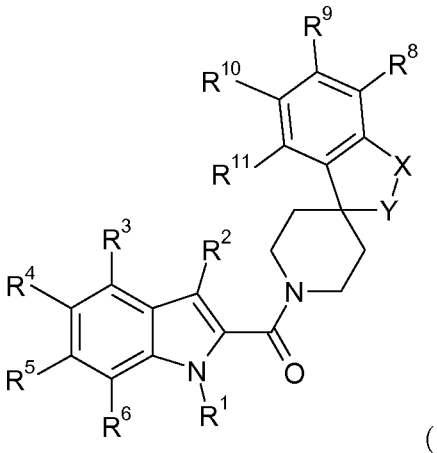
SPIRO-PIPERIDINE DERIVATIVES AS V1A RECEPTOR ANTAGONISTS

The present invention is concerned with novel indol-2-yl-carbonyl-spiro-piperidine derivatives as V1a receptor antagonists, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful in the prevention and/or treatment of anxiety and depressive disorders and other diseases.

In particular, the present invention is concerned with compounds of the general formula (I)



(I)

wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or $–CH_2CH_2-$;

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

$-(C_{1-6}\text{-alkylene})-C(O)-NR^aR^b$,

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

-(C_{1-6}-alkylene)-$C(O)R^f$,

benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

R^3 is hydrogen, halo, or C_{1-6}-alkyl;

R^4 is hydrogen,

halo,

C_{1-6}-alkyl,

halo-C_{1-6}-alkyl,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy, or

-O-C_{2-10}-alkenyl;

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

$-R^4–R^5-$ is $–O-(CH_2)_n–O–$ wherein n is 1 or 2;

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h,

-(C_{1-6}-alkylene)-$C(O)-NR^iR^j$,

-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

nitro,

halo,

cyano,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy,

halo-C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-$C(O)R^f$,

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-

membered heterocycloalkyl or 3 to 6-membered cycloalkyl,

each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

$-R^5-R^6-$ is $-O-(CH_2)_n-C(O)-$,

$-C(O)-(CH_2)_n-O-$, or

$-O-(CH_2)_n-O-$ wherein n is 1 or 2;

R^7 is hydrogen or C_{1-6}-alkyl;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}alkoxy;

R^a, R^b, R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

$-(C_{1-6}$-alkylene$)-NR^kR^l$,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,

or R^a and R^b, or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

R^c, R^d , R^g and R^h are each independently

hydrogen,

C_{1-6}-alkyl,

$-C(O)R^e$, or $-S(O)_2R^e$

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;

R^f is selected from the group of

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy; and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or a pharmaceutically acceptable salt thereof.

The compounds of formula (I) can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the text or in the examples, or by methods known in the art.

The compounds of formula (I) possess pharmaceutical activity, in particular they are modulators of V1a receptor activity. More particular, the compounds are antagonists of the V1a receptor.

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-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 mouse 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 (Michelini, 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).

It is therefore an object of the present invention to provide compounds which act as V1a receptor modulators, and in particular as V1a receptor antagonists. Such 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.

In the present description, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated hydrocarbon radical. The term "C_{1-6}-alkyl" denotes a saturated straight- or branched-chain hydrocarbon group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, *tert*-butyl, the isomeric pentyls and the like. A preferred sub-group of C_{1-6}-alkyl is C_{1-4}-alkyl, i.e. with 1 - 4 carbon atoms.

In the present invention, the term "alkylene" refers to a linear or branched saturated divalent hydrocarbon radical. In particular, "C_{1-6}-alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g. methylene, ethylene, 2,2-dimethylethylene, n-propylene, 2-methylpropylene, and the like.

In the present description, the term "alkoxy" and "C_{1-6}-alkoxy" refers to the group R'-O-, wherein R' is C_{1-6}-alkyl as defined above. Examples of alkoxy groups are methoxy,

ethoxy, n-propoxy, isopropoxy, n-butoxy, *tert*-butoxy, *sec*-butoxy and the like. A preferred sub-group of C_{1-6}-alkoxy, and still more preferred alkoxy groups are methoxy and/or ethoxy.

In the present description, the term "thioalkyl" and "C_{1-6}-thioalkyl" refers to the group R'-S-, wherein R' is C_{1-6}-alkyl as defined above.

The term "C_{1-6}-hydroxyalkyl" or "C_{1-6}-alkyl substituted by OH" denotes a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a hydroxyl group.

The term "C_{1-6}-cyanoalkyl" or "C_{1-6}-alkyl substituted by CN" denotes a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a CN group.

The term "halo" or "halogen" refers to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I) with fluorine, chlorine and bromine being preferred.

The term "halo-C_{1-6}-alkyl" denotes a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Examples of halo-C_{1-6}-alkyl 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. Among the preferred halo-C_{1-6}-alkyl groups are difluoro- or trifluoro-methyl or -ethyl.

The term "halo-C_{1-6}-alkoxy" denotes a C_{1-6}-alkoxy group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated alkoxy groups are difluoro- or trifluoro-methoxy or –ethoxy.

The term "C_{2-12}-alkenyl", alone or in combination, denotes a straight-chain or branched hydrocarbon residue of 2 to 12 carbon atoms comprising at least one double bond. A preferred sub-group of C_{2-12}-alkenyl is C_{2-6}-alkyenyl. Examples of the preferred alkenyl groups are ethenyl, propen-1-yl, propen-2-yl (allyl), buten-1-yl, buten-2-yl, buten-3-yl, penten-1-yl, penten-2-yl, penten-3-yl, penten-4-yl, hexen-1-yl, 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 "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 membered heteroaryl can optionally be substituted with one, two, three or four substituents, wherein each substituent may independently be selected from the group consisting of hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, halo, cyano, nitro, halo-C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-alkoxycarbonyl, amino, C_{1-6}-alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Preferred substituents are halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, and cyano. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, optionally substituted oxazolyl, optionally substituted thiazolyl, optionally substituted pyrazinyl, optionally substituted pyrrolyl, optionally substituted pyrazinyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted furanyl, and those which are specifically exemplified herein.

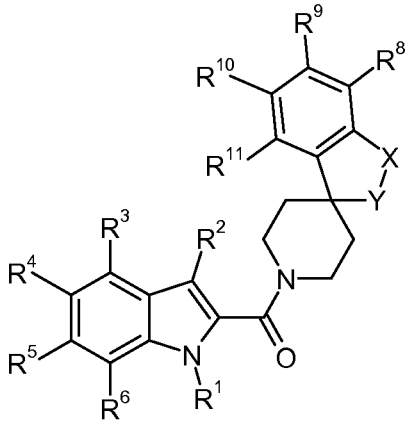
The term "heterocycloalkyl" means a monovalent saturated moiety, consisting of one ring of 3 to 7, preferably from 4 to 6 atoms as ring members, including one, two, or three heteroatoms selected from nitrogen, oxygen or sulfur, the rest being carbon atoms. 3 to 7 membered heterocycloalkyl can optionally be substituted with one, two, or three substituents, wherein each substituent is independently hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, halo, cyano, nitro, halo-C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-alkoxycarbonyl, amino, C_{1-6}-alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Preferred substituents are halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, and cyano. Examples of heterocyclic moieties include, but are not limited to, 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.

