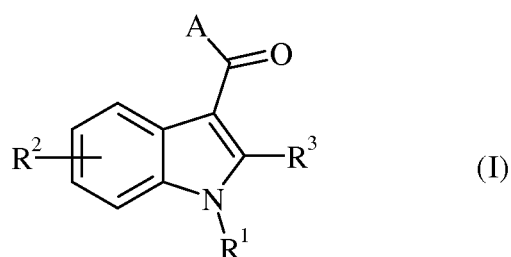


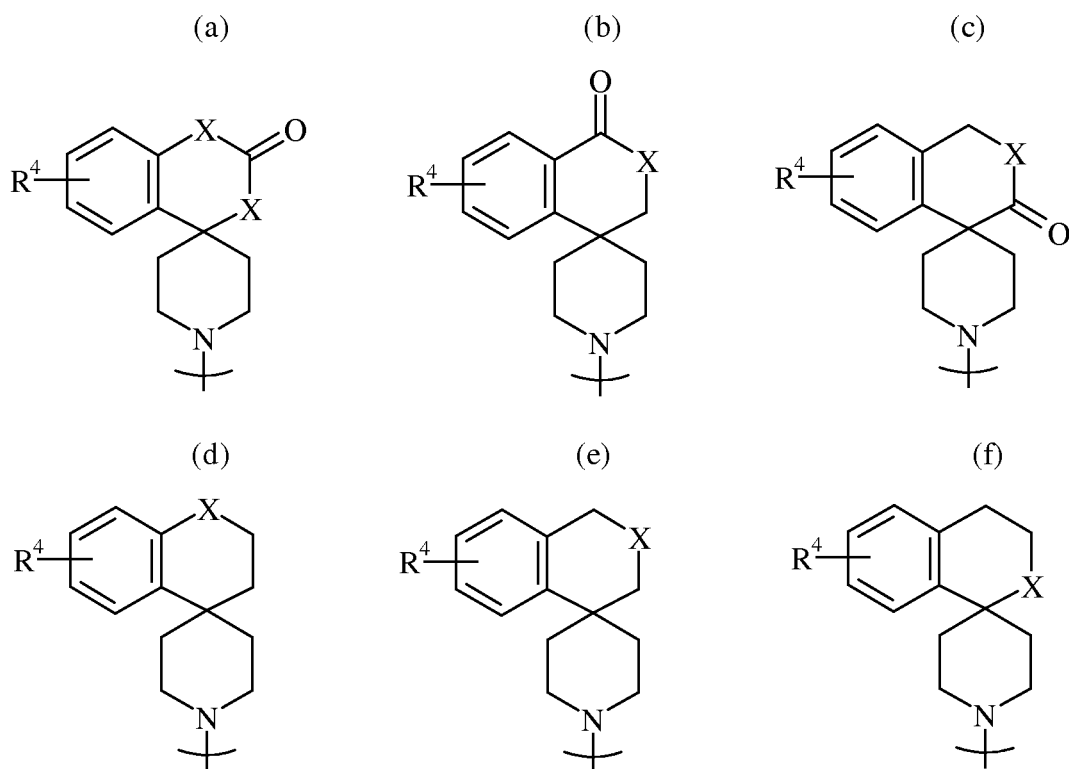
INDOL-3-YL-CARBONYL-SPIRO-PIPERIDINE DERIVATIVES

The present invention relates to compounds of formula (I):



wherein

5 A is selected from the following groups (a), (b), (c), (d), (e) and (f):



X is can be the same or different and is CRⁱⁱⁱR^{iv}, NRⁱⁱⁱ or O, wherein in (a), only one X can be O, the other being CRⁱⁱⁱR^{iv} or NRⁱⁱⁱ;

R¹ is H,

10 C₁₋₆-alkyl optionally substituted by CN,

or is aryl, 5 or 6 membered heteroaryl or sulfonylaryl which are optionally substituted by one or more B,

or is $-(CH_2)_m-R^a$ wherein R^a is:

OR^i ,

5 NR^iR^{ii} ,

C_{3-6} -cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B,

or is $-(CH_2)_n-(CO)-R^b$ or $-(CH_2)_n-(SO_2)-R^b$, wherein R^b is:

C_{1-6} -alkyl,

10 C_{1-6} -alkoxy,

C_{3-6} -cycloalkyl,

$-(CH_2)_m-NR^{iii}R^{iv}$,

NR^iR^{ii} ,

C_{3-6} -cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered

15 heteroaryl which are optionally substituted by one or more B,

or R^1 and R^3 together with the indole ring to which they are attached form a 5 or 6 membered heterocycloalkyl which can be substituted by (CO);

R^2 is one or more of H, OH, halo, CN, nitro, C_{1-6} -alkyl optionally substituted by $NR^{iii}R^{iv}$, C_{1-6} -alkoxy, $-O-CH_2-C_{2-6}$ -alkenyl, benzyloxy, or C_{1-6} -haloalkyl,

20 or two R^2 may form an oxo or dioxo bridge together with the indole ring to which they are attached;

R^3 is H,

or is halo,

or is $-(CO)-R^c$, wherein R^c is:

25 C_{1-6} -alkyl,

$-(CH_2)_n-NR^iR^{ii}$,

$-(CH_2)_n-NR^{iii}R^{iv}$,

5 or 6 membered heterocycloalkyl optionally substituted by C_{1-6} -alkyl,

or is C_{1-6} -alkyl or aryl, which are optionally substituted by

30 halo,

$-O(CO)-C_{1-6}$ -alkyl,

or by $-NH(CO)R^d$, wherein R^d is C_{1-6} -alkyl optionally substituted by halo or nitro, or R^d is aryl or a 5 or 6 membered heteroaryl, which are optionally substituted by halo, nitro, C_{1-6} -alkyl or C_{1-6} -haloalkyl;

- R^4 is one or more of H, halo, C_{1-6} alkyl or C_{1-6} alkoxy, CN, or two R^4 may form an oxo or dioxo bridge together with the phenyl ring to which they are attached
- B is halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN, halo or C_{1-6} -alkoxy, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)NR^iR^{ii}$, -
- 5 $C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$, $(CR^{iii}R^{iv})_n$ -phenyl, or $(CR^{iii}R^{iv})_n$ -5 or 6 membered heteroaryl wherein the phenyl or 5 or 6 membered heteroaryl moiety is optionally substituted by one or more substituent(s) selected from the group consisting of:
- halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN or C_{1-6} -alkoxy,
- 10 C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)-NR^iR^{ii}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$;
- R^i and R^{ii} are H, C_{1-6} -alkyl, C_{1-6} -alkylene- $NR^{iii}R^{iv}$, $-(CO)O-C_{1-6}$ -alkyl, $-C(O)-NR^{iii}R^{iv}$, -
- $C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl or $-S(O)_2-NR^{iii}R^{iv}$;
- R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $N(R^{iv})_2$;
- 15 R^{iv} is H or C_{1-6} -alkyl;
- m is 1 to 6;
- n is 0 to 4;
- as well as pharmaceutically acceptable salts thereof.

- The compounds of formula (I) may contain some asymmetric carbon atoms.
- 20 Accordingly, the present invention includes all stereoisomeric forms of the compounds of formula (I), including each of the individual enantiomers and mixtures thereof.

- It has been found that the compounds of formula (I) have a good activity on the V1a receptor. Therefore, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of medicaments for the
- 25 treatment of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

- Vasopressin is a 9 amino acid peptide mainly produced by the paraventricular nucleus of the hypothalamus. Three vasopressin receptors, all belonging to the class I G-
- 30 protein coupled receptors, are known. The V1a receptor is expressed in the brain, liver, vascular smooth muscle, lung, uterus and testis, the V1b or V3 receptor is expressed in the brain and pituitary gland, the V2 receptor is expressed in the kidney where it regulates water excretion and mediates the antidiuretic effects of vasopressin.

In the periphery vasopressin acts as a neurohormone and stimulates vasoconstriction, glycogenolysis and antidiuresis. In the brain vasopressin acts as a neuromodulator and is elevated in the amygdala during stress (Ebner, K., C. T. Wotjak, et al. (2002). "Forced swimming triggers vasopressin release within the amygdala to modulate stress-coping strategies in rats." Eur J Neurosci 15(2): 384-8). The V1a receptor is extensively expressed in the brain and particularly in limbic areas like the amygdala, lateral septum and hippocampus which are playing an important role in the regulation of anxiety. Indeed V1a knock-out mice show a reduction in anxious behavior in the plus-maze, open field and light-dark box (Bielsky, I. F., S. B. Hu, et al. (2003). "Profound Impairment in Social Recognition and Reduction in Anxiety-Like Behavior in Vasopressin V1a Receptor Knockout Mice." Neuropsychopharmacology). The downregulation of the V1a receptor using antisense oligonucleotide injection in the septum also causes a reduction in anxious behavior (Landgraf, R., R. Gerstberger, et al. (1995). "V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats." Regul Pept 59(2): 229-39).

The V1a receptor is also mediating the cardiovascular effects of vasopressin in the brain by centrally regulating blood pressure and heart rate in the solitary tract nucleus (Micheline, L. C. and M. Morris (1999). "Endogenous vasopressin modulates the cardiovascular responses to exercise." Ann N Y Acad Sci 897: 198-211). In the periphery it induces the contraction of vascular smooth muscles and chronic inhibition of the V1a receptor improves hemodynamic parameters in myocardial infarcted rats (Van Kerckhoven, R., I. Lankhuizen, et al. (2002). "Chronic vasopressin V(1A) but not V(2) receptor antagonism prevents heart failure in chronically infarcted rats." Eur J Pharmacol 449(1-2): 135-41).

Thus vasopressin receptor antagonists are useful as therapeutics in the conditions of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

The preferred indications with regard to the present invention are the treatment of anxiety and depressive disorders.

As used herein, the term "aryl" means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. Examples of aryl moieties

include, but are not limited to, optionally substituted phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, and diphenylisopropylidenyl, as well as those specifically illustrated by the examples herein below. Substituents for aryl

5 include, but are not limited to, halogen, C₁₋₆-alkyl, and C₁₋₆-alkoxy. Preferred aryl are phenyl and naphthyl, and still more preferably phenyl. The aryl moieties of the invention further can be ortho substituted by two substituents which together with the carbons of the aryl moiety form a fused, saturated or partially saturated, 5- to 6-membered ring containing one or two heteroatoms selected from O and N. Preferably the additional ring

10 is a 5- to 6- membered ring containing two oxygen atoms. Examples of such substituted aryl moieties include, but are not limited to, benzodioxanyl, dihydro-benzofuranyl, benzodioxolyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperidiny, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, methylenedioxyphenyl, ethylenedioxyphenyl, as well as those specifically illustrated by the examples herein below

15 The term "C₁₋₆-alkyl" denotes a saturated straight or branched hydrocarbon chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl and the like. Preferred C₁₋₆-alkyl groups are C₁₋₄-groups, i.e. with 1 - 4 carbon atoms.

The term "C₁₋₆-alkoxy" denotes a group wherein the alkyl residues are as defined

20 above, and which is attached via an oxygen atom. Preferred C₁₋₆-alkoxy groups are methoxy and ethoxy as well as those specifically illustrated by the examples herein below.

The term "C₂₋₆-alkenyl" denotes a carbon chain of 2 to 6 carbon atoms comprising a double bond in its chain. C₂₋₆-alkenyl groups include ethenyl, propen-1-yl, propen-2-yl, buten-1-yl, buten-3-yl, penten-1-yl, penten-2-yl, penten-3-yl, penten-4-yl, hexen-1-yl,

25 hexen-2-yl, hexen-3-yl, hexen-4-yl and hexen-5-yl, as well as those specifically illustrated by the examples herein below.

The term "benzyloxy" denotes a benzyl group attached via an oxygen atom.

The term "halogen" or "halo" denotes chlorine (Cl), iodine (I), fluorine (F) and bromine (Br).

30 The term "C₁₋₆-haloalkyl" denotes a C₁₋₆-alkyl group as defined above which is substituted by one or more halogen. Examples of C₁₋₆-haloalkyl include but are not

limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C₁₋₆-haloalkyl are difluoro- or trifluoro-methyl or ethyl.

5 “C₁₋₆-haloalkoxy” denotes a C₁₋₆-alkoxy group as defined above which is substituted by one or more halogen. Examples of C₁₋₆-haloalkoxy include but are not limited to methoxy or ethoxy, substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred C₁₋₆-haloalkoxy are difluoro- or trifluoro-methoxy or ethoxy.

