu)(Me ₂), CH, CH	3-fluorophenyl	CH,CH,CH,N	Azetidiny	110-112
19	CH, -Si(cHex)(Me ₂), CH, CH	3-fluorophenyl	CH,CH,CH,N	Pyrrolidiny	192-194
20	CH, -Si(Me ₂)Ph, CH, CH	3-fluorophenyl	CH,CH,CH,N	Azetidiny	200-202
21	CH, -Si(<i>i</i> Pr)(Me ₂), CH, CH	3-fluorophenyl	CH,CH,CH,N	Azetidiny	179-180
22	CH, -Si(Et ₂)(Me), CH, CH	3-fluorophenyl	CH,CH,CH,N	Azetidiny	171-173

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

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

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

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

- 10 The neurones of the DRG naturally express the TRPV1 receptor.
Newborn rat DRG primary cultures are prepared from 1-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 gentamicin and 50 ng/ml of NGF, and then deposited onto laminin-coated glass coverslips (0.2 × 10⁶ cells per coverslip) which are then placed in Corning 12-well dishes. The cells are incubated at 37°C in a humidified atmosphere containing 5% CO₂ 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 coverslips are transferred
- 20 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 $\times 400$. 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, constituted by 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 controlled by Pclamp8 software (Axon Instruments). 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 control period (stabilization of the capsaicin response alone), the test compounds 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 example in Table 2).

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

Table 2

Compound No.	% inhibition in DRG patch
2	84% (1 nM)
3	95% (10nM)

The results of these tests show that the most active compounds of the invention block the effects induced by 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.

5

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, 10 cancer-related pain, facial neuralgia, headaches, migraine, dental pain, burns, sunburn, animal bites or insect bites, post-herpetic neuralgia, muscle pain, a trapped nerve (central and/or peripheral), spinal column and/or brain trauma, ischaemia (of the spinal cord and/or of the brain), neurodegeneration, haemorrhagic strokes (of the spinal cord and/or of the brain) and post-stroke pain.

15 The compounds of the invention can 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, nephretic colic, pelvic hypersensitivity and pelvic pain.

20 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 reflux disorder, stomach ulcers, duodenal ulcers, functional dyspepsia, colitis, IBS, Crohn's disease, 25 pancreatitis, oesophagitis or biliary colic.

The compounds of the invention can also be used for the preparation of a medicament for preventing and/or treating metabolic disorders such as diabetes.

Similarly, the products of the invention can be used in the prevention and/or treatment of respiratory disorders such as asthma, coughing, COPD, bronchoconstriction and 30 inflammatory disorders. These products can also be used for preventing and/or treating psoriasis, pruritus, 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.

35 The compounds of the invention could also be used for treating central nervous system diseases such as multiple sclerosis.

The compounds of the invention could also be used for treating cancers.

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According to another of its aspects, the present invention relates to pharmaceutical compositions comprising, as active ingredient, a compound of formula (I) according to the invention. These pharmaceutical compositions contain an effective dose of at least one compound of formula (I) 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 humans for the prophylaxis or treatment of the disorders or diseases mentioned above.

The appropriate unit administration forms include oral forms such as tablets, soft or hard gelatin 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 croscarmellose	6.0 mg
Maize starch	15.0 mg
Hydroxypropylmethylcellulose	2.25 mg
Magnesium stearate	3.0 mg

Said unit forms contain a dose 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 galenical 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,

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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.

5 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 a compound according to the invention, or a pharmaceutically acceptable salt, a hydrate or a solvate thereof.

10 In this specification where reference has been made to patent specifications, other external documents, or other sources of information, this is generally for the purpose of providing a context for discussing the features of the invention. Unless specifically stated otherwise, reference to such external documents is not to be construed as an admission that such documents, or such sources of information, in any jurisdiction, are prior art, or form part of the common general knowledge in the art.