The term "heterocycle" in the definition "R^a and R^b, R^c and R^d, R^g and R^h, R^i and R^j, together with the nitrogen to which they are bound form a five- or six-membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur" means either heterocycloalkyl or heteroaryl in the above-given sense, which may optionally be substituted as described above. Preferably, the "heterocycle" may optionally be substituted with one, two or three substituents selected from halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, and cyano. Preferred heterocycles are piperazine, N-methylpiperazine, morpholin, piperidine and pyrrolidine.

The phrase "one or more" substituents preferably means one, two or three optional substituents per ring.

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 and the like.

In detail, the present invention relates to compounds of the general formula (I)



(I)

wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or $–CH_2CH_2$-;

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b;

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

-(C_{1-6}-alkylene)-C(O)R^f,

benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

R^3 is hydrogen, halo, or C_{1-6}-alkyl;

R^4 is hydrogen,

halo,

C_{1-6}-alkyl,

halo-C_{1-6}-alkyl,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy, or

-O-C_{2-10}-alkenyl;

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

$-R^4–R^5-$ is $–O-(CH_2)_n–O–$ wherein n is 1 or 2;

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h,

-(C_{1-6}-alkylene)-$C(O)-NR^iR^j$,

-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

nitro,

halo,

cyano,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy,

halo-C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-$C(O)R^f$,

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,

each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

$-R^5-R^6-$ is $-O-(CH_2)_n-C(O)-$,

$-C(O)-(CH_2)_n-O-$, or

$-O-(CH_2)_n-O-$ wherein n is 1 or 2;

R^7 is hydrogen or C_{1-6}-alkyl;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}alkoxy;

R^a, R^b, R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

$-(C_{1-6}$-alkylene$)-NR^kR^l$,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,

or R^a and R^b, or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

R^c, R^d , R^g and R^h are each independently

hydrogen,

C_{1-6}-alkyl,

$-C(O)R^e$, or $-S(O)_2R^e$

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;

R^f is selected from the group of

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy; and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or a pharmaceutically acceptable salt thereof.

In certain embodiments of the invention, R^a and R^b, R^c and R^d, R^i and R^j, or R^g and R^h together with the nitrogen to which they are bound form piperazine, 4-(C_{1-6}-alkyl)-piperazine, 4-methylpiperazine, morpholine, piperidine or pyrrolidine.

In certain embodiments of the invention, R^a and R^b, R^c and R^d, R^i and R^j, or R^g and R^h together with the nitrogen to which they are bound form 4-methylpiperazine, or morpholine.

In certain embodiments of the invention, wherein R^m is a 5- to 6-membered heteroaryl, the preferred heteroaryl is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, imidazole, pyrazole, oxazole, and isoxazole.

In embodiments of the invention, wherein R^m is a 4- to 6-membered heterocycloalkyl, the preferred heterocycloalkyl is selected from the group consisting of pyrrolidine, oxethane, tetrahydropyrane, piperidine, morpholine, and piperazine.

In certain embodiments of the invention,

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl.

In certain embodiments of the invention,

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently

hydrogen,

-$C(O)R^e$, or -$S(O)_2R^e$

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, and

phenyl, optionally substituted by one or more halo,

halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-

alkoxy, nitro, or cyano, or

R^c and R^d together with the nitrogen to which they are bound form

isoindole-1,3-dione,

-(C_{1-6}-alkylene)-C(O)R^f,

wherein R^f is selected from the group of

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy, and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

In certain embodiments of the invention, R^2 is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy.

In certain embodiments of the invention, R^3 is hydrogen or halo.

In certain embodiments of the invention, R^4 is hydrogen; halo, preferably fluoro, chloro or bromo; C_{1-6}-alkyl, preferably methyl; C_{1-6}-alkoxy, preferably methoxy or –O-*iso*-propyl; halo-C_{1-6}-alkoxy, preferably trifluoromethoxy; or -O-C_{2-10}-alkenyl, preferably allyl.

In certain embodiments of the invention, R^5 is hydrogen; halo, preferably bromo; C_{1-6}-alkyl, preferably methyl; or C_{1-6}-alkoxy, preferably methoxy.

In certain embodiments of the invention, R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein -R^4–R^5- is –O-CH_2–O– .

In certain embodiments of the invention,

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h

wherein R^g and R^h are each independently selected from hydrogen, or

C_{1-6}-alkyl;

or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms

selected from the group of nitrogen, oxygen and sulfur;

-(C_{1-6}-alkylene)-C(O)-NR^iR^j

wherein R^i and R^j are each independently

hydrogen;

C_{1-6}-alkyl;

-(C_{1-6}-alkylene)-NR^kR^l;

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{-1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

nitro;

halo;

cyano;

C_{1-6}-alkoxy;

halo-C_{1-6}-alkoxy;

halo-C_{1-6}-alkyl;

-(C_{1-6}-alkylene)-C(O)R^f;

wherein R^f is selected from

hydrogen;

C_{1-6}-alkyl;

C_{1-6}-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,

each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

In certain embodiments of the invention,

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h,

wherein R^g and R^h are each independently selected from hydrogen, or

C_{1-6}-alkyl, or wherein

R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen,

-(C_{1-6}-alkylene)-C(O)-NR^iR^j,

wherein R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen.

In certain embodiments of the invention, R^7 is hydrogen or C_{1-6}-alkyl, preferably hydrogen.

In certain embodiments all R^8 to R^{11} are hydrogen.

In certain embodiments, R^8 to R^{11} are independently hydrogen or halo.

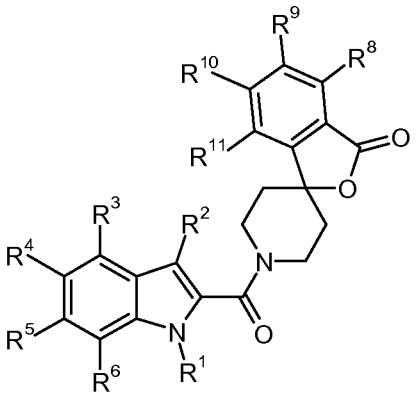
In certain embodiments, R^9 is fluoro, and R^8, R^{10} and R^{11} are hydrogen.

In certain embodiments, R^8, R^9 and R^{11} are hydrogen and R^{10} is bromo.

In certain embodiments, R^8 to R^{11} are independently hydrogen or methyl.