10 The term “C₃₋₆-cycloalkyl” denotes a monovalent or divalent saturated carbocyclic moiety consisting of a monocyclic ring. Cycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, halogen, amino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include optionally substituted cyclopropyl, optionally substituted
15 cyclobutyl, optionally substituted cyclopentyl and optionally substituted cyclohexyl as well as those specifically illustrated by the examples herein below.

 The term “4 to 7 membered heterocycloalkyl” means a monovalent saturated moiety, consisting of one ring of 4 to 7 atoms as ring members, including one, two, or three heteroatoms chosen from nitrogen, oxygen or sulfur, the rest being carbon atoms. 4
20 to 7 membered heterocycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-thioalkyl, halo, C₁₋₆-haloalkyl, C₁₋₆-hydroxyalkyl, alkoxycarbonyl, amino, C₁₋₆-alkylamino, di(C₁₋₆)alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Examples of heterocyclic moieties include, but are not limited to,
25 optionally substituted oxetane, optionally substituted tetrahydro-furanyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted morpholinyl, optionally substituted piperazinyl, and the like or those which are specifically exemplified herein. Substituents can be selected from C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-haloalkyl, halo, CN, OH, NH₂, as well as those substituents which are specifically
30 illustrated in the examples hereinafter.

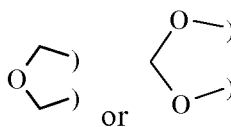
 The term “5 or 6 membered heteroaryl” means an aromatic ring of 5 or 6 ring atoms as ring members containing one, two, or three ring heteroatoms selected from N, O, or S, the rest being carbon atoms. 5 or 6 heteroaryl can optionally be substituted with

one, two, three or four substituents, wherein each substituent is independently hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-thioalkyl, halo, C₁₋₆-haloalkyl, C₁₋₆-hydroxyalkyl, alkoxy carbonyl, amino, C₁₋₆-alkylamino, di(C₁₋₆)alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Examples of heteroaryl moieties
 5 include, but are not limited to, optionally substituted imidazolyl, optionally substituted oxazolyl, optionally substituted thiazolyl, optionally substituted pyrrolyl, optionally substituted pyrazinyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted furanyl, and those which are specifically exemplified herein.

The term “sulfonylaryl” denotes an aryl group as defined hereinabove which is
 10 attached via a sulfonyl group.

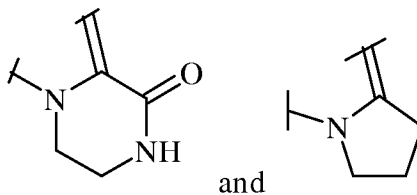
The term “one or more” when related to R² and R⁴ means from one to four residues which may be independently selected from the groups given below. Preferably, “one or more” in this context means one or two residues R² and R⁴, respectively, the rest being hydrogen.

15 The expression “two R² together with the indole ring to which they are attached may form an oxo or dioxo bridge” denotes an oxo or dioxo bridge of the following formulae:



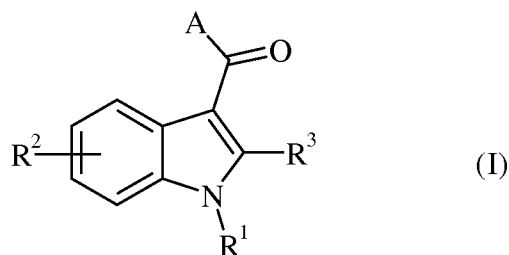
which bind two adjacent carbon atoms of the phenyl or indole ring of the compound of
 20 formula (I) to which either R² is binding.

Examples of groups illustrating the expression “R¹ and R³ together with the indole ring to which they are attached form a 5 or 6 membered heterocycloalkyl which is optionally substituted by =O” are:



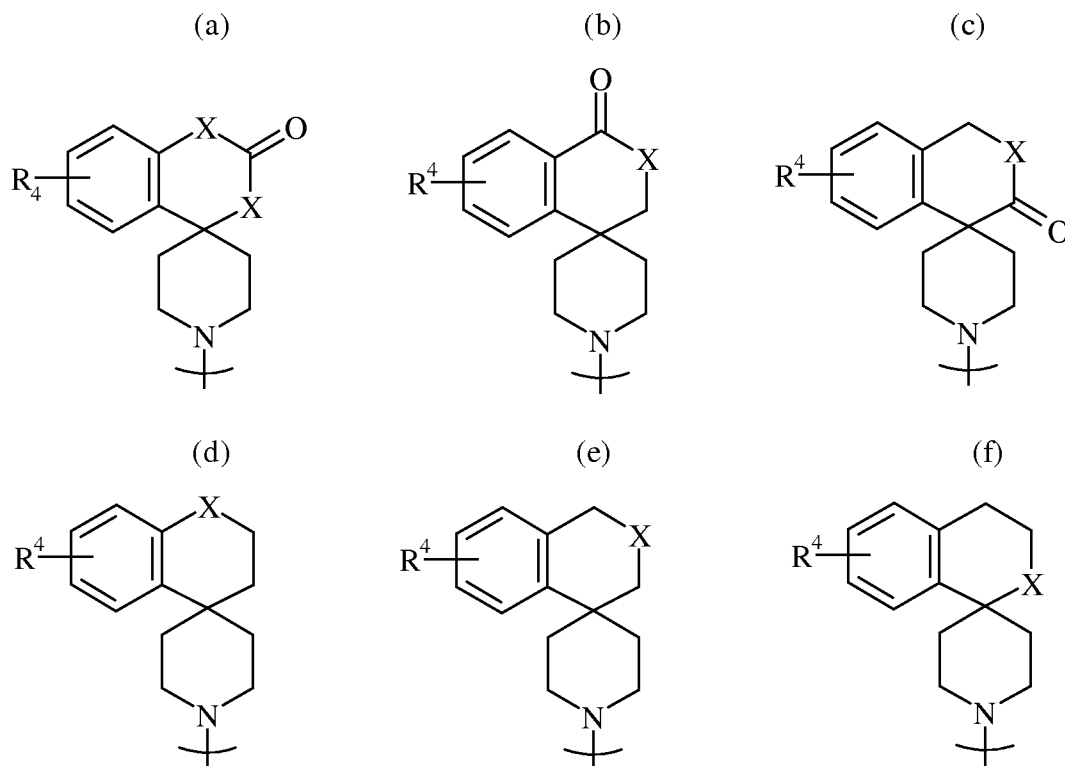
The term “pharmaceutically acceptable acid (addition) salts” embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid, as well as those
5 specifically illustrated by the examples herein below.

In detail, a certain embodiment of the present invention relates to compounds of
10 the general formula (I):



wherein

A is selected from the following groups (a), (b), (c), (d), (e) and (f):



X is can be the same or different and is $\text{CR}^{\text{iii}}\text{R}^{\text{iv}}$, NR^{iii} or O, wherein in (a), only one X can be O, the other being $\text{CR}^{\text{iii}}\text{R}^{\text{iv}}$ or NR^{iii} ;

R^1 is H,

5 C_{1-6} -alkyl optionally substituted by CN,
or is aryl, 5 or 6 membered heteroaryl or sulfonylaryl which are optionally substituted by one or more B,

or is $-(\text{CH}_2)_m-\text{R}^a$ wherein R^a is:

OR^{i} ,

10 $\text{NR}^{\text{i}}\text{R}^{\text{ii}}$,

C_{3-6} -cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B,

or is $-(\text{CH}_2)_n-(\text{CO})-\text{R}^b$ or $-(\text{CH}_2)_n-(\text{SO}_2)-\text{R}^b$, wherein R^b is:

C_{1-6} -alkyl,

15 C_{1-6} -alkoxy,

C_{3-6} -cycloalkyl,

$-(\text{CH}_2)_m-\text{NR}^{\text{iii}}\text{R}^{\text{iv}}$,

$\text{NR}^{\text{i}}\text{R}^{\text{ii}}$,

C_{3-6} -cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered

20 heteroaryl which are optionally substituted by one or more B,

or R^1 and R^3 together with the indole ring to which they are attached form a 5 or 6 membered heterocycloalkyl which can be substituted by (CO);

R^2 is one or more of H, OH, halo, CN, nitro, C_{1-6} -alkyl optionally substituted by – $NR^{iii}R^{iv}$, C_{1-6} -alkoxy, $-O-CH_2-C_{2-6}$ -alkenyl, benzyloxy,

5 or two R^2 may form an oxo or dioxo bridge together with the indole ring to which they are attached;

R^3 is H,
or is halo,
or is $-(CO)-R^c$, wherein R^c is:

10 C_{1-6} -alkyl,
 $-(CH_2)_n-NR^iR^{ii}$,
 $-(CH_2)_n-NR^{iii}R^{iv}$,
5 or 6 membered heterocycloalkyl optionally substituted by C_{1-6} -alkyl,
or is C_{1-6} -alkyl or aryl, which are optionally substituted by
15 halo,
 $-O(CO)-C_{1-6}$ -alkyl,
or by $-NH(CO)R^d$, wherein R^d is C_{1-6} -alkyl optionally substituted by halo or nitro, or R^d is aryl or a 5 or 6 membered heteroaryl, which are optionally substituted by halo, nitro, C_{1-6} -alkyl or C_{1-6} -haloalkyl;

20 R^4 is one or more of H, halo, C_{1-6} alkyl or C_{1-6} alkoxy, CN, or two R^4 may form an oxo or dioxo bridge together with the phenyl ring to which they are attached

B is halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN, halo or C_{1-6} -alkoxy, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)NR^iR^{ii}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$, $(CR^{iii}R^{iv})_n$ -phenyl, or

25 $(CR^{iii}R^{iv})_n$ -5 or 6 membered heteroaryl wherein the phenyl or 5 or 6 membered heteroaryl moiety is optionally substituted by one or more substituent(s) selected from the group consisting of:

halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN or C_{1-6} -alkoxy, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)-NR^iR^{ii}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$;

30 R^i and R^{ii} are H, C_{1-6} -alkyl, C_{1-6} -alkyl- $NR^{iii}R^{iv}$, $-(CO)O-C_{1-6}$ -alkyl, $-C(O)-NR^{iii}R^{iv}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl or $-S(O)_2-NR^{iii}R^{iv}$;

R^{iii} and R^{iv} are H or C_{1-6} -alkyl;

m is 1 to 6;

35 n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

In a certain embodiment of the invention, A, X, R¹ to R⁴, R^a, R^b, R^c, R^d, B, Rⁱ, Rⁱⁱ, m and n are as described above, and

Rⁱⁱⁱ is H, C₁₋₆-alkyl or C₁₋₆-alkylene-N(R^{iv})₂; and

5 R^{iv} is H or C₁₋₆-alkyl.

In certain embodiments of the invention, R¹ is selected from the group consisting of

H,

C₁₋₆-alkyl optionally substituted by CN,

or is aryl or 5 or 6 membered heteroaryl which are optionally substituted by one

10 or more B,

or is -(CH₂)_m-R^a wherein R^a is:

4 to 7 membered-heterocycloalkyl or aryl, which are optionally substituted by one or more B,

or is -(CH₂)_n-(CO)-R^b, wherein R^b is:

15 C₁₋₆-alkoxy,

NRⁱRⁱⁱ,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B;

B is halo, C₁₋₆-alkyl or phenyl;

20 Rⁱ and Rⁱⁱ are independently H or C₁₋₆-alkyl.

In certain embodiments of the invention, R² is one or more residues selected from the group consisting of H, halo, C₁₋₆-alkyl, or C₁₋₆-alkoxy. Preferably, R² is located at the 5 and/or 6-position of the indole. More preferably, R² is -OMe in the 5-position; or F in the 5-position and Cl in the 6-position; or Me in the 5-position and Cl in the 6-position; 25 or H in the 6-position; or Cl in the 6-position of the indole. Even more preferably, R² is Cl in the 6-position of the indole; or H in the 6-position of the indole. Most preferably, R² is Cl in the 6-position of the indole.

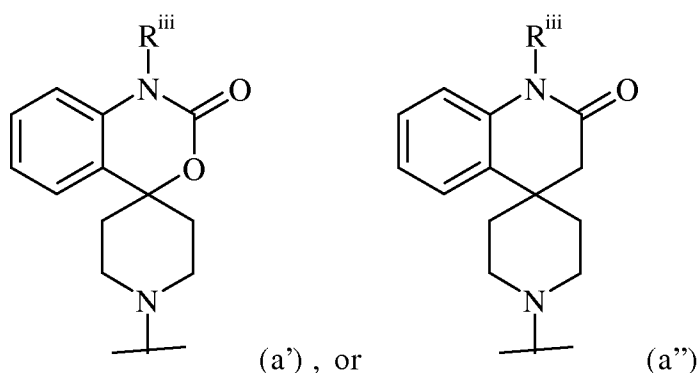
In certain embodiments of the invention, R³ is hydrogen or C₁₋₆-alkyl.