15

In the description in this specification reference may be made to subject matter that is not within the scope of the claims of the current application. That subject matter should be readily identifiable by a person skilled in the art and may assist in putting into practice the invention as defined in the claims of this application.

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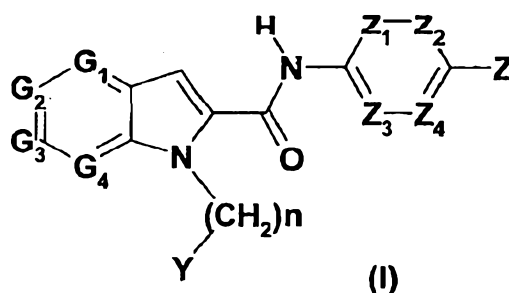
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CLAIMS

1. Compound corresponding to formula (I)



in which:

G₁, G₂, G₃ and G₄ are, independently of one another, a C-X group or a nitrogen atom; X is chosen from a hydrogen atom, a halogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, cyano, C₁-C₆-thioalkyl, NR₁R₂, aryl-C₁-C₆-alkylene-O-, aryl, heteroaryl or -Si(X₁)(X₂)(X₃) group; the C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₃-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl and C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O- groups being optionally substituted with a hydroxyl, C₁-C₆-alkoxyl or NR₄R₅ group; the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

one of G₁, G₂, G₃ and G₄ and at most one of G₁, G₂, G₃ and G₄ is a C-X group where X is an -Si(X₁)(X₂)(X₃) group;

X₁, X₂ and X₃ are, independently of one another, a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkyl, hydroxyl, aryl or heteroaryl group;

the aryl or heteroaryl groups of X₁, X₂, X₃ being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

the C₁-C₆-alkyl, C₃-C₇-cycloalkyl and C₃-C₇-cycloalkyl-C₁-C₆-alkyl groups of X₁, X₂, X₃ being optionally substituted with one or more substituents chosen from a hydroxyl, C₁-C₆-alkoxyl, aryl-O-, NR₁R₂, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl,

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C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

it also being possible for X₁ and X₂ to form, together with the silicon atom which bears them, a 4- to 7-membered ring optionally containing a heteroatom chosen from O, S and N;

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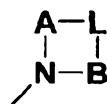
n is equal to 0, 1, 2 or 3;

Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more substituents chosen from a halogen atom or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, hydroxyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, cyano, C₁-C₆-thioalkyl, thiol, -S(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, C(O)NR₁R₂, SO₂NR₁R₂, SF₅, nitro, OCONR₁R₂, NR₃COR₄, NR₃CONR₁R₂, NR₁R₂, NR₃SO₂NR₁R₂, NR₃COR₄, NR₃SO₂R₅, aryl-C₁-C₆-alkylene or aryl group; the aryl and the aryl-C₁-C₆-alkylene being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

Z₁, Z₂, Z₃, Z₄ are, independently of one another, a nitrogen atom or a C(R₆) group, at least one corresponding to a nitrogen atom and at least one corresponding to a C(R₆) group; the nitrogen atom or one of the nitrogen atoms present in the ring, defined as nitrogen of position 1, being optionally substituted with R₇ when the carbon atom at position 2 or 4 relative to this reference nitrogen is substituted with an oxo or thio group;

Z is

either a cyclic amine linked via the nitrogen atom, of formula:



in which:

A is a C₁-C₇-alkylene group optionally substituted with one or two R₈ groups;

B is a C₁-C₇-alkylene group optionally substituted with one or two R₉ groups;

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being optionally substituted with an R₁₀ or R₁₁;

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

or an acyclic amine, linked via the nitrogen atom, of formula $NRaRb$ in which Ra and Rb 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_6 -alkylene, C_1 - C_6 -fluoroalkyl, hydroxyl, C_1 - C_6 -alkoxyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene-O-, C_1 - C_6 -fluoroalkoxyl, C_1 - C_6 -alkyl-C(O)-, HO-C(O)- C_1 - C_6 -alkylene, C_1 - C_6 -alkyl-O-C(O)- C_1 - C_6 -alkylene, aryl or heteroaryl group, it being possible for Ra and Rb to be optionally substituted with one or more R_c groups which may be identical to or different from one another;