In certain embodiments, R^8 to R^{10} are hydrogen and R^{11} is methyl.

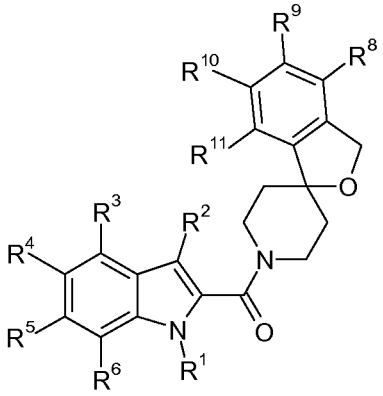
In certain embodiments of the invention, X is C=O and Y is O, i.e. compounds of formula (Ia)



(Ia)

wherein R^1 to R^{11} are as defined herein above.

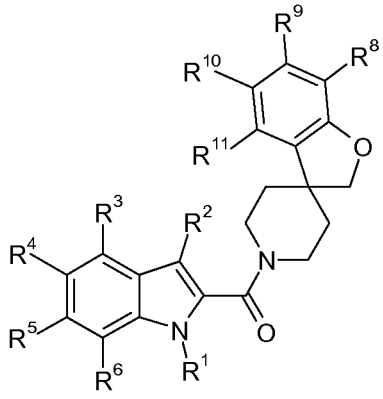
In certain embodiments of the invention, X is CH_2, and Y is O, i.e. compounds of formula (Ib)



(Ib)

wherein R^1 to R^{11} are as defined herein above.

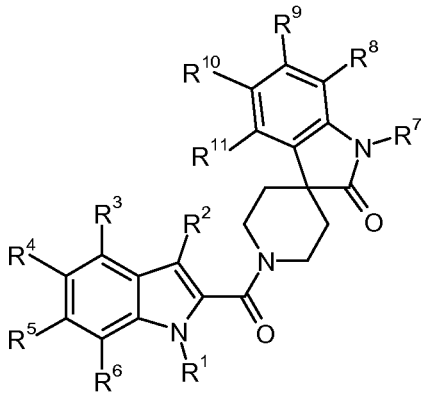
In certain embodiments of the invention, X is O and Y is CH_2, i.e. compounds of formula (Ic)



(Ic)

wherein R^1 to R^{11} are as defined herein above.

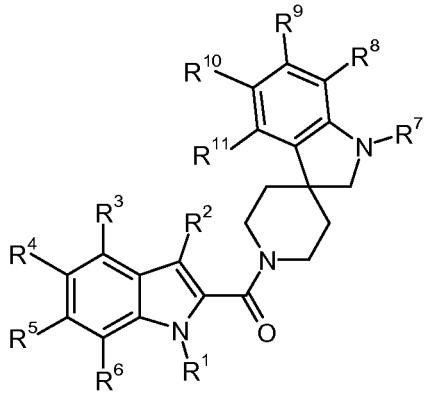
In certain embodiments of the invention, X is NR^7 and Y is C=O, i.e. compounds of formula (Id)



(Id)

wherein R^1 to R^{11} are as defined herein above.

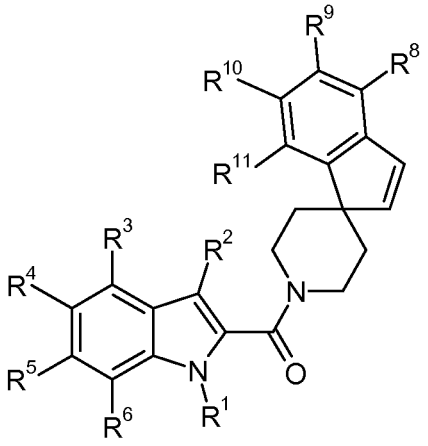
In certain embodiments of the invention, X is NR^7 and Y is CH_2, i.e. compounds of formula (Ie)



(Ie)

wherein R^1 to R^{11} are as defined herein above.

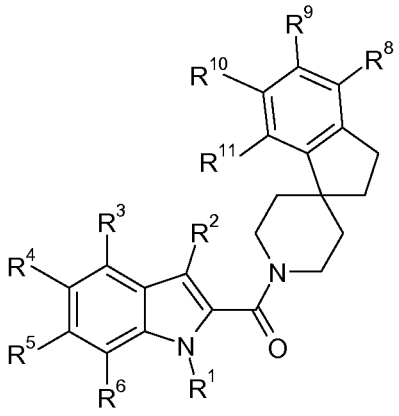
In certain embodiments of the invention, -X-Y- is –CH=CH-, i.e. compounds of formula (If)



(If)

wherein R^1 to R^6 and R^8 to R^{11} are as defined herein above.

In certain embodiments of the invention, -X-Y- is -CH_2 CH_2-, i.e. compounds of formula (Ig)



(Ig)

wherein R^1 to R^6 and R^8 to R^{11} are as defined herein above.

In certain embodiments of the invention, R^1 to R^6 are not all hydrogen.

In certain embodiments of the invention, R^1 to R^{11} are not all hydrogen.

The invention further encompasses an embodiment with the compound of formula (I), wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or $–CH_2CH_2$-;

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently

hydrogen,

-C(O)R^e, or -$S(O)_2R^e$,

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

or R^c and R^d together with the nitrogen to which they are bound form isoindole-1,3-dione,

-(C_{1-6}-alkylene)-C(O)R^f,

wherein R^f is selected from the group of

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy; and,

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

R^3 is hydrogen, halo, or C_{1-6}-alkyl;

R^4 is hydrogen,
halo,
C_{1-6}-alkyl,
halo-C_{1-6}-alkyl,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy, or
-O-C_{2-10}-alkenyl;
R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;
or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
-R^4–R^5- is –O-$(CH_2)_n$–O– wherein n is 1 or 2,
R^6 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH,
-(C_{1-6}-alkylene)-NR^gR^h,
wherein R^g and R^h are each independently selected from hydrogen, or
C_{1-6}-alkyl;
or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur,
-(C_{1-6}-alkylene)-C(O)-NR^iR^j,
wherein R^i and R^j are each independently
hydrogen,
C_{1-6}-alkyl,
-(C_{1-6}-alkylene)-NR^kR^l,
wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;
or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur,
-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
nitro,
halo,
cyano,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy,
halo-C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-C(O)R^f,

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl, each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

-R^5–R^6- is –O-$(CH_2)_n$–C(O)–,

-C(O)-$(CH_2)_n$-O-, or

–O-$(CH_2)_n$–O– wherein n is 1 or 2;

R^7 is hydrogen or C_{1-6}-alkyl;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl or halo-C_{1-6}-alkyl.