Preferably, R⁴ is hydrogen.

A further embodiment of the invention includes compounds of formula (I) as described herein, or pharmaceutically acceptable salts thereof, with the proviso that not all R^1 , R^2 , and R^3 are H at the same time.

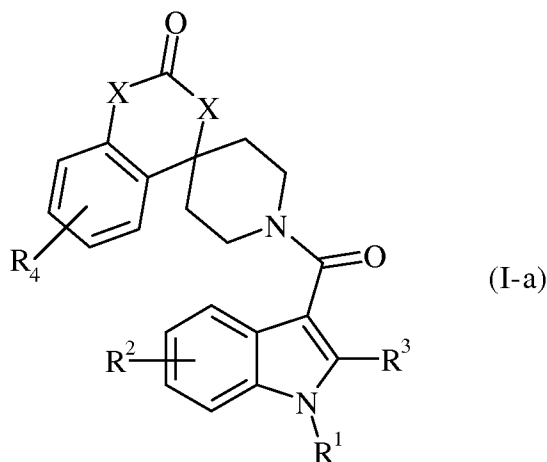
A further embodiment of the invention includes compounds of formula (I) as
5 described herein, or pharmaceutically acceptable salts thereof, with the proviso that not all R^1 , R^2 , R^3 and R^4 are H at the same time.

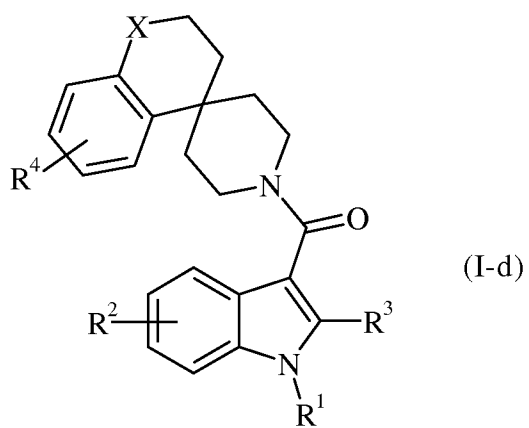
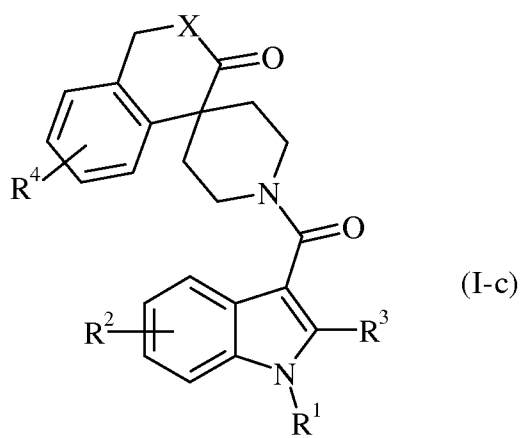
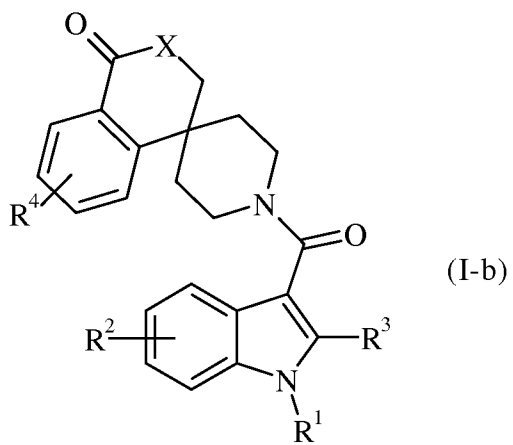
In certain embodiments of the invention, group (a) of the compound of formula (I) is selected from (a') and (a''):



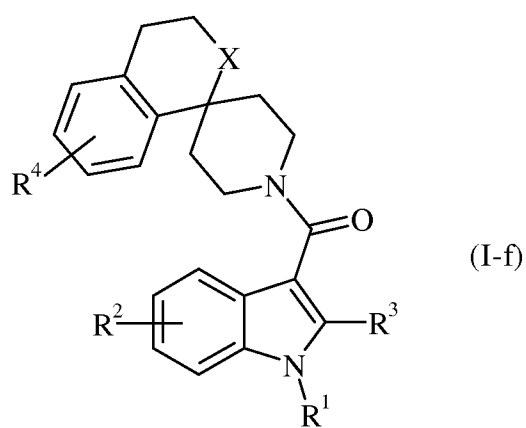
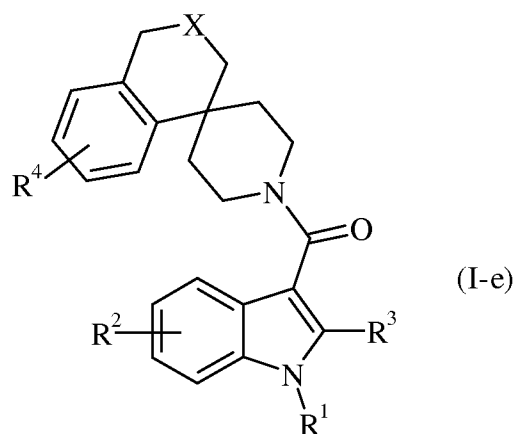
10 wherein R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $N(R^{iv})_2$ and R^{iv} is H or C_{1-6} -alkyl; preferably, R^{iii} is H or C_{1-6} -alkyl; most preferably, R^{iii} is H.

As it can be seen from the definition of A in the compounds of formula (I), said compounds of formula (I) encompass the compounds of formulae (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) as follows:



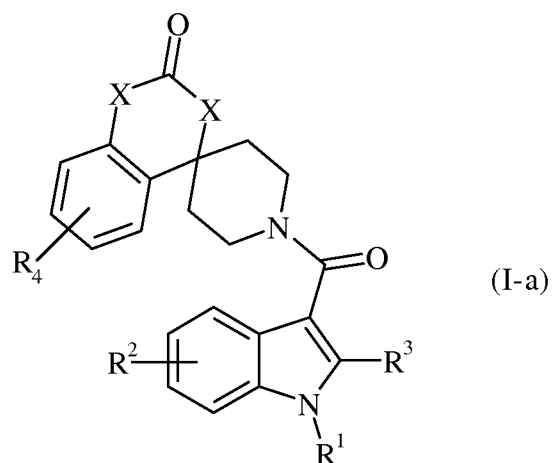


- 14 -



wherein R^1 to R^4 and X are as defined hereinabove in connection with formula (I).

In a certain embodiment the compounds of the invention are those compounds of
5 formula (I-a):



wherein:

X is can be the same or different and is $CR^{iii}R^{iv}$, NR^{iii} or O, wherein only one X can
be O, the other being $CR^{iii}R^{iv}$ or NR^{iii} ;

- R^1 is H,
 C_{1-6} -alkyl optionally substituted by CN,
 or is aryl optionally substituted by one or more B,
 or is $-(CH_2)_m-R^a$ wherein R^a is:
- 5 NR^iR^{ii} ,
 aryl optionally substituted by one or more B,
 or is $-(CH_2)_n-(CO)-R^b$ or $-(CH_2)_n-(SO_2)-R^b$, wherein R^b is:
 C_{1-6} -alkoxy,
 NR^iR^{ii} ,
- 10 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which
 are optionally substituted by one or more B,
- R^2 is one or more of H or halo, e.g. Cl,
 R^3 is H,
 or is C_{1-6} -alkyl,
- 15 R^4 is one or more of H, halo, C_{1-6} alkyl or C_{1-6} alkoxy or CN;
 B is halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN, halo or C_{1-6} -alkoxy,
 C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)NR^iR^{ii}$, -
 $C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$, $(CR^{iii}R^{iv})_n$ -phenyl, or
 20 $(CR^{iii}R^{iv})_n$ -5 or 6 membered heteroaryl wherein the phenyl or 5 or 6 membered
 heteroaryl moiety is optionally substituted by one or more substituent(s)
 selected from the group consisting of:
 halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN or C_{1-6} -alkoxy,
 C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)-$
 NR^iR^{ii} , $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$;
- 25 R^i and R^{ii} are H, C_{1-6} -alkyl, C_{1-6} -alkylene- $NR^{iii}R^{iv}$, $-(CO)O-C_{1-6}$ -alkyl, $-C(O)-NR^{iii}R^{iv}$, -
 $C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl or $-S(O)_2-NR^{iii}R^{iv}$;
- R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $N(R^{iv})_2$;
 R^{iv} is H or C_{1-6} -alkyl;
 m is 1 to 6;
- 30 n is 0 to 4;
- as well as pharmaceutically acceptable salts thereof.

In this embodiment, preferably (a) is selected from (a') and (a'').

In a certain embodiment the compounds of formula (I-a) are those compounds wherein R^1 is H, for example the following compounds:

1'-[(6-Chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

6'-Bromo-1-(1H-indol-3-ylcarbonyl)-1'H-spiro[piperidine-4,4'-quinolin]-2'(3'H)-one;

5 6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]-1-[2-(dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one; and

6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

In a certain embodiment the compounds of formula (I-a) are those compounds
10 wherein R¹ is aryl optionally substituted by one or more B and B is as defined hereinabove for formula (I-a), for example the following compound: 1'-[[6-chloro-1-(3,5-difluorophenyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

In a certain embodiment the compounds of formula (I-a) are those compounds
15 wherein R¹ is -(CH₂)_m-R^a wherein R^a is CN, NRⁱRⁱⁱ, or aryl optionally substituted by one or more B and m, Rⁱ, Rⁱⁱ and B are as defined for formula (I-a) hereinabove, for example the following compounds:

1'-[[6-Chloro-1-(3,5-difluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

20 1'-[[6-Chloro-1-(3-fluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

3-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile; and

25 2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile.

In a certain embodiment the compounds of formula (I-a) are those compounds
wherein R¹ is -(CH₂)_n-(CO)-R^b or -(CH₂)_n-(SO₂)-R^b, wherein R^b is C₁₋₆-alkoxy, NRⁱRⁱⁱ, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B and n, Rⁱ, Rⁱⁱ and B are as defined for formula (I-
30 a) hereinabove, for example the following compounds:

1'-[[6-Chloro-1-(3-fluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

- 1'-[[6-Chloro-1-(2-fluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-[[6-Chloro-1-(2,3-difluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 5 1'-({6-Chloro-1-[(3,5-difluorophenyl)sulfonyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-({6-Chloro-1-[2-(3-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-({6-Chloro-1-[2-(3,4-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 10 1'-[[1-(Biphenyl-3-ylcarbonyl)-6-chloro-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-[[6-Chloro-1-(2-oxo-2-piperidin-1-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 15 1'-[[6-Chloro-1-(2-morpholin-4-yl-2-oxoethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide;
- 2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-diethylacetamide;
- 20 1'-[[6-Chloro-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- tert-Butyl {6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}acetate;
- 25 1'-[[6-Chloro-1-(3,5-difluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-({6-Chloro-1-[2-(3,5-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 1'-({6-Chloro-1-[2-(2-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;
- 30 1'-[[6-Chloro-1-(2-oxo-2-pyridin-2-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one; and
- 1'-({6-Chloro-1-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

In the compounds of formula (I-a), and independently of the definitions of R^1 to R^4 , one X can be NH and the other one O.

In a certain embodiment of the invention, formula (I) encompasses the compound of formula (I-b) wherein X and R^1 to R^4 are as defined above, preferably

5 X is NH;

R^1 is H,

C₁₋₆-alkyl optionally substituted by CN,

or is aryl or 5 or 6 membered heteroaryl which are optionally substituted by one or more B,

10 or is $-(CH_2)_m-R^a$ wherein R^a is:

4 to 7 membered-heterocycloalkyl or aryl, which are optionally substituted by one or more B,

or is $-(CH_2)_n-(CO)-R^b$, wherein R^b is:

C₁₋₆-alkoxy,

15 NR^iR^{ii} ,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B;

B is halo, C₁₋₆-alkyl or phenyl;

R^i and R^{ii} are independently H or C₁₋₆-alkyl;

20 more preferably, R^1 is $-(CH_2)_n-(CO)-R^b$, wherein R^b is NR^iR^{ii} and R^i and R^{ii} are independently H or C₁₋₆-alkyl.