R_c is a halogen atom, or a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, 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, cyano, C(O)NR₁R₂, NR₁R₂, SO₂NR₁R₂, NR₃COR₄, NR₃SO₂R₅, OC(O)NR₁R₂, NR₃COOR₅, NR₃CONR₁R₂, NR₃SO₂NR₁R₂, hydroxyl, thiol, oxo, thio, aryl- C_1 - C_6 -alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, C_1 - C_6 -fluoroalkoxyl, nitro or cyano group;

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_6 -alkylene, aryl- C_1 - C_6 -alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, C_1 - C_6 -fluoroalkoxyl, nitro or cyano group; or R_1 and R_2 form, together with the nitrogen atom which bears them, an azetidiny, 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_6 -alkylene, aryl- C_1 - C_6 -alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl, C_3 - C_7 -cycloalkyl- C_1 - C_6 -alkylene, C_1 - C_6 -fluoroalkyl, C_1 - C_6 -alkoxyl, C_1 - C_6 -fluoroalkoxyl, nitro or cyano 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_6 -alkylene, aryl- C_1 - C_6 -alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a

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C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

or R₃ and R₄ together form a (C₂-C₅)alkylene group;

or R₁ and R₃ together form a (C₂-C₆)alkylene group;

5

R₅ is a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, aryl-C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl,

10

C₁-C₆-fluoroalkoxyl, nitro or cyano group;

or R₃ and R₅ together form a (C₂-C₅)alkylene group;

R₆ is a hydrogen or halogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, C₁-C₆-thioalkyl, -S(O)-C₁-C₆-alkyl, -S(O)₂-C₁-C₆-alkyl, hydroxyl, thiol, oxo, thio, aryl, aryl-C₁-C₆-alkylene or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

20

R₇ is a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, aryl, aryl-C₁-C₆-alkylene or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

25

R₈, R₉ and R₁₀ are defined such that:

two R₈ groups may together form a bond or a C₁-C₆-alkylene group;

30

two R₉ groups may together form a bond or a C₁-C₆-alkylene group;

R₈ and R₉ may together form a bond or a C₁-C₆-alkylene group;

R₈ and R₁₀ may together form a bond or a C₁-C₆-alkylene group;

R₉ and R₁₀ may together form a bond or a C₁-C₆-alkylene group;

35

R₁₁ is a hydrogen atom, or a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, hydroxyl, C₁-C₆-alkyl-CO-, COOR₅, C(O)NR₁R₂, aryl-

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C₁-C₆-alkylene, aryl or heteroaryl group, the aryl and the heteroaryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

5

R₁₂ is a fluorine atom, a C₁-C₆-alkyl group optionally substituted with an R₁₃ group; C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-cycloalk-1,1-diyl, C₃-C₇-heterocycloalk-1,1-diyl optionally substituted on a nitrogen atom with an R₁₁ group; C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C₁-C₆-fluoroalkoxyl, CO₂H, C(O)O-C₁-C₆-alkyl, C(O)NR₁R₂, NR₁R₂, NR₃COR₄, OC(O)NR₁R₂, NR₃COOR₅, NR₃CONR₁R₂, hydroxyl, thiol, oxo, thio, aryl-C₁-C₆-alkylene or aryl; the aryl being optionally substituted with one or more substituents chosen from a halogen, and a C₁-C₆-alkyl, C₃-C₇-cycloalkyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene, C₁-C₆-fluoroalkyl, C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₁-C₆-fluoroalkoxyl, nitro or cyano group;

10

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R₁₃ is a C₁-C₆-alkoxyl, C₃-C₇-cycloalkoxyl, C₃-C₇-cycloalkyl-C₁-C₆-alkylene-O-, C(O)NR₁R₂, NR₁R₂, NR₃COR₄, OC(O)NR₁R₂, NR₃COOR₅ or hydroxyl group;

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

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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.