The invention further encompasses an embodiment with the compound of formula (I), wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or –CH_2CH_2-;

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

R^3 is hydrogen or halo;

R^4 is hydrogen,

halo,

C_{1-6}-alkyl,

halo-C_{1-6}-alkyl,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy, or

-O-C_{2-10}-alkenyl;

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

-R^4–R^5- is –O-$(CH_2)_n$–O– wherein n is 1 or 2;

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h,

wherein R^g and R^h are each independently selected from hydrogen, or

C_{1-6}-alkyl,

or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen,

-(C_{1-6}-alkylene)-C(O)-NR^iR^j,

wherein R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen;

R^7 is hydrogen or C_{1-6}-alkyl;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl or halo-C_{1-6}-alkyl.

The invention further encompasses an embodiment with the compound of formula (Ia), wherein

R^1 is hydrogen, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl;

R^2 is hydrogen;

R^3 is hydrogen;

R^4 is hydrogen or halo;

R^5 is hydrogen;

R^6 is hydrogen, or

C_{1-6}-alkyl, optionally substituted by CN;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen or halo.

The invention further encompasses an embodiment with the compound of formula (Ib), wherein

R^1 is hydrogen;

R^2 is hydrogen or C_{1-6}-alkoxy;

R^3 is hydrogen or halo;

R^4 is hydrogen or halo;

R^5 is hydrogen or C_{1-6}-alkoxy;

R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN,

-(C_{1-6}-alkylene)-NR^gR^h,

wherein R^g and R^h are each independently selected from hydrogen, or

C_{1-6}-alkyl,

or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen;

-(C_{1-6}-alkylene)-C(O)-NR^iR^j,

wherein R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen;

R^8, R^9, R^{10}, and R^{11} are each hydrogen.

The invention further encompasses an embodiment with the compound of formula (Ic), wherein

R^1 is hydrogen, or

C_{1-6}-alkyl, optionally substituted by CN,

R^2 is hydrogen or C_{1-6}-alkyl;

R^3 is hydrogen;

R^4 is hydrogen,

halo,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

halo-C_{1-6}-alkoxy, or

-O-C_{2-10}-alkenyl;

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

$-R^4–R^5-$ is $–O-(CH_2)_n–O–$ wherein n is 1 or 2;

R^6 is hydrogen, or

C_{1-6}-alkyl, optionally substituted by CN;

R^8, R^9, R^{10}, and R^{11} are each hydrogen.

The invention further encompasses an embodiment with the compound of formula (Id), wherein

R^1 is hydrogen, or

C_{1-6}-alkyl, optionally substituted by CN;

R^2 is hydrogen or C_{1-6}-alkyl;

R^3 is hydrogen or halo;

R^4 is hydrogen, halo, or C_{1-6}-alkoxy;

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

$-R^4–R^5-$ is $–O-(CH_2)_n–O–$ wherein n is 1 or 2;

R^6 is hydrogen, or

C_{1-6}-alkyl, optionally substituted by CN;

R^7 is hydrogen;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, or C_{1-6}-alkyl.

The invention further encompasses an embodiment with the compound of formula (Ie), wherein

R^1 to R^3 and R^5 to R^{11} are hydrogen; and R^4 is halo.

Preferred compounds of the invention are:

Preferred compounds of formula Ia:

{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-7-yl}acetonitrile,

2-{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide,

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one, and

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one.

Preferred compounds of formuly Ib:

[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetonitrile,

1'-({5-chloro-7-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],

1-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N,N-dimethylmethanamine,

1'-{[5-chloro-7-(morpholin-4-ylmethyl)-1H-indol-2-yl]carbonyl}-3H-spiro[2-benzofuran-1,4'-piperidine],

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],

2-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N-[2-(dimethylamino)ethyl]acetamide,

1'-[(5-fluoro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],

1'-({5-chloro-7-[(4-methylpiperazin-1-yl)methyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine], and

1'-[(4-bromo-3-methoxy-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine].

Preferred compounds of formula Ic:

1'-[(3,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine], and

1'-[(3,6,7-trimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine].

A preferred compound of Id:

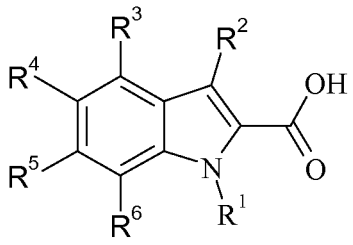
{2-[(5-bromo-2-oxo-1,2-dihydro-1'H-spiro[indole-3,4'-piperidin]-1'-yl)carbonyl]-5-chloro-1H-indol-1-yl}acetonitrile.

The invention also encompasses the compounds of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), or (Ig) 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), (Ia), (Ib), (Ic), (Id), (Ie), (If), or (Ig), which pharmaceutical 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 pharmaceutical composition may further comprise at least one pharmaceutically acceptable excipient.

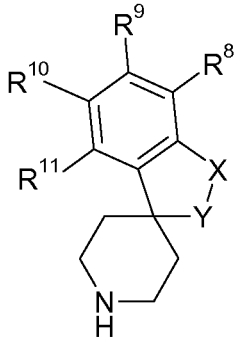
The invention further encompasses the use of a compound of formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), or (Ig) for the preparation of a medicament which is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

In a certain embodiment, the compound of the invention can be manufactured according to a process comprising the step of reacting a compound of formula (II):



II

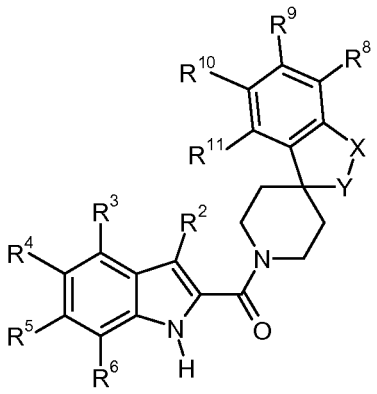
with an amine of the formula 1



(1)

wherein R^1 to R^6 and R^8 to R^{11} and X and Y are as defined above.

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

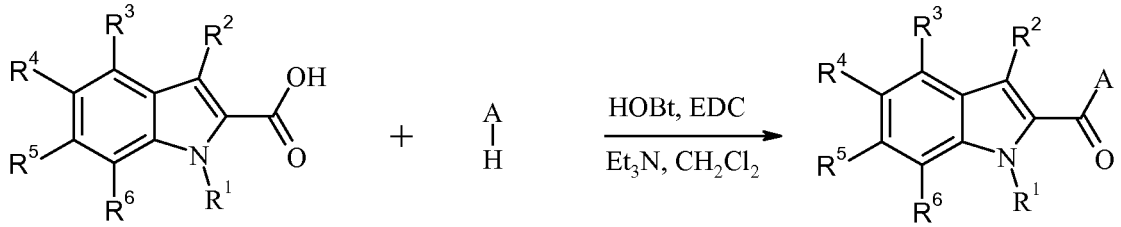


(I-1)

with an electophilic reagent of formula R^1-hal, to give a compound of general formula (I) as defined herein above.