R^2 is H or halo;

R^3 is H;

R^4 is H.

25

An example of a compound of formula (I-B) is 2-{6-chloro-3-[(1-oxo-2,3-dihydro-1H,1'H-spiro[isoquinoline-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N-methylacetamide.

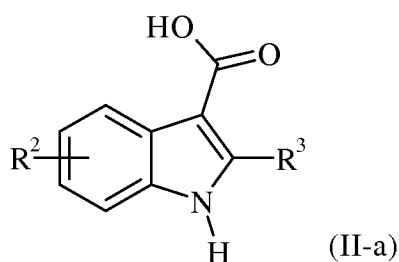
The invention also encompasses the compounds of formula (I), (I-a), (I-b), (I-c),
30 (I-d), (I-e) or (I-f) for a use in the prevention or treatment of dysmenorrhea,

hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) which pharmaceutical
5 composition is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

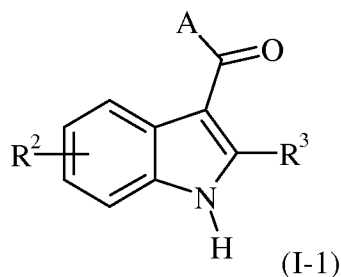
The invention further encompasses the use of a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) for the preparation of a medicament which is useful against
10 dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

In a certain embodiment, the compounds of formula (I) of the invention wherein R^1 is H can be manufactured according to a process comprising the step of reacting a
15 compound of formula (II-a):



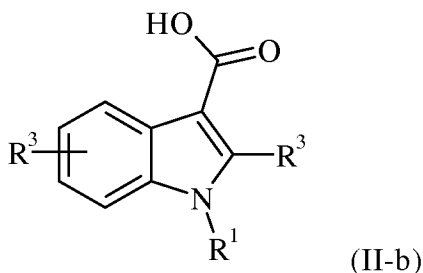
with a compound of formula A-H to obtain the compound of formula (I), wherein R^1 is H and A, R^2 and R^3 are as defined hereinabove.

In another embodiment, the compounds of formula (I) of the invention can be
20 manufactured according to a process comprising the step of reacting a compound of formula (I-1):



with an electrophile compound of formula R^1 -Z to obtain the compound of formula (I), wherein A, R^1 , R^2 and R^3 are as defined hereinabove and Z is halo, preferably Br or Cl.

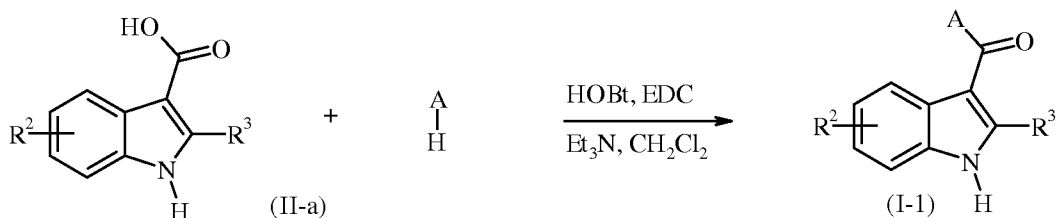
In still another embodiment, the compounds of formula (I) of the invention can be manufactured according to a process comprising the step of reacting a compound of formula (II-b):



with a compound of formula A-H to obtain the compound of formula (I), wherein R^1 , R^2 , R^3 , and A are as defined hereinabove.

The preparation of the compounds of the invention of formulae (I), (I-a), (I-b), (I-c), (I-d), (I-e) and (I-f) is described more in details with the following general schemes A, B and C, wherein R^1 , R^2 , R^3 and A are as defined hereinabove:

General scheme A

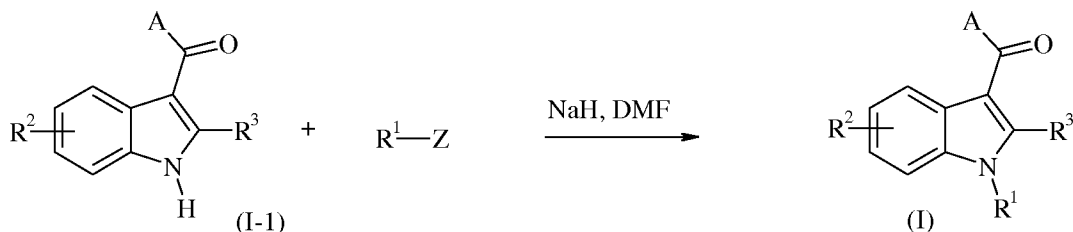


General procedure A

Compounds of formula (I-1) (compounds of formula (I) wherein R^1 is H) can be prepared via an amide coupling between an indole 3-carboxylic acid (II-a) and a spiropiperidine (A-H), see e.g. the general procedure for the amide coupling hereinafter. Indole 3-carboxylic acids (II-a) are either commercially available or readily prepared using a procedure described in. *JMed.Chem.* 1991, 34, 140. Alternatively, (II-a) can be prepared following the sequence in scheme C. The spiropiperidine derivatives A-H are

either commercially available, either prepared using published procedures or prepared using procedures described hereinafter in the examples.

General scheme B



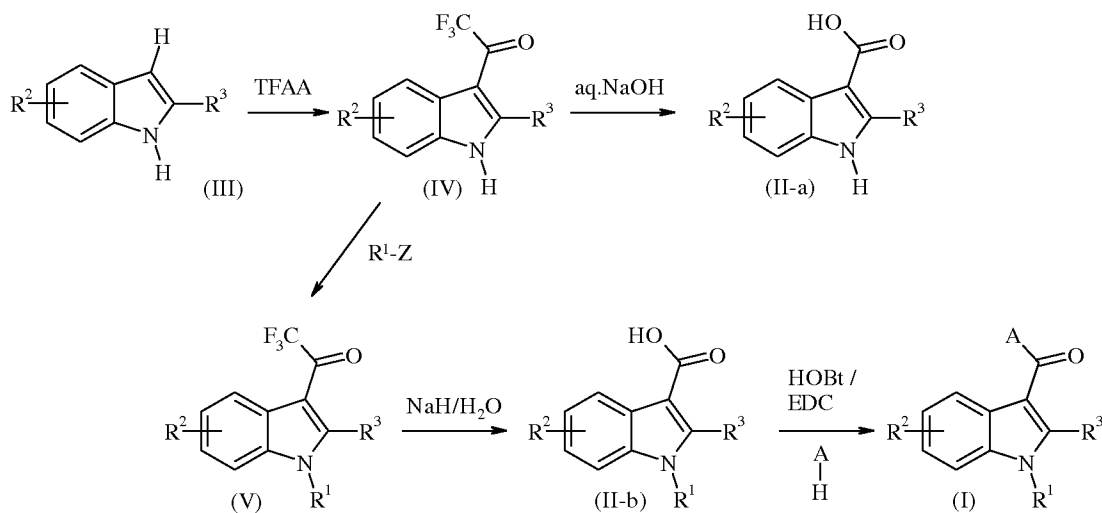
5

General procedure B

Compounds of formula (I) wherein R^1 is different from H, can be prepared by an alkylation of an indole derivative (I-1) with an electrophile R^1-Z , wherein Z is halo, (commercially available) using standard procedures. Derivatives (I-1) are prepared are prepared using the method described in the general scheme A.

10

General scheme C



15

General procedure C

The treatment of an indole (III) with trifluoroacetic anhydride gives (IV), which can be hydrolyzed to the corresponding 3-carboxylic acid indole (II-a). Alternatively, (IV) can be further elaborated into (V) by coupling with a reagent R^1-Z , wherein Z is halo, using well known procedure. The hydrolysis of (V) affords (II-b), which under standard amide coupling with A-H afford derivatives (I).

The general schemes and corresponding procedures presented hereinabove are further illustrated with the preparation of the compounds of the invention hereinafter.

Results – V1a activity

10 Material & Method:

The human V1a receptor was cloned by RT-PCR from total human liver RNA. The coding sequence was subcloned in an expression vector after sequencing to confirm the identity of the amplified sequence. To demonstrate the affinity of the compounds from the present invention to the human V1a receptor binding studies were performed. Cell membranes were prepared from HEK293 cells transiently transfected with the expression vector and grown in 20 liter fermenters with the following protocol.

50g of cells are resuspended in 30ml freshly prepared ice cold Lysis buffer (50mM HEPES, 1mM EDTA, 10mM $MgCl_2$ adjusted to pH= 7.4 + complete cocktail of protease inhibitor (Roche Diagnostics)). Homogenized with Polytron for 1min and sonicated on ice for 2x 2 minutes at 80% intensity (Vibracell sonicator). The preparation is centrifuged 20 min at 500 g at 4°C, the pellet is discarded and the supernatant centrifuged 1hour at 43'000g at 4°C (19'000rpm). The pellet is resuspended in 12.5 ml Lysis buffer+12.5ml Sucrose 20% and homogenized using a Polytron for 1-2 min. The protein concentration is determined by the Bradford method and aliquots are stored at -80°C until use. For binding studies 60mg Yttrium silicate SPA beads (Amersham) are mixed with an aliquot of membrane in binding buffer (50 mM Tris, 120mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 10 mM $MgCl_2$) for 15 minutes with mixing. 50ul of bead/membrane mixture is then added to each well of a 96 well plate, followed by 50ul of 4 nM 3H-Vasopressin (American Radiolabeled Chemicals). For total binding measurement 100ul of binding buffer are added to the respective wells, for non-specific binding 100ul of 8.4mM cold vasopressin and for compound testing 100ul of a serial dilution of each compound in 2%DMSO. The plate is incubated 1h at room temperature, centrifuged 1 min at 1000g and counted on a Packard Top-Count. Non-specific binding counts are subtracted from each well and data is

normalized to the maximum specific binding set at 100%. To calculate an IC 50 the curve is fitted using a non-linear regression model (XLfit) and the Ki is calculated using the Cheng-Prusoff equation.

Example	Ki (nM) [human V1a]	Example	Ki (nM) [human V1a]
1	32	16	20
2	2053	17	5.7
3	402	18	6
4	310	19	46
5	130	20	10
6	118	21	88
7	117	22	200
8	136	23	2
10	3	24	10
11	5	25	28
12	7	26	8
13	8	27	29
15	7	28	166

5 The compounds of formula (I) as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g.
 10 in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

 The compounds of formula (I) and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients
 15 e.g. for tablets, dragées and hard gelatine capsules.

 Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

- 5 Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still
10 other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula (I) should be appropriate, although the above upper limit can also be
15 exceeded when necessary.

The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

Example A

Tablets of the following composition are manufactured in the usual manner:

20		<u>mg/tablet</u>
	Active substance	5
	Lactose	45
	Corn starch	15
	Microcrystalline cellulose	34
25	Magnesium stearate	1
	Tablet weight	100

Example B

Capsules of the following composition are manufactured:

5		<u>mg/capsule</u>
	Active substance	10
	Lactose	155
	Corn starch	30
	Talc	5
10	Capsule fill weight	200

The active substance, lactose and corn starch are firstly mixed in a mixer and then in a comminuting machine. The mixture is returned to the mixer, the talc is added thereto and mixed thoroughly. The mixture is filled by machine into hard gelatine capsules.

15 Example C

Suppositories of the following composition are manufactured:

		<u>mg/supp.</u>
	Active substance	15
	Suppository mass	1285
20	Total	1300

The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool; the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.

EXAMPLES

Examples of compounds of formula (I-1)

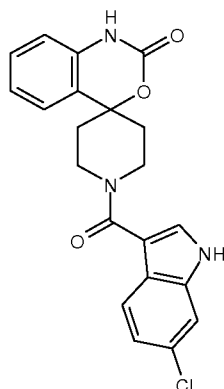
General procedure for the amide coupling:

To a stirred solution of an indole-3-carboxylic acid derivative (1 mmol) in 10 ml CH₂Cl₂ was added (1.3 mmol) EDC, (1.3 mmol) HOBT, (1.3 mmol) Et₃N and (1 mmol) of the
5 amine derivative. The mixture was stirred overnight at RT and then poured onto water and extracted with CH₂Cl₂. The combined organic phases were dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography or preparative HPLC afforded the title compound.

- 10 Where references are cited in the examples, the example was performed using the starting material listed with the reactants and conditions cited in the reference. All procedures in such references are well known to those of ordinary skill in the art. All journal references cited herein are incorporated by reference.

Example 1

- 15 1'-[(6-Chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



Amide coupling: - Amine: spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (*J. Med. Chem.*, 1983, 26(5), 657)

- Acid: 6-Chloro-1H-indole-3-carboxylic acid

- 20 ES-MS m/e (%): 396.1 (M+H⁺).