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2. Compound of formula (I) according to Claim 1, wherein one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an $-\text{Si}(X_1)(X_2)(X_3)$ group; the others of G_1 , G_2 , G_3 and G_4 being a CH group;

5 X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl 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.

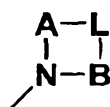
10 3. Compound of formula (I) according to Claim 1 or 2, wherein n is equal to 1; in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

15 4. Compound of formula (I) according to any one of Claims 1 to 3, wherein Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more groups chosen from a halogen atom or a C_1 - C_6 -fluoroalkyl 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.

20 5. Compound of formula (I) according to any one of Claims 1 to 4, wherein Z_1 , Z_2 , Z_3 and Z_4 are, independently of one another, a nitrogen atom or a $\text{C}(\text{R}_6)$ group, one corresponding to a nitrogen atom and the others corresponding to a $\text{C}(\text{R}_6)$ group; R_6 is 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.

25 6. Compound of formula (I) according to any one of Claims 1 to 5, wherein Z is a cyclic amine linked via the nitrogen atom, of formula:



30 in which:

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

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

L is a bond, or a sulphur, oxygen or nitrogen atom; the nitrogen atom being

35 optionally substituted with an R_{10} or R_{11} group;

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

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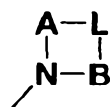
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R_8 , R_9 , R_{10} , R_{11} and R_{12} being as defined in general formula (I) according to Claim 1; in the form of a base or of an addition salt with an acid, and also in the form of a hydrate or of a solvate.

- 5 7. Compound of formula (I) according to any one of Claims 1 to 6, wherein Z is a cyclic amine linked via the nitrogen atom, of formula:



10 in which:

A is a C_1 - C_3 -alkylene group;

B is a C_1 - C_3 -alkylene group;

L is a bond;

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

20

8. Compound of formula (I) according to any one of Claims 1 to 5, wherein Z is an acyclic amine, linked via the nitrogen atom, of formula $NRaRb$ in which Ra and Rb are, independently of one another, a hydrogen atom or 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.

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9. Compound of formula (I) according to any one of Claims 1 to 8, wherein one of G_1 , G_2 , G_3 and G_4 is a C-X group where X is an $-Si(X_1)(X_2)(X_3)$ group; the others of G_1 , G_2 , G_3 and G_4 being a CH group;

- 30 X_1 , X_2 and X_3 are, independently of one another, a C_1 - C_6 -alkyl, C_3 - C_7 -cycloalkyl or aryl group;

n is equal to 1;

Y is an aryl or a heteroaryl; the aryl or the heteroaryl being optionally substituted with one or more groups chosen from a halogen atom or a C_1 - C_6 -fluoroalkyl group;

- 35 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; R_6 is a hydrogen atom;

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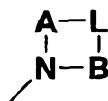
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Z is:

either a cyclic amine linked via the nitrogen atom, of formula:



in which:

A is a C₁-C₃-alkylene group;B is a C₁-C₃-alkylene group;

L is a bond;

the carbon atoms of the cyclic amine Z being optionally substituted with one or more R₁₂ groups which may be identical to or different from one another;

R₁₂ is a hydroxyl group;

or an acyclic amine, linked via the nitrogen atom, of formula NRaRb in which Ra and Rb are, independently of one another, a hydrogen atom or a C₁-C₆-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.