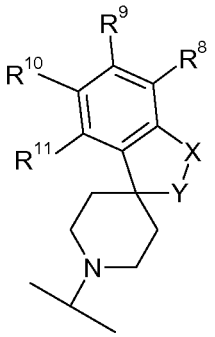
The synthesis of compounds of general formula (I) will be described in more detail below and in the examples.

General scheme A



II I

wherein A is:



wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

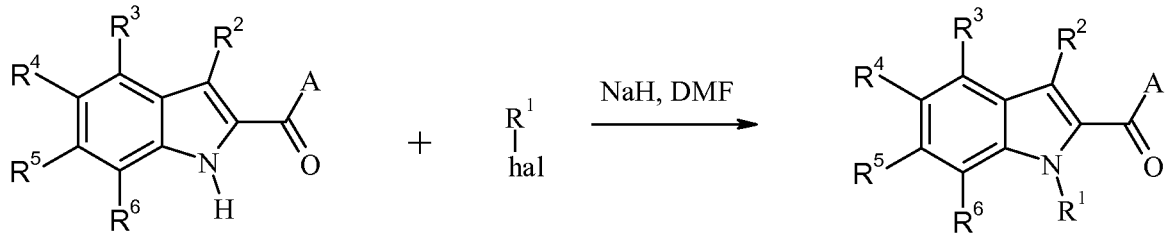
X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or $–CH_2CH_2$-

Compounds of formula (I) can be prepared via an amide coupling between an indole 2-carboxylic acid (II) and a compound of formula (A-H), wherein A is defined as hereinabove. The usual reagents and protocols known in the art can be used to effect the amide coupling. Indole 2-carboxylic acids (II) are either commercially available or readily prepared using procedures described hereinafter. The compounds of formula (A-H) are either commercially available or prepared using methods known in the art starting from commercially available materials. General scheme A is hereinafter further illustrated with general procedure I.

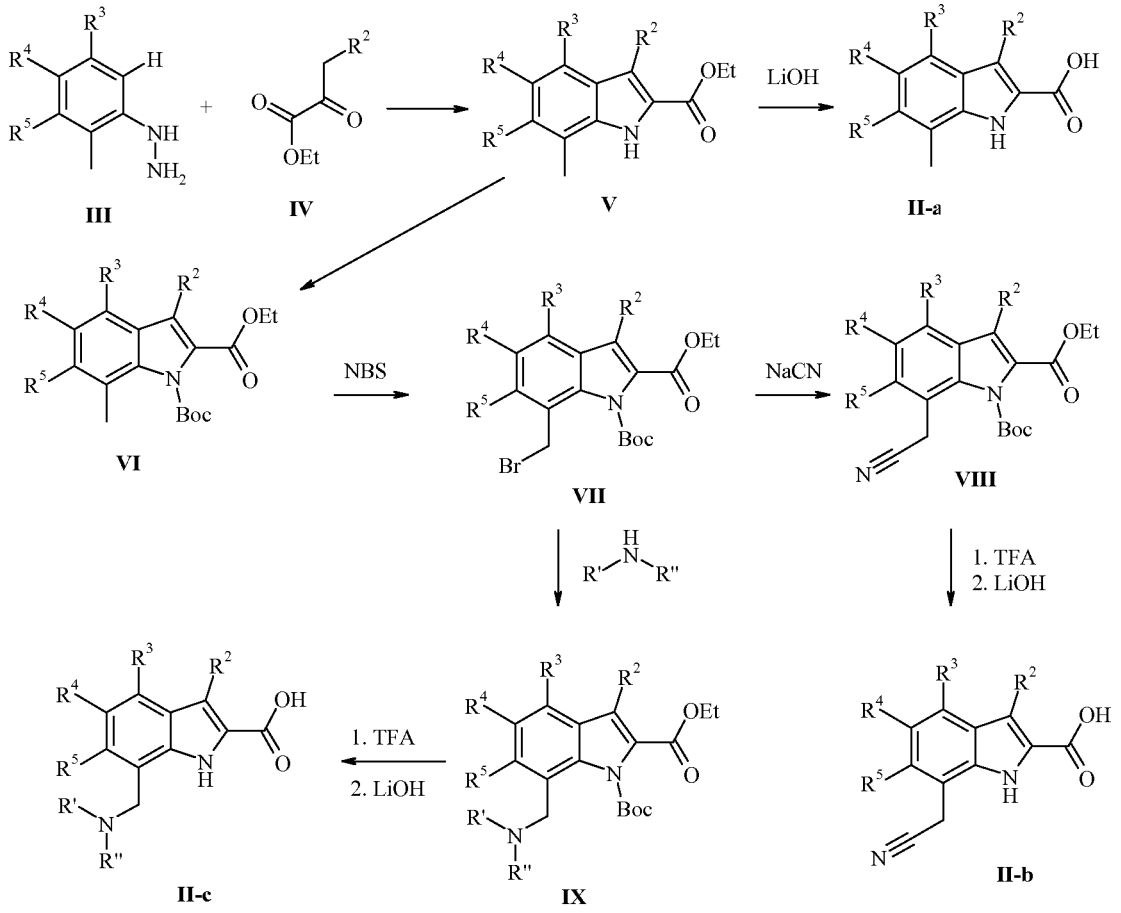
General scheme B



I-1 **I-2**

Compounds of formula (I-2) (compounds of formula (I) wherein R^1 is different from H), can be prepared by alkylation of the indole derivative of formula (I-1), with an electrophilic reagent of formula R^1-hal (commercially available, wherein hal is halo, preferably Cl or Br) using standard procedures. Derivatives (I-1) are prepared using the amide coupling as described in the general scheme A.

General scheme C: preparation of acids II



Substituted indole 2-carboxylic acids can be prepared according to the general scheme C. Indoles V are obtained by a Fischer indole synthesis from an aryl hydrazine III and a α-ketoester IV. Saponification gives an acid of formula II-a. Alternatively, Boc protection of the indole nitrogen gives VI. Selective bromination of the methyl group in the 7-position of the indole using NBS affords VII. Subsequent nucleophilic substitution of 7-bromomethyl indole intermediate VII with NaCN or a secondary amine yields intermediates VIII and IX, respectively. After N-deprotection and saponification of the ester moiety, the corresponding carboxylics acids II-b and II-c are obtained.

Abbreviations used:

NBS = N-Bromosuccinimide

Boc = tert-buthoxycarbonyl

EDC = N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide hydrochloride

HOBt = 1-hydroxybenzotriazole

DMF = N,N-dimethylformamide

DMSO = dimethylsulfoxide

DMAP = 4-dimethylaminopyridine

TFA = trifluoroacetic acid

The compounds of the present invention exhibit V1a activity, which may be detected as described below:

V1a activity

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 MgCl2 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 CaCl2, 10 mM MgCl2) 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-Prussoff equation.