6-Chloro-1H-indole-3-carboxylic acid

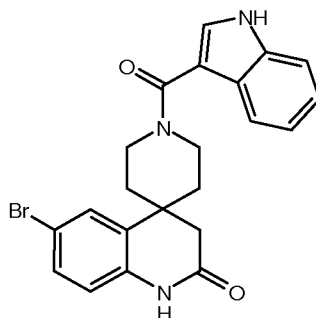
Using a procedure described in *J. Med. Chem.* 1991, 34, 140, from 7.0 g (0.046 mmol) of 6-Chloro-1H-indole was prepared 5.80 g (64%) of 6-chloro-1H-indole-3-carboxylic acid as a light brown solid. ES-MS m/e (%): 194 (M-H⁺).

25

Example 2

6'-Bromo-1-(1H-indol-3-ylcarbonyl)-1'H-spiro[piperidine-4,4'-quinolin]-2'(3'H)-one

- 27 -



Amide coupling: - Amine: 6'-bromo-1'-H-spiro[piperidine-4,4'-quinolin]-2'-(3'H)-one
 - Acid: 1H-Indole-3-carboxylic acid (commercial)

5 ES-MS m/e (%): 439.1 (M+H⁺).

6'-Bromo-1'-H-spiro[piperidine-4,4'-quinolin]-2'-(3'H)-one

A stirred solution of 1'-H-spiro[piperidine-4,4'-quinolin]-2'-(3'H)-one (described in US6013652) was treated with 7 g of solid sodium bicarbonate, di-tert-butyl pyrocarbonate (7.2g) in 250 mL of methylene chloride and stirred for 2 hours at ambient
 10 temperature. The organic layer was separated out and the aqueous part was washed with methylene chloride (2x50 mL). The combined organic extract and washings were washed with brine, dried (anhydrous Na₂SO₄), concentrated under vacuo to provide a foamy material which was chromatographed over silica (1:3 ethyl acetate-hexane followed by 1:1 ethyl acetate hexane) to provide 1'-(tert-butyloxycarbonyl)spiro(tetrahydro quinol-2-one)-4'-piperidine as a creamish white solid, mp 198 °C; GC-MS (EI) m/z 316.

This compound (10g, 31.6 mmol) in solution in dry acetonitrile (250 mL) was cooled to -10 °C, and N-bromosuccinimide (5.62g, 31.6 mmol) was added portion wise with stirring. The reaction mixture was stirred for 1h at -10 °C, 2h at 0 °C and finally at ambient temperature for 24 h. The solvent was removed and the residue dissolved in
 20 methylene chloride (500 mL), organic extract washed with brine-water (1:1) (3x50 mL), dried (anhydrous Na₂SO₄), concentrated in vacuo to provide a creamish white solid which was chromatographed over silica (1:3 ethyl acetate-hexane followed by 1:1 ethyl acetate hexane) to give 6-bromo-1'-(tert-butyloxycarbonyl) spiro (tetrahydro quinol-2-one)-4'-piperidine (11.8g, 94%) as a white solid of mp 226 °C; GC-MS (EI) m/z (M-100)
 25 294.

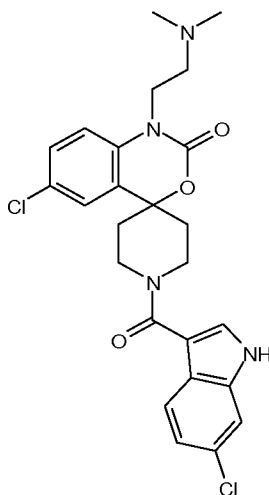
This compound (10g, 25.3 mmol) in 750 mL of methanol, dry HCl was passed for 10 hrs and the stirring was continued for overnight. The reaction mixture was neutralized with liquor ammonia (75 mL) under ice-cold condition. Methanol and excess ammonia were removed under vacuo and the residue dissolved in methylene chloride (500 mL) followed
 30 by the addition of 25 mL of liquor ammonia to dissolve the remaining solid. The organic

layer was separated out and the aqueous part washed extracted with methylene chloride (3 x 150 mL), dried (anhydrous Na₂SO₄), concentrated under vacuo to provide the title compound as a creamish white solid (7.0g, 94%) of mp 218 °C; GC-MS (EI) m/z 294.

5

Example 3

10 6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]-1-[2-(dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



Amide coupling: - Amine: 6-Chloro-1-[2-(dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described herein after)
 15 - Acid: 6-Chloro-1H-indole-3-carboxylic acid (described in example 2)

ES-MS m/e (%): 501.2 (M+H⁺).

6-Chloro-1-[2-(dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

To a solution of 0.100 g (0.283 mmol) tert-butyl 6-chloro-2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidine]-1'-carboxylate (described in WO0122919 A2, and prepared also using the procedure described in "*J. Med. Chem.*, 1983, 26(5), 657" starting from 4-chloro aniline) in 7 ml THF was added 0.025 g (0.566 mmol) NaH. After 20 30 minutes at RT, 0.063 g (0.566 mmol) (2-chloro-ethyl)-dimethyl-amine was added. The reaction mixture was stirred at 60 °C overnight, then poured onto an aqueous solution of NH₄Cl and extracted twice with EtOAc. The combined organic phases were 25 dried over Na₂SO₄ and concentrated in vacuo yielded 60 mg of a white solid. This crude

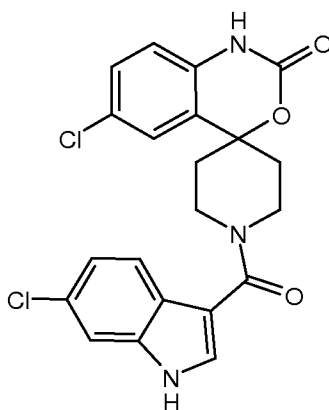
material was then dissolved in 5 ml CH₂Cl₂ and 1 ml of TFA was added. After 2 hours at RT, the solvent were removed under vacuo and the resulting oil was taken up in CH₂Cl₂ and washed with an aqueous solution of NaHCO₃. The organic phase was dried with Na₂SO₄ and concentrated under vacuo to afford 6-chloro-1-[2-

5 (dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one as a white solid.

10

Example 4

6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-
2(1H)-one



15

Amide coupling: - Amine: 6-chlorospiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one
(described in WO0122919 A2, or prepared using the same procedure
described in *J. Med. Chem.*, 1983, 26(5), 657 starting with 4-chloro-
aniline)

20

- Acid: 6-Chloro-1H-indole-3-carboxylic acid (described in example 2)

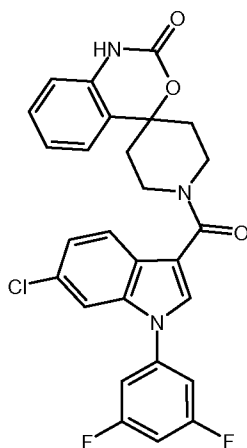
ES-MS m/e (%): 431.4 (M+H⁺).

Example 5

1'-{[6-Chloro-1-(3,5-difluorophenyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-
4,4'-piperidin]-2(1H)-one

25

- 30 -



Amide coupling: - Amine: spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (*J. Med. Chem.*, 1983, 26(5), 657)

- Acid: 6-Chloro-1-(3,5-difluoro-phenyl)-1H-indole-3-carboxylic acid

5 ES-MS m/e (%): 508.0 (M+H⁺).

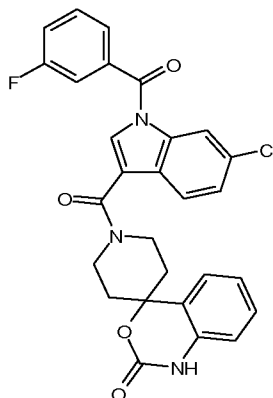
6-Chloro-1-(3,5-difluoro-phenyl)-1H-indole-3-carboxylic acid

To a solution of 200 mg (0.807 mmol) 1-(6-chloro-1H-indol-3-yl)-2,2,2-trifluoro-ethanone (prepared from 6-chloro indole and trifluoroacetic anhydride, described in US 2004067939 A1) in 8 ml CH₂Cl₂, 293 mg (1.615 mmol) Cu(OAc)₂, 0.26 ml (3.23 mmol) pyridine and 383 mg (2.42 mmol) 3,5-difluorophenyl boronic acid were added. The reaction mixture was stirred at RT overnight, filtered on decalit, and concentrated under vacuo. Column chromatography over silica (hexane followed by 1:9 ethyl acetate hexane) provided 206 mg (71%) of 1-[6-chloro-1-(3,5-difluoro-phenyl)-1H-indol-3-yl]-2,2,2-trifluoro-ethanone as a light brown solid. This compound was put in suspension in 10 ml H₂O and 1.2 g NaOH was added. The reaction mixture was stirred at 70 °C for 2 days, cooled down to RT, and acidified with aqueous HCl (1N) until pH = 1. The product was extracted with CH₂Cl₂, and the organic phase dried over Na₂SO₄. Evaporation of the solvent under vacuo afforded 120 mg (70%) of 6-chloro-1-(3,5-difluoro-phenyl)-1H-indole-3-carboxylic acid as a white solid.

20

Example 6

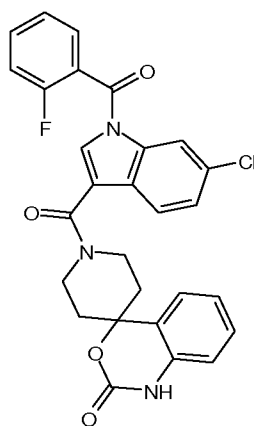
1'-[[6-Chloro-1-(3-fluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



To a solution of 100 mg (0.252 mmol) 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) in dry DMF (5 ml) was added 10 mg NaH (0.25 mmol, 60% in oil). After 15 minutes at RT, 43.9 mg (0.277
 5 mmol) of 3-fluoro-benzoyl chloride was added and stirring continued overnight. The reaction mixture was poured onto an aqueous solution of ammonium chloride, and the product extracted twice with ethyl acetate. The combined organic phases were dried on Na₂SO₄ and the solvent evaporated under reduced pressure. Purification by preparative HPLC yielded 1'-{[6-chloro-1-(3-fluorobenzoyl)-1H-indol-3-yl]carbonyl}spiro[3,1-
 10 benzoxazine-4,4'-piperidin]-2(1H)-one.
 ES-MS m/e (%): 518.4 (M+H⁺).

Example 7

1'-{[6-Chloro-1-(2-fluorobenzoyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-
 15 piperidin]-2(1H)-one

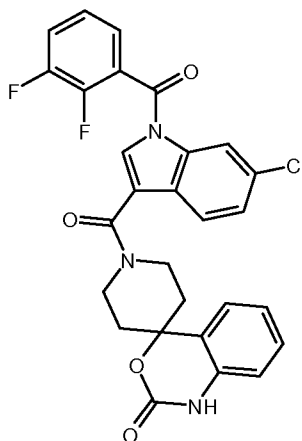


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-fluoro-benzoyl chloride was prepared 1'-{[6-chloro-1-(2-fluorobenzoyl)-1H-indol-3-
 20 yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 518.4 (M+H⁺).

Example 8

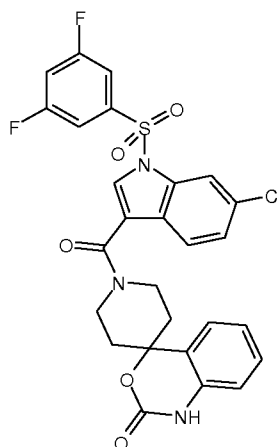
1'-{[6-Chloro-1-(2,3-difluorobenzoyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-
5 4,4'-piperidin]-2(1H)-one



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)
carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and
2,3-difluoro-benzoyl chloride was prepared 1'-{[6-chloro-1-(2,3-difluorobenzoyl)-1H-
10 indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.
ES-MS m/e (%): 536.4 (M+H⁺).

Example 9

15 1'-({6-Chloro-1-[(3,5-difluorophenyl)sulfonyl]-1H-indol-3-yl}carbonyl)spiro[3,1-
benzoxazine-4,4'-piperidin]-2(1H)-one



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)
carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and
20 3,5-difluoro-benzenesulfonyl chloride was prepared 1'-({6-chloro-1-[(3,5-

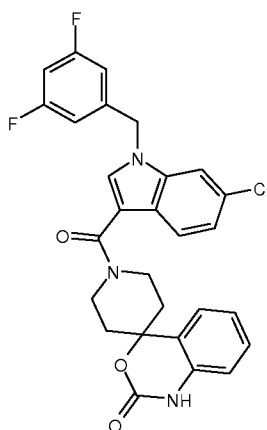
difluorophenyl)sulfonyl]-1H-indol-3-yl]carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 572.3 (M+H⁺).