10. Compound of formula (I) according to Claim 1, chosen from:

N-[6-(azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-7-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(Dimethylamino)pyridin-3-yl]-5-trimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-(ethyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-1*H*-indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-

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1H-indole-2-carboxamide*N*-[6-(azetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-*1H*-indole-2-carboxamide*N*-[6-(3-hydroxyazetidin-1-yl)pyridin-3-yl]-6-trimethylsilyl-1-[[3-5 trifluoromethyl)phenyl]methyl]-*1H*-indole-2-carboxamide*N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-(diphenyl)methylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-

indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-trimethylsilyl-1-[[3-(trifluoromethyl)phenyl]methyl]-*1H*-

indole-2-carboxamide

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

indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]pyridin-3-yl]-6-trimethylsilyl-1-[(pyridin-4-yl)methyl]-*1H*-

15 indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-triethylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-indole-2-

carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-tert-butyl(dimethyl)silyl-1-[(3-fluorophenyl)methyl]-*1H*-

indole-2-carboxamide

20 *N*-[6-(Pyrrolidin-1-yl)pyridin-3-yl]-5-(cyclohexyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-indole-2-carboxamide*N*-[6-(azetidin-1-yl)pyridin-3-yl]-5-phenyldimethylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-

indole-2-carboxamide

N-[6-(azetidin-1-yl)pyridin-3-yl]-5-(isopropyl)dimethylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-

25 Indole-2-carboxamide

N-[6-(Azetidin-1-yl)pyridin-3-yl]-5-(methyl)diethylsilyl-1-[(3-fluorophenyl)methyl]-*1H*-

indole-2-carboxamide.

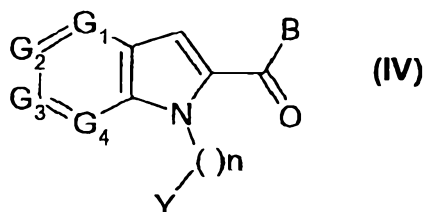
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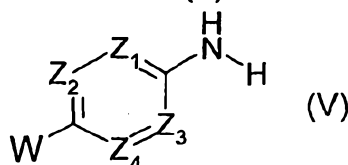
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11. Process for preparing a compound of formula (I) according to any one of Claims 1 to 10, wherein a compound of general formula (IV)

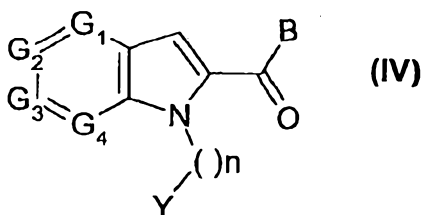


- 5 in which G_1 , G_2 , G_3 and G_4 , Y and n are as defined in general formula (I) according to Claim 1 and B is a chlorine atom,
is reacted with an amine of general formula (V)

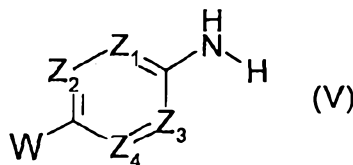


- 10 in which $W = Z$ and Z, Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) according to Claim 1, in a solvent.

12. Process for preparing a compound of formula (I) according to any one of Claims 1 to 10,
wherein a compound of general formula (IV)



- 15 in which G_1 , G_2 , G_3 and G_4 , Y and n are as defined in general formula (I) according to Claim 1 and B is a hydroxyl group,
is reacted with an amine of general formula (V)



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

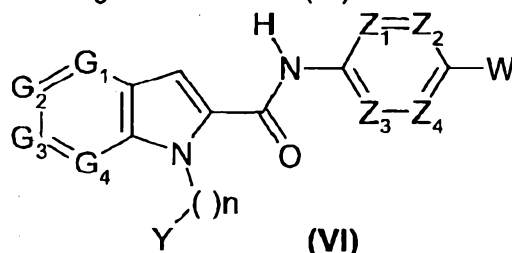
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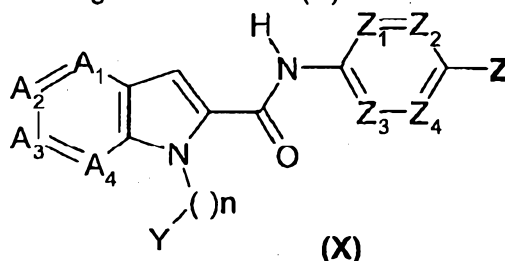
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13. Process for preparing a compound of formula (I) according to any one of Claims 1 to 10, wherein a compound of general formula (VI)



in which G_1 , G_2 , G_3 and G_4 , Y , n , Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) according to Claim 1 and W is a halogen atom,
is reacted with an amine of formula $Z-H$, in which Z is as defined in general formula (I) according to Claim 1.