Example	pKi	Example	pKi
1	7.38	11	8.42
2	7.49	12	7.67
4	7.76	13	8.11
5	8.18	14	8.56
6	7.75	15	8.44
8	7.52	24	8.01
9	8.26	26	8.14
10	8.68	46	7.67

The compounds of formula (I), and (Ia) to (Ig) 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. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula (I), (Ia) to (Ig) 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 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.

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 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 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:

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

Example B

Capsules of the following composition are manufactured:

	mg/capsule
Active substance	10
Lactose	155
Corn starch	30

Talc		5
	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.

Example C

Suppositories of the following composition are manufactured:

		mg/supp.
Active substance		15
Suppository mass		1285
	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.

In the following, the synthesis of compounds of formula (I) is further exemplified:

EXAMPLES

General procedure I - amide coupling:

To a 0.1 M stirred solution of an indole-2-carboxylic acid derivative of type (II) in CH_2Cl_2 are added EDC (1.3 eq), HOBt (1.3 eq), Et_3N (1.3 eq) and the amine derivative (A-H, as defined above, 1 eq). The mixture is stirred overnight at room temperature and then poured onto water and extracted with CH_2Cl_2. The combined organic phases are dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography or preparative HPLC affords a compound of formula (I).

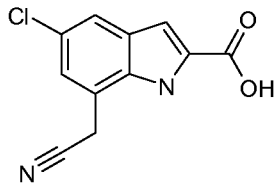
General procedure II - alkylation:

To a 0.1 M stirred solution of a derivative of general formula (I-1) in DMF is added NaH (60% in oil, 2.1 eq.). After stirring the mixture at room temperature for 30 min. the

electrophilic reactant R^1-hal (1.1 eq.) is added. The mixture is stirred an additional 14 hours at 60 °C and then poured onto water and extracted with ethyl acetate. The combined organic phases are dried over Na_2SO_4 and concentrated in vacuo. Purification by preparative HPLC affords the corresponding derivatives of general formula (I-2).

Preparation of acids II

Acid 1: 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid



a) 2-[(4-Chloro-2-methyl-phenyl)-hydrazono]-propionic acid ethyl ester

To a stirred solution of 0.55 g (2.85 mmol) of (4-chloro-2-methyl-phenyl)-hydrazine in acetic acid (5 ml), was added 0.34 g (2.91 mmol) of ethyl pyruvate. The mixture was stirred 2 hours at 35 °C, poured onto an aqueous solution of sat. $NaHCO_3$ and then extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo, to afford 0.702 g (97%) of 2-[(4-chloro-2-methyl-phenyl)-hydrazono]-propionic acid ethyl ester as a light orange solid.

b) 5-Chloro-7-methyl-1H-indole-2-carboxylic acid ethyl ester

To a solution of 0.70 g (2.75 mmol) of 2-[(4-chloro-2-methyl-phenyl)-hydrazono]-propionic acid ethyl ester in a sealed tube was added toluene (10 ml) and amberlyst 15 (1.60 g). The reaction mixture was heated at 120 °C over the night.The reaction mixture was concentrated under vacuo and purified by flash chromatography (SiO2, EtOAc/Hex 1/6) to afford 0.22 g (34%) of 5-chloro-7-methyl-1H-indole-2-carboxylic acid ethyl ester as a white solid. ES-MS m/e (%): 238.1 ($M+H^+$).

c) 5-Chloro-7-methyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

To a solution of 0.22 g (0.9 mmol) of 5-chloro-7-methyl-1H-indole-2-carboxylic acid ethyl ester in CH_2Cl_2 (10 ml), 0.21 g of di-tert-butyl dicarbonate, 0.13 ml of Et_3N and 23 mg of DMAP were added. The reaction mixture was stirred at RT for 2 hours, poured onto an aqueous solution of HCl 1M and extracted with CH_2Cl_2. The reaction mixture was concentrated under vacuo and purified by flash chromatography (SiO2, EtOAc/Hex 1/9) to

afford 0.30 g (97%) of 5-chloro-7-methyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light yellow solid.

d) 7-Bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

To a solution of 0.30 g (0.9 mmol) of 5-chloro-7-methyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in CCl_4 (10 ml), 016 g N-bromosuccinimide (NBS) and 11 mg of benzoyl peroxide were added. The reaction mixture was heated at reflux for one hour and cooled down to RT. The succinimide was filtered off and the solvent removed under reduced pressure to afford 0.35 g (95%) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light brown solid. This product was directly used in the next step (unstable).

e) 5-Chloro-7-cyanomethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester

To a solution of 1.00 g (2.4 mmol) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in DMSO (10 ml) at RT, 012 g of sodium cyanide was added. The reaction mixture was stirred at RT for one hour, poored on a saturated aqueous ammonium chloride solution and the product was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (SiO_2, EtOAc/Hex 9/1) afforded 0.31 g (36%) of 5-chloro-7-cyanomethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light yellow oil.

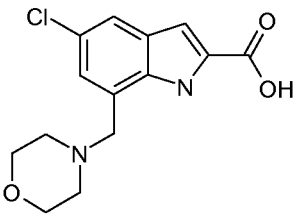
f) 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester

To a solution of 0.30 g (0.8 mmol) of 5-chloro-7-cyanomethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in CH_2Cl_2 (8 ml) at RT was added 2 ml of TFA. The reaction mixture was stirred at RT for one hour and concentrated under vacuo. The crude was taken up in EtOAc and neutralized with aqueous NaHCO3. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Preparative HPLC (30% CH_3CN / H_2O) afforded 81 mg (35%) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester as a white solid.

g) 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid

To a solution of 81 mg (0.3 mmol) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester in THF/EtOH/H_2O (5 ml) at RT was added 39 mg of $LiOH.H_2O$. The reaction mixture was stirred at 40 °C for three hours and then acidified with aqueous HCl 1M. The product was extracted with EtOAc and concentrated under vacuo to afford 71 mg (98%) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid as a white solid. ES-MS m/e (%): 232.9 ($M-H^+$).