5

Example 10

1'-[[6-Chloro-1-(3,5-difluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

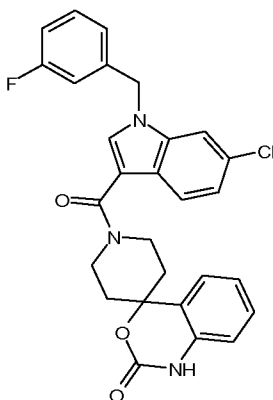


- 10 Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 1-bromomethyl-3,5-difluoro-benzene was prepared 1'-[[6-chloro-1-(3,5-difluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

- 15 ES-MS m/e (%): 522.4 (M+H⁺).

Example 11

1'-[[6-Chloro-1-(3-fluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



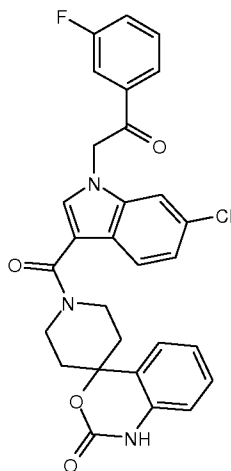
20

Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 1-bromomethyl-3,5-difluoro-benzene was prepared 1'-{[6-chloro-1-(3-fluorobenzyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

5 ES-MS m/e (%): 504.4 (M+H⁺).

Example 12

1'-({6-Chloro-1-[2-(3-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



10

Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-(3-fluoro-phenyl)-ethanone was prepared 1'-({6-chloro-1-[2-(3-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

15

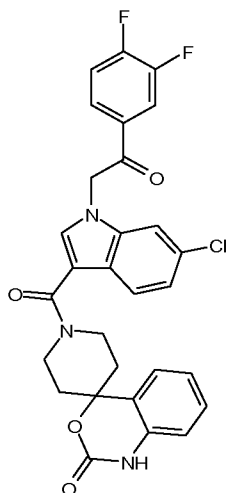
ES-MS m/e (%): 532.4 (M+H⁺).

Example 13

1'-({6-Chloro-1-[2-(3,4-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

20

- 35 -

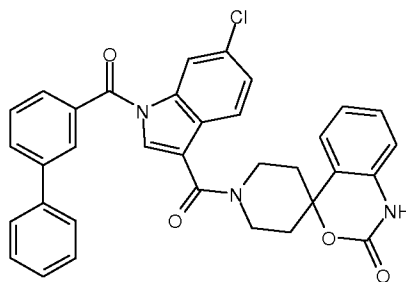


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-(3,4-difluoro-phenyl)-ethanone was prepared 1'-({6-chloro-1-[2-(3,4-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 550.4 (M+H⁺).

Example 14

1'-[[1-(Biphenyl-3-ylcarbonyl)-6-chloro-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

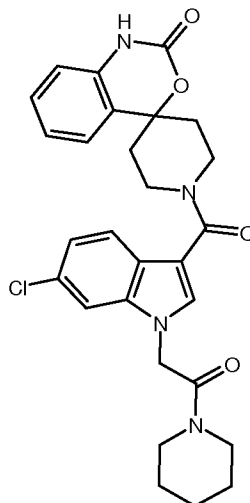


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and biphenyl-3-carbonyl chloridewas prepared 1'-[[1-(biphenyl-3-ylcarbonyl)-6-chloro-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 576.4 (M+H⁺).

Example 15

1'-[[6-Chloro-1-(2-oxo-2-piperidin-1-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

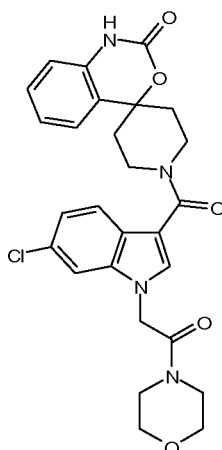
5 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-chloro-1-piperidin-1-yl-ethanone was prepared 1'-[[6-chloro-1-(2-oxo-2-piperidin-1-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 521.1 (M+H⁺).

10

Example 16

1'-[[6-Chloro-1-(2-morpholin-4-yl-2-oxoethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



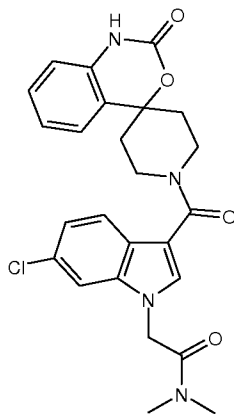
Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

15 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-chloro-1-morpholin-4-yl-ethanone was prepared 1'-[[6-chloro-1-(2-morpholin-4-yl-2-oxoethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 523.2 ($M+H^+$).

Example 17

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide

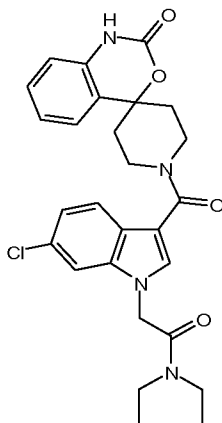


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-chloro-N,N-dimethylacetamide was prepared 2-{6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide.

ES-MS m/e (%): 481.0 ($M+H^+$).

Example 18

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-diethylacetamide



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-chloro-N,N-diethylacetamide was prepared 2-{6-chloro-3-[(2-oxo-1,2-dihydro-1'H-

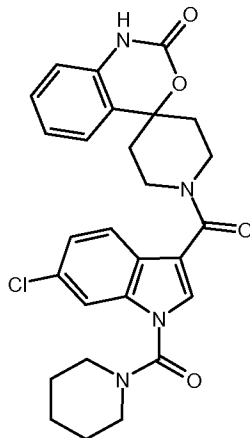
spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-diethylacetamide.

ES-MS m/e (%): 509.1 ($M+H^+$).

5

Example 19

1'-{[6-Chloro-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

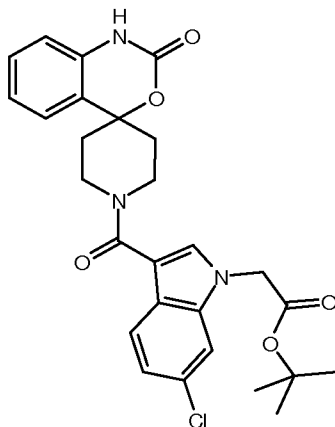


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and piperidine-1-carbonyl chloride was prepared 1'-{[6-chloro-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.
ES-MS m/e (%): 507.1 ($M+H^+$).

15

Example 20

tert-Butyl {6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}acetate



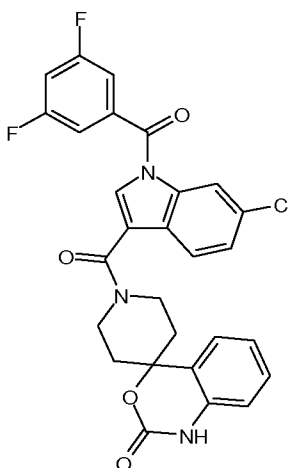
Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl) carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and bromo-acetic acid tert-butyl ester was prepared tert-butyl {6-chloro-3-[(2-oxo-1,2-

5 yl}acetate.

ES-MS m/e (%): 510.5 (M+H⁺).

Example 21

1'-{[6-Chloro-1-(3,5-difluorobenzoyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-
10 4,4'-piperidin]-2(1H)-one

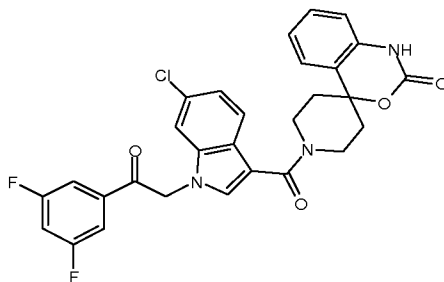


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl) carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 3,5-difluoro-benzoyl chloride was prepared 1'-{[6-chloro-1-(3,5-difluorobenzoyl)-1H-
15 indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 536.3 (M+H⁺).

Example 22

1'-({6-Chloro-1-[2-(3,5-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-
20 benzoxazine-4,4'-piperidin]-2(1H)-one



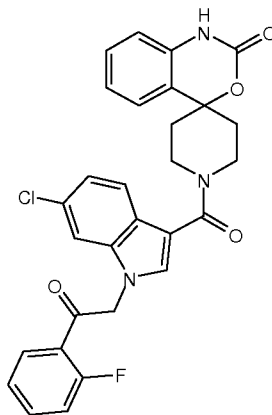
Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-(3,5-difluoro-phenyl)-ethanone was prepared 1'-({6-chloro-1-[2-(3,5-

5 difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 550.3 (M+H⁺).

Example 23

10 1'-({6-Chloro-1-[2-(2-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one

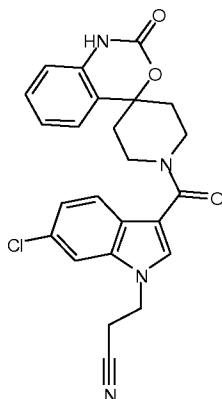


Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-(2-fluoro-phenyl)-ethanone was prepared 1'-({6-chloro-1-[2-(2-

15 fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 532.3 (M+H⁺).

3-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

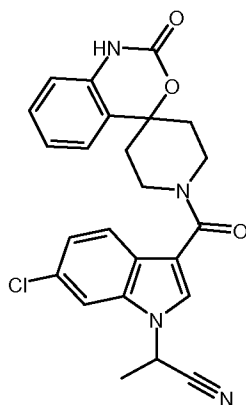
5 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 3-chloro-propionitrile was prepared 3-{6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile.

ES-MS m/e (%): 449.0 (M+H⁺).

10

Example 25

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile



Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

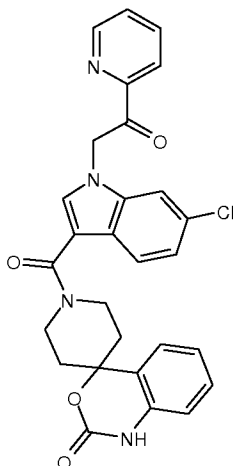
15 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-chloro-propionitrile was prepared 2-{6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile.

ES-MS m/e (%): 449.0 (M+H⁺).

20

Example 26

1'-[[6-Chloro-1-(2-oxo-2-pyridin-2-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



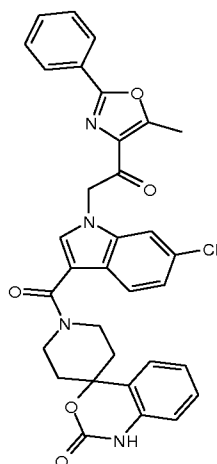
Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

5 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-pyridin-2-yl-ethanone was prepared 1'-[[6-chloro-1-(2-oxo-2-pyridin-2-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one. ES-MS m/e (%): 515.4 (M+H⁺).

10

Example 27

1'-({6-Chloro-1-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one



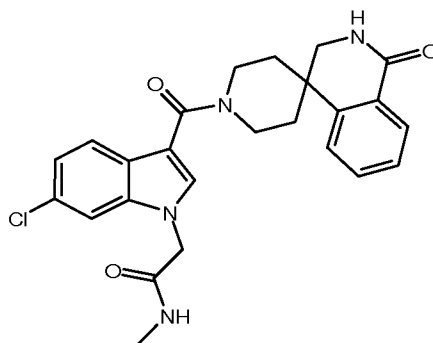
Using the same procedure described in example 6, from 1'-[(6-chloro-1H-indol-3-yl)

15 carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one (described in example 1) and 2-bromo-1-(5-methyl-2-phenyl-oxazol-4-yl)-ethanone (described in *J.Med.Chem.* 1992, 35(14), 2617) was prepared 1'-({6-chloro-1-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

ES-MS m/e (%): 595.0 ($M+H^+$).

Example 28

2-[6-chloro-3-[(1-oxo-2,3-dihydro-1H,1'H-spiro[isoquinoline-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl]-N-methylacetamide



To a stirred solution of an 6-chloro-1-methylcarbamoylmethyl-1H-indole-3-carboxylic acid (described below) (1 eq) in DMF were added HATU, (1.1 eq.), Et_3N (2eq.) and (2 eq) of the 2,3-dihydro-1H-spiro[isoquinoline-4,4'-piperidin]-1-one (described previously in WO9909984) . The mixture was stirred overnight at RT and then poured onto water and extracted with CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Preparative HPLC afforded the title compound. ES-MS m/e (%): 465.3 ($M+H^+$).