14. Process for preparing a compound of formula (I) according to any one of Claims 1 to 10, wherein a compound of general formula (X)



in which Y , n , Z , Z_1 , Z_2 , Z_3 and Z_4 are as defined in general formula (I) according to Claim 1 and A_1 , A_2 , A_3 and A_4 are, independently of one another, a $C-X$ group or a nitrogen atom; X being as defined in general formula (I); one of A_1 , A_2 , A_3 and A_4 and at most one of A_1 , A_2 , A_3 and A_4 is a $C-q$ group where q is a halogen atom in the position where the silyl group should be introduced,
is reacted with a silane of formula $SiH(X_1)(X_2)(X_3)$ in which X_1 , X_2 and X_3 are as defined in general formula (I) according to Claim 1,
in the presence of a catalytic amount of a metal complex and of a base in a solvent.

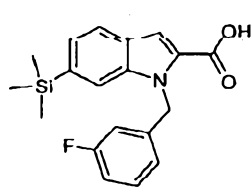
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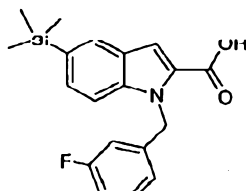
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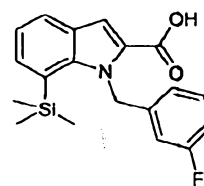
15. Compound (IVa), (IVb), (IVc), (IVd), (IVe) or (IVf):



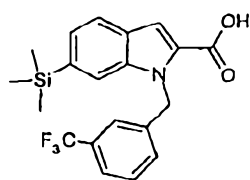
(IVa)



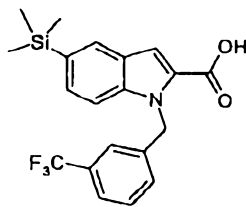
(IVb)



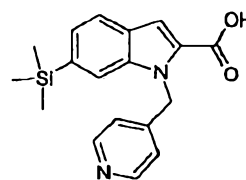
(IVc)



(IVd)



(IVe)



(IVf)

16. Medicament, comprising a compound of formula (I) according to any one of Claims 1 to 10, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I).

17. Pharmaceutical composition, comprising a compound of formula (I) according to any one of Claims 1 to 10, or a pharmaceutically acceptable salt, a hydrate or a solvate of this compound, and also at least one pharmaceutically acceptable excipient.

18. Use of a compound of formula (I) according to any one of Claims 1 to 10, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I) for the preparation of a medicament for preventing and treating pathologies in which TRPV1-type receptors are involved.

19. Use of a compound of formula (I) according to any one of Claims 1 to 10, or an addition salt of this compound with a pharmaceutically acceptable acid, or else a hydrate or a solvate of the compound of formula (I) for the preparation of a medicament for preventing or treating pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritus, dermal, ocular or mucosal irritations, herpes, shingles, multiple sclerosis, depression or cancers.

20. A method of preventing or treating pathologies in which receptors of TRPV1

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type are involved, pain, inflammation, metabolic disorders, urological disorders, gynaecological disorders, gastrointestinal disorders, respiratory disorders, psoriasis, pruritus, dermal, ocular or mucous irritations, herpes, zona, multiple sclerosis, depression and cancers, the method comprising administering to a patient an effective

5 dose of a compound according to any one of claims 1 to 10, or a pharmaceutically acceptable salt, or hydrate or solvate thereof.