Acid 2: 5-Chloro-7-morpholin-4ylmethl-1H-indole-2-carboxylic acid



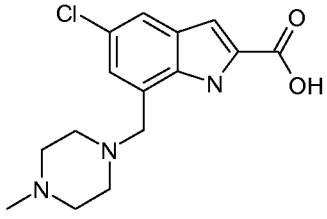
a) 5-Chloro-7-morpholin-4-ylmethyl-1H-indole-2-carboxylic acid ethyl ester

To a solution of 0.11 g (0.26 mmol) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in THF (1 ml) at RT, 40 µl of morpholine was added. The reaction mixture was stirred at 40 °C for one hour and concentrated under vacuo. The crude was dissolved in CH_2Cl_2 (1 m) and at RT, 0.2 ml of TFA was added and stirring was continued over night. Preparative HPLC (30% CH_3CN / H_2O) afforded 53 mg (62%) of 5-chloro-7-morpholin-4-ylmethyl-1H-indole-2-carboxylic acid ethyl ester as colorless oil.

b) 5-Chloro-7-morpholin-4-ylmethyl-1H-indole-2-carboxylic acid

To a solution of 53 mg (0.16 mmol) of 5-chloro-7-morpholin-4-ylmethyl-1H-indole-2-carboxylic acid ethyl ester in THF/EtOH/H_2O (2.5 ml) at RT was added 21 mg of LiOH.H_2O. The reaction mixture was stirred at 45 °C for one hour and then acidified with aqueous HCl 1M. The product was extracted with EtOAc and concentrated under vacuo to afford 12 mg (25%) of 5-chloro-7-morpholin-4-ylmethyl-1H-indole-2-carboxylic acid as a white solid. ES-MS m/e (%): 293.1($M-H^+$).

Acid 3: 5-Chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid



a) 5-Chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid ethyl ester

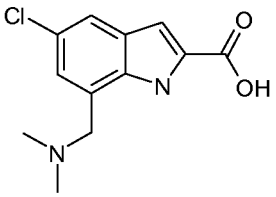
To a solution of 0.125 g (0.30 mmol) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in THF (1 ml) at RT, 55 mg of 1-methyl-piperazine was added. The reaction mixture was stirred at 40 °C for one hour and concentrated under vacuo. The crude was dissolved in CH_2Cl_2 (1 m) and at RT 0.2 ml of TFA was added and stirring was continued over night. Preparative HPLC (30% CH_3CN / H_2O) afforded 30 mg

(29%) of 5-chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid ethyl ester as colorless oil.

b) 5-Chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid

To a solution of 30 mg (0.09 mmol) of 5-chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid ethyl ester in THF/EtOH/H_2O (2.5 ml) at RT was added 6 mg of LiOH.H_2O. The reaction mixture was stirred at 45 °C for one hour and then acidified with aqueous HCl 1M. The product was extracted with EtOAc and concentrated under vacuo to afford 10 mg (36%) of 5-chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid as a white solid. ES-MS m/e (%): 306.2 ($M-H^+$).

Acid 4: 5-Chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid



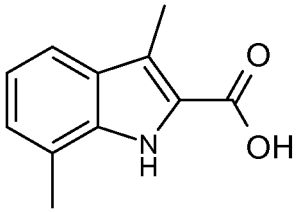
a) 5-Chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid ethyl ester

To a solution of 0.200 g (0.48 mmol) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester (previously described) in THF (3 ml) at RT, 0.17 ml of dimethyl amine (5.6 M in EtOH) was added. The reaction mixture was stirred at RT for one hour and concentrated under vacuo. The crude was dissolved in CH_2Cl_2 (1 m) and at RT 0.2 ml of TFA was added and stirring was continued over night. Preparative HPLC (30% CH_3CN / H_2O) afforded 67 mg (50%) of 5-chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid ethyl ester as colorless oil. ES-MS m/e (%): 281.3 ($M+H^+$).

b) 5-Chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid

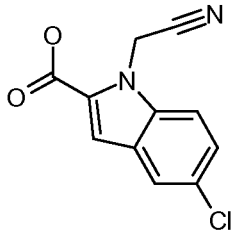
To a solution of 90 mg (0.32 mmol) of 5-chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid ethyl ester in THF/EtOH/H_2O (5 ml) at RT was added 23 mg of LiOH.H_2O. The reaction mixture was stirred at 45 °C for one hour and then acidified with aqueous HCl 1M. The product was extracted with EtOAc and concentrated under vacuo to afford 34 mg (42%) of 5-chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid as a white solid. ES-MS m/e (%): 251.3 ($M-H^+$).

Acid 5: 3,7-Dimethyl-1H-indole-2-carboxylic acid



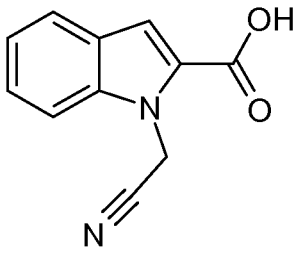
The title compound is prepared by saponification of 3,7-dimethyl-1H-indole-2-carboxylic acid ethyl ester (prepared by Fischer indole synthesis as described in Tetrahedron Lett. 2003, 44, 5665) using the procedure described above for the synthesis of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid (acid 1, step g)).

Acid 6: 5-Chloro-1-cyanomethyl-1H-indole-2-carboxylic acid



To a solution of 1.0 eq. of 5-chloro-1-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester (prepared according to Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1989), 28B(12), 1065-8) in a mixture of THF/H_2O ((9/1) was added LiOH.H_2O (1.0 eq.) and the R/M stirred 6h at R/T, acidified to pH2 and then partially concentrated until precipitation of the crude product which was filtered off and washed with Et_2O and then dried to give the desired product as a light yellow solid (84%).

Acid 7: Cyanomethyl-1H-indole-2-carboxylic acid



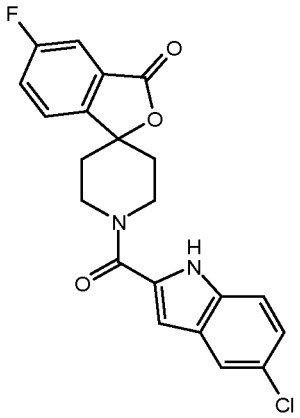
To a solution of 1.0 eq. of 1-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester in a mixture of THF/H_2O ((9/1) was added LiOH.H_2O (1.0 eq.) and the reaction mixture stirred 6h at RT, acidified to pH2 and then partially concentrated until precipitation of the crude product which was filtered off and washed with Et_2O and then dried to give the desired product as a light yellow solid (70%).

ES-MS m/e (%): 199.0 ($M-H^+$).

Examples

Example 1

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



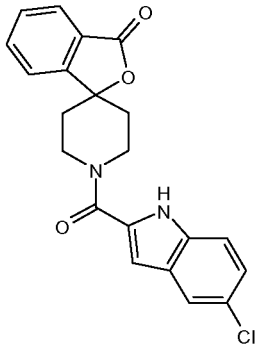
Amide coupling according to general procedure I:

- Amine: 5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in WO01/14376),
- Acid: 5-Chloro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 399.1 ($M+H^+$).

Example 2

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure I:

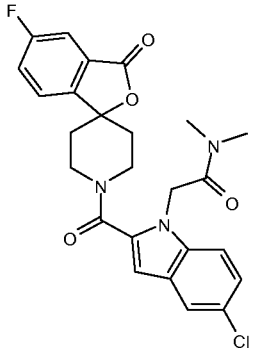
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in J. Org. Chem. 1975, 40, 1427),

- Acid: 5-Chloro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 381.1 ($M+H^+$).