6-Chloro-1-methylcarbamoylmethyl-1H-indole-3-carboxylic acid

a) 2-[6-Chloro-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N-methyl-acetamide

To a stirred solution of 1-(6-chloro-1H-indol-3-yl)-2,2,2-trifluoro-ethanone (described previously in US 2004067939) in DMF were added 2.1eq. NaH (60% in oil). The mixture was stirred at RT for 30 min. and then the (commercially available) 2-chloro-N-methyl-acetamide (1.1eq.) was added. The mixture was stirred an additional 14 hours at 60 °C and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Purification by preparative HPLC gave the title compound.

ES-MS m/e (%): 319.3 ($M+H^+$).

b) 6-Chloro-1-methylcarbamoylmethyl-1H-indole-3-carboxylic acid

2-[6-Chloro-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N-methyl-acetamide was suspended in DCE and treated with (2.2 eq.) of sodium trimethylsilanolate. After shaking at room

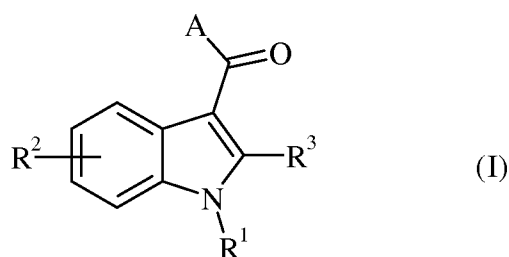
- 44 -

temperature for 20 min, the mixture was concentrated in vacuo and purified by prep. HPLC to give the title compound.

ES-MS m/e (%): 265.0 (M-H⁺).

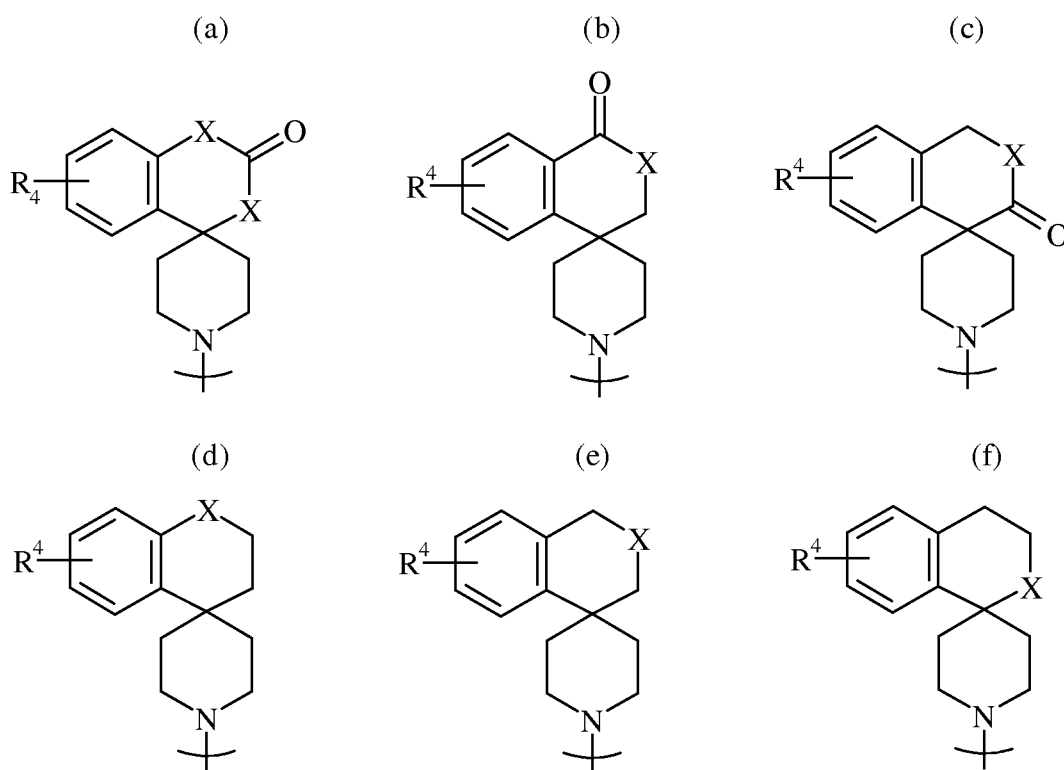
Claims

1. Compounds of the general formula (I)



wherein

5 A is selected from the following groups (a), (b), (c), (d), (e) and (f):



X is can be the same or different and is CRⁱⁱⁱR^{iv}, NRⁱⁱⁱ or O, wherein in (a), only one X can be O, the other being CRⁱⁱⁱR^{iv} or NRⁱⁱⁱ;

Rⁱ is H,

10 C₁₋₆-alkyl optionally substituted by CN,
or is aryl, 5 or 6 membered heteroaryl or sulfonylaryl which are optionally
substituted by one or more B,
or is -(CH₂)_m-R^a wherein R^a is:

ORⁱ,

15 NRRⁱRⁱⁱ,

C₃₋₆-cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B, or is -(CH₂)_n-(CO)-R^b or -(CH₂)_n-(SO₂)-R^b, wherein R^b is:

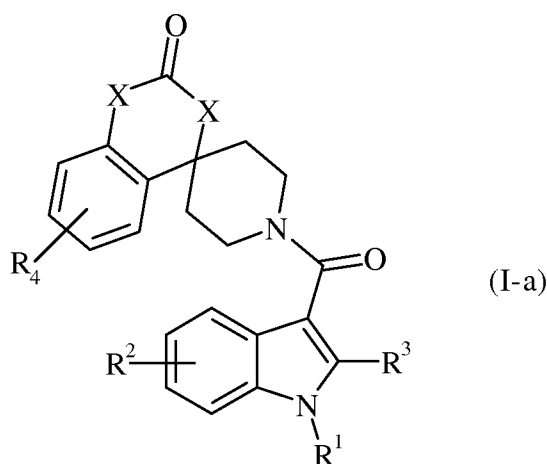
- 5 C₁₋₆-alkyl,
C₁₋₆-alkoxy,
C₃₋₆-cycloalkyl,
-(CH₂)_m-NRⁱⁱⁱR^{iv},
NRⁱRⁱⁱ,
C₃₋₆-cycloalkyl, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered
10 heteroaryl which are optionally substituted by one or more B,
or R¹ and R³ together with the indole ring to which they are attached form a 5 or 6 membered heterocycloalkyl which can be substituted by (CO);
- R² is one or more of H, OH, halo, CN, nitro, C₁₋₆-alkyl optionally substituted by – NRⁱⁱⁱR^{iv}, C₁₋₆-alkoxy, -O-CH₂-C₂₋₆-alkenyl, benzyloxy, or C₁₋₆-haloalkyl,
15 or two R² may form an oxo or dioxo bridge together with the indole ring to which they are attached;
- R³ is H,
or is halo,
or is -(CO)-R^c, wherein R^c is:
20 C₁₋₆-alkyl,
-(CH₂)_n-NRⁱRⁱⁱ,
-(CH₂)_n-NRⁱⁱⁱR^{iv},
5 or 6 membered heterocycloalkyl optionally substituted by C₁₋₆-alkyl,
or is C₁₋₆-alkyl or aryl, which are optionally substituted by
25 halo,
-O(CO)-C₁₋₆-alkyl,
or by -NH(CO)R^d, wherein R^d is C₁₋₆-alkyl optionally substituted by halo or nitro, or R^d is aryl or a 5 or 6 membered heteroaryl, which are optionally substituted by halo, nitro, C₁₋₆-alkyl or C₁₋₆-haloalkyl;
- 30 R⁴ is one or more of H, halo, C₁₋₆ alkyl or C₁₋₆ alkoxy, CN, or two R⁴ may form an oxo or dioxo bridge together with the phenyl ring to which they are attached
- B is halo, CN, NRⁱRⁱⁱ, C₁₋₆-alkyl optionally substituted by CN, halo or C₁₋₆-alkoxy, C₁₋₆-alkoxy, C₁₋₆-haloalkoxy, C₃₋₆-cycloalkyl, -C(O)O-C₁₋₆-alkyl, -C(O) NRⁱRⁱⁱ, - C(O)-C₁₋₆-alkyl, -S(O)₂-C₁₋₆-alkyl, -S(O)₂- NRⁱRⁱⁱ, (CRⁱⁱⁱR^{iv})_n-phenyl, or
35 (CRⁱⁱⁱR^{iv})_n-5 or 6 membered heteroaryl wherein the phenyl or 5 or 6 membered

heteroaryl moiety is optionally substituted by one or more substituent(s) selected from the group consisting of:

- halo, CN, $\text{NR}^{\text{i}}\text{R}^{\text{ii}}$, C_{1-6} -alkyl optionally substituted by CN or C_{1-6} -alkoxy, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-\text{C}(\text{O})\text{O}-\text{C}_{1-6}$ -alkyl, $-\text{C}(\text{O})-\text{NR}^{\text{i}}\text{R}^{\text{ii}}$, $-\text{C}(\text{O})-\text{C}_{1-6}$ -alkyl, $-\text{S}(\text{O})_2-\text{C}_{1-6}$ -alkyl, $-\text{S}(\text{O})_2-\text{NR}^{\text{i}}\text{R}^{\text{ii}}$;
 R^{i} and R^{ii} are H, C_{1-6} -alkyl, C_{1-6} -alkylene- $\text{NR}^{\text{iii}}\text{R}^{\text{iv}}$, $-(\text{CO})\text{O}-\text{C}_{1-6}$ -alkyl, $-\text{C}(\text{O})-\text{NR}^{\text{iii}}\text{R}^{\text{iv}}$, $-\text{C}(\text{O})-\text{C}_{1-6}$ -alkyl, $-\text{S}(\text{O})_2-\text{C}_{1-6}$ -alkyl or $-\text{S}(\text{O})_2-\text{NR}^{\text{iii}}\text{R}^{\text{iv}}$;
 R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $\text{N}(\text{R}^{\text{iv}})_2$;
 R^{iv} is H or C_{1-6} -alkyl;
 10 m is 1 to 6;
 n is 0 to 4;
 as well as pharmaceutically acceptable salts thereof.

2. The compound of formula (I) according to claim 1, wherein
 R^2 is one or more of H, OH, halo, CN, nitro, C_{1-6} -alkyl optionally substituted by $-\text{NR}^{\text{iii}}\text{R}^{\text{iv}}$, C_{1-6} -alkoxy, $-\text{O}-\text{CH}_2-\text{C}_{2-6}$ -alkenyl, benzyloxy,
 15 or two R^2 may form an oxo or dioxo bridge together with the indole ring to which they are attached; and
 R^{iii} and R^{iv} are H or C_{1-6} -alkyl.

- 20 3. The compound of formula (I-a) according to claim 1 or 2:



wherein:

- X is can be the same or different and is $\text{CR}^{\text{iii}}\text{R}^{\text{iv}}$, NR^{iii} or O, wherein only one X can be O, the other being $\text{CR}^{\text{iii}}\text{R}^{\text{iv}}$ or NR^{iii} ;;
 25 R^1 is H,
 C_{1-6} -alkyl optionally substituted by CN,

or is aryl optionally substituted by one or more B,

or is $-(CH_2)_m-R^a$ wherein R^a is:

NR^iR^{ii} ,

aryl optionally substituted by one or more B,

5 or is $-(CH_2)_n-(CO)-R^b$ or $-(CH_2)_n-(SO_2)-R^b$, wherein R^b is:

C_{1-6} -alkoxy,

NR^iR^{ii} ,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B,

10 R^2 is one or more of H or halo,

R^3 is H,

or is C_{1-6} -alkyl,

R^4 is one or more of H, halo, C_{1-6} alkyl or C_{1-6} alkoxy or CN;

B is halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN, halo or C_{1-6} -alkoxy,

15 C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)NR^iR^{ii}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$, $(CR^{iii}R^{iv})_n$ -phenyl, or $(CR^{iii}R^{iv})_n$ -5 or 6 membered heteroaryl wherein the phenyl or 5 or 6 membered heteroaryl moiety is optionally substituted by one or more substituent(s) selected from the group consisting of:

20 halo, CN, NR^iR^{ii} , C_{1-6} -alkyl optionally substituted by CN or C_{1-6} -alkoxy, C_{1-6} -alkoxy, C_{1-6} -haloalkoxy, C_{3-6} -cycloalkyl, $-C(O)O-C_{1-6}$ -alkyl, $-C(O)-NR^iR^{ii}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl, $-S(O)_2-NR^iR^{ii}$;

R^i and R^{ii} are H, C_{1-6} -alkyl, C_{1-6} -alkylene- $NR^{iii}R^{iv}$, $-(CO)O-C_{1-6}$ -alkyl, $-C(O)-NR^{iii}R^{iv}$, $-C(O)-C_{1-6}$ -alkyl, $-S(O)_2-C_{1-6}$ -alkyl or $-S(O)_2-NR^{iii}R^{iv}$;

25 R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $N(R^{iv})_2$;

R^{iv} is H or C_{1-6} -alkyl;

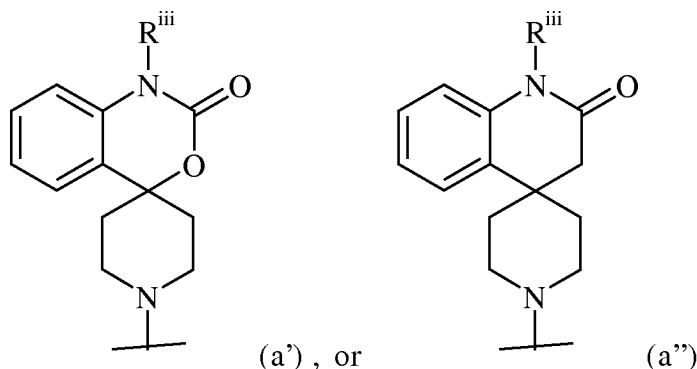
m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

30 4. The compound of formula (I-a) according to claim 3, wherein R^{iii} and R^{iv} is H or C_{1-6} -alkyl.

5. The compound of formula (I) according to claim 3 or 4, wherein group (a) of the compound of formula (I-a) is selected from (a') and (a''):



wherein R^{iii} is H, C_{1-6} -alkyl or C_{1-6} -alkylene- $N(R^{iv})_2$ and R^{iv} is H or C_{1-6} -alkyl.

6. The compound of formula (I-a) according to any one of claims 3 to 5, wherein R^1 is H.

5 7. The compounds of formula (I-a) according to claim 6, wherein said compounds are selected from the group consisting of:

1'-[(6-Chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

6'-Bromo-1-(1H-indol-3-ylcarbonyl)-1'H-spiro[piperidine-4,4'-quinolin]-2'(3'H)-
10 one;

6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]-1-[2-(dimethylamino)ethyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one; and

6-Chloro-1'-[(6-chloro-1H-indol-3-yl)carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

15 8. The compounds of formula (I-a) according to any one of claims 3 to 5, wherein R^1 is or is aryl optionally substituted by one or more B and B is as defined in claim 3.

9. The compound of formula (I-a) according to claim 8, wherein said compound is 1'-{[6-chloro-1-(3,5-difluorophenyl)-1H-indol-3-yl]carbonyl}spiro[3,1-
20 benzoxazine-4,4'-piperidin]-2(1H)-one.

10. The compounds of formula (I-a) according to any one of claims 3 to 5, wherein R^1 is $-(CH_2)_m-R^a$ wherein R^a is CN, NR^iR^{ii} , or aryl optionally substituted by one or more B and m, R^i , R^{ii} and B are as defined in claim 3.

11. The compounds of formula (I-a) according to claim 10, wherein said
25 compounds are selected from the group consisting of:

1'-[[6-Chloro-1-(3,5-difluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-[[6-Chloro-1-(3-fluorobenzyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

5 3-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile; and

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}propanenitrile.

12. The compounds of formula (I-a) according to any one of claims 3 to 5,
10 wherein R¹ is -(CH₂)_n-(CO)-R^b or -(CH₂)_n-(SO₂)-R^b, wherein R^b is C₁₋₆-alkoxy, NRⁱRⁱⁱ, 4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more B and n, Rⁱ, Rⁱⁱ and B is as defined in claim 3.

13. The compounds of formula (I-a) according to claim 12, wherein said compounds are selected from the group consisting of:

15 1'-[[6-Chloro-1-(3-fluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-[[6-Chloro-1-(2-fluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

20 1'-[[6-Chloro-1-(2,3-difluorobenzoyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-({6-Chloro-1-[(3,5-difluorophenyl)sulfonyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-({6-Chloro-1-[2-(3-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

25 1'-({6-Chloro-1-[2-(3,4-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-{[1-(Biphenyl-3-ylcarbonyl)-6-chloro-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

30 1'-[[6-Chloro-1-(2-oxo-2-piperidin-1-ylethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-[[6-Chloro-1-(2-morpholin-4-yl-2-oxoethyl)-1H-indol-3-yl]carbonyl]spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide;

2-{6-Chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-diethylacetamide;

1'-{[6-Chloro-1-(piperidin-1-ylcarbonyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

5 tert-Butyl {6-chloro-3-[(2-oxo-1,2-dihydro-1'H-spiro[3,1-benzoxazine-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}acetate;

1'-{[6-Chloro-1-(3,5-difluorobenzoyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

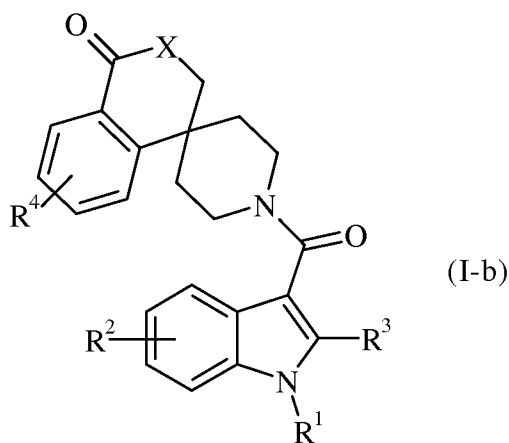
10 1'-({6-Chloro-1-[2-(3,5-difluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-({6-Chloro-1-[2-(2-fluorophenyl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one;

1'-{[6-Chloro-1-(2-oxo-2-pyridin-2-ylethyl)-1H-indol-3-yl]carbonyl}spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one; and

15 1'-({6-Chloro-1-[2-(5-methyl-2-phenyl-1,3-oxazol-4-yl)-2-oxoethyl]-1H-indol-3-yl}carbonyl)spiro[3,1-benzoxazine-4,4'-piperidin]-2(1H)-one.

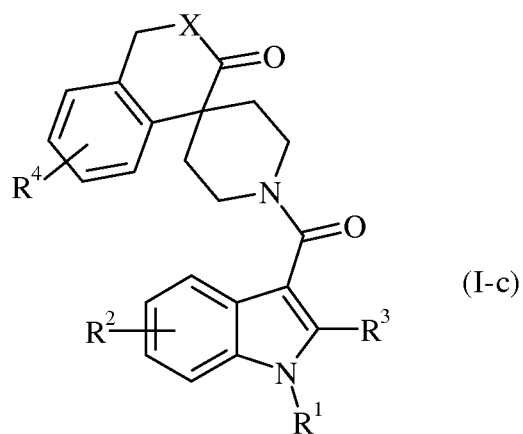
14. The compounds of formula (I-b) according to claim 1 or 2, wherein the compound is selected from formula (I-b):



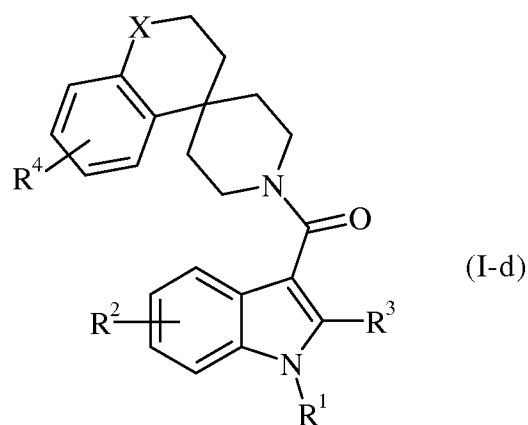
20 15. The compound of formula (I-b) according to claim 14, wherein said compound is 2-{6-chloro-3-[(1-oxo-2,3-dihydro-1H,1'H-spiro[isoquinoline-4,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N-methylacetamide.

16. The compounds of formula (I-c) according to claim 1 or 2, wherein the compound is selected from formula (I-c):

- 52 -

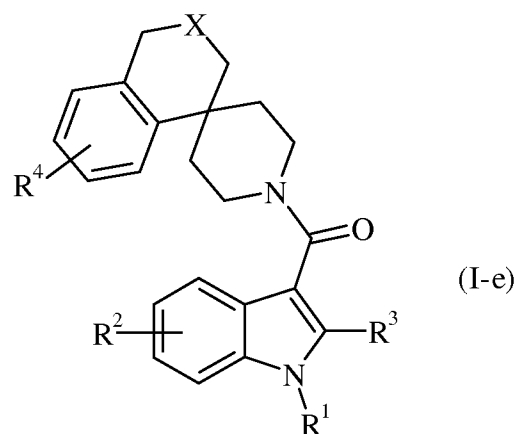


17. The compounds of formula (I-d) according to claim 1 or 2, wherein the compound is selected from formula (I-d):

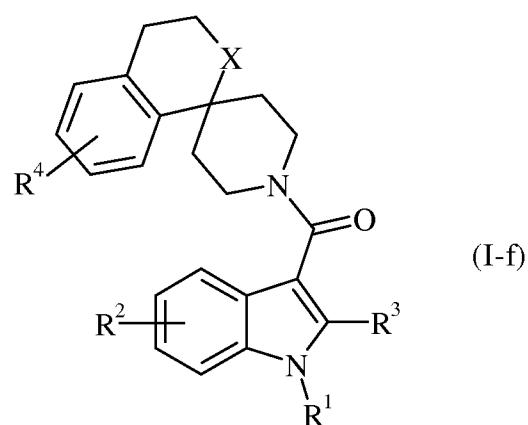


18. The compounds of formula (I-e) according to claim 1 or 2, wherein the compound is selected from formula (I-e):

- 53 -

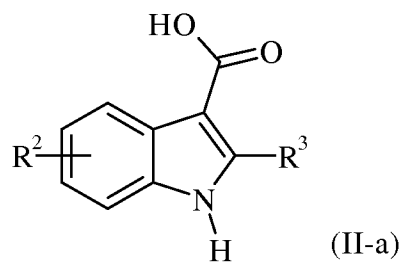


19. The compounds of formula (I-f) according to claim 1 or 2, wherein the compound is selected from formula (I-f):



5

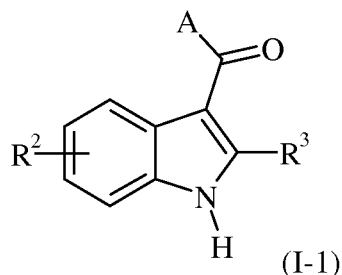
20. A process for the preparation of the compounds of formula (I) wherein R^1 is H according to any one of claims 1 to 19 comprising the step of reacting a compound of formula (II-a):



10

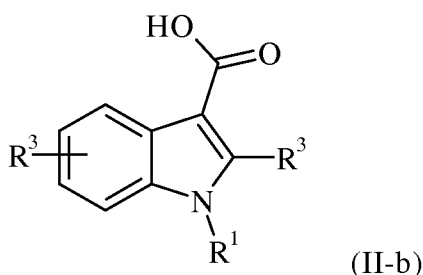
with a compound of formula A-H to obtain the compound of formula (I), wherein R^1 is H and A, R^2 and R^3 are as defined in any one of claim 1 or 2.

21. A process for the preparation of the compounds of formula (I) according to any one of claims 1 to 19 comprising the step of reacting a compound of formula (I-1):



with an electrophile compound of formula R^1 -Z to obtain the compound of formula (I), wherein A, R^1 , R^2 and R^3 are as defined in any one of claim 1 or 2 and Z is halo.

22. A process for the preparation of the compounds of formula (I) according to any one of claims 1 to 15 comprising the step of reacting a compound of formula (II-b):



with a compound of formula A-H to obtain the compound of formula (I), wherein R^1 , R^2 , R^3 , and A are as defined in any one of claim 1 or 2.

23. A compound formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) obtainable by a process according to any one of claims 20 to 22.

24. A compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) according to any one of claims 1 to 19 for a use in the prevention or treatment of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

25. A pharmaceutical composition comprising a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) according to any one of claims 1 to 19.

26. A pharmaceutical composition according to claim 25, wherein it is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

27. Use of a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e) or (I-f) according to any one of claims 1 to 19 for the preparation of a medicament.

28. Use according to claim 27, wherein the medicament is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of
5 vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

29. The invention as described hereinabove.