Example 3

2-{5-chloro-2-[(5-fluoro-3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide

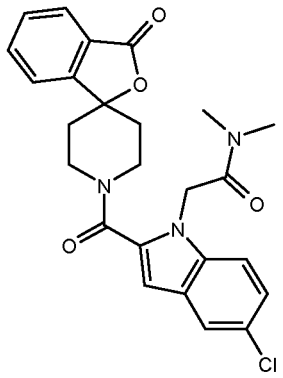


To a stirred solution of 60 mg (0.15 mmol) of 1'-[(5-chloro-1H-indol-2-yl)carbonyl]-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one in DMF (4 ml) at RT was added 7 mg (0.16 mmol) of NaH (in oil, 55%). After 20 minutes, 18 mg (0.015 mmol) of 2-chloro-N,N-dimethyl-acetamide was added and stirring was continued over night. The reaction mixture was concentrated in vacuo and purification by preparative HPLC (30% CH_3CN / H_2O) afforded 70 mg (96%) of 2-{5-chloro-2-[(5-fluoro-3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide as a white solid.

ES-MS m/e (%): 484.5 ($M+H^+$).

Example 4

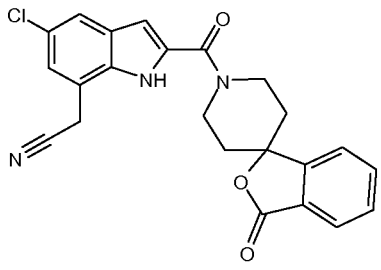
2-{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide



To a stirred solution of 60 mg (0.15 mmol) of 1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one in DMF (4 ml) at RT was added 7 mg (0.16 mmol) of NaH (in oil, 55%). After 20 minutes, 19 mg (0.015 mmol) of 2-chloro-N,N-dimethyl-acetamide was added and stirring was continued over night. The reaction mixture was concentrated in vacuo and purification by preparative HPLC (30% CH_3CN / H_2O) afforded 60 mg (82%) of 2-{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide as a white solid.
ES-MS m/e (%): 466.3 ($M+H^+$).

Example 5

{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-7-yl}acetonitrile



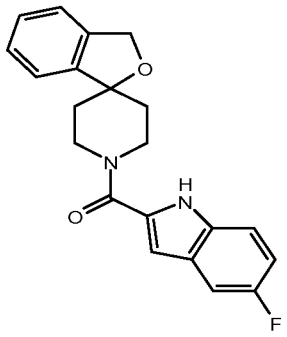
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in J. Org. Chem. 1975, 40, 1427),
- Acid: 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 420.1 ($M+H^+$).

Example 6

1'-[(5-fluoro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



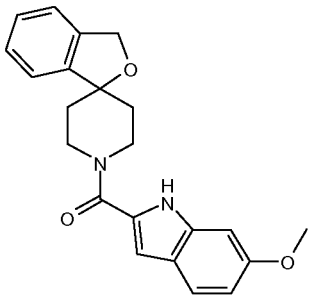
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine]
- Acid: 5-Fluoro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 351.5 ($M+H^+$).

Example 7

1'-[(6-methoxy-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



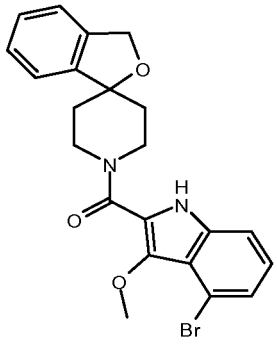
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine]
- Acid: 6-Methoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 363.5 ($M+H^+$).

Example 8

1'-[(4-bromo-3-methoxy-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



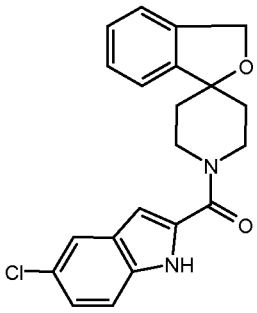
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine]
- Acid: 4-Bromo-3-methoxy-1H-indole-2-carboxylic acid (described in European Journal of Medicinal Chemistry (1997), 32(3), 253-261),

ES-MS m/e (%): 441.4 ($M+H^+$).

Example 9

1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



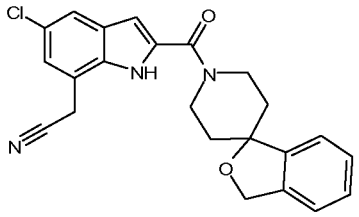
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine]
- Acid: 5-Chloro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 365.0 ($M+H^+$).

Example 10

[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetonitrile



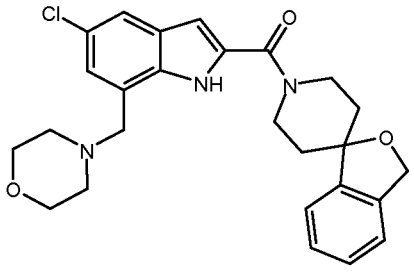
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (described in J. Org. Chem. 1976, 41, 2628),
- Acid: 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 406.2($M+H^+$).

Example 11

1'-{[5-chloro-7-(morpholin-4-ylmethyl)-1H-indol-2-yl]carbonyl}-3H-spiro[2-benzofuran-1,4'-piperidine]



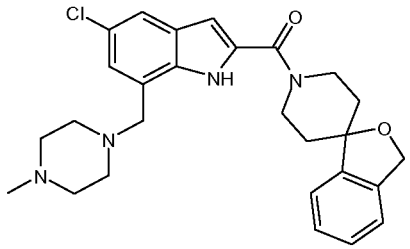
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (described in J. Org. Chem. 1976, 41, 2628),
- Acid: 5-Chloro-7-morpholin-4ylmethl-1H-indole-2-carboxylic acid

ES-MS m/e (%): 466.3($M+H^+$).

Example 12

1'-({5-chloro-7-[(4-methylpiperazin-1-yl)methyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



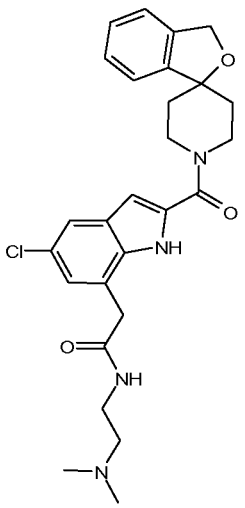
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (described in J. Org. Chem. 1976, 41, 2628),
- Acid: 5-Chloro-7-(4-methyl-piperazin-1-ylmethyl)-1H-indole-2-carboxylic acid

ES-MS m/e (%): 479.3 ($M+H^+$).

Example 13

2-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N-[2-(dimethylamino)ethyl]acetamide



a) [5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetic acid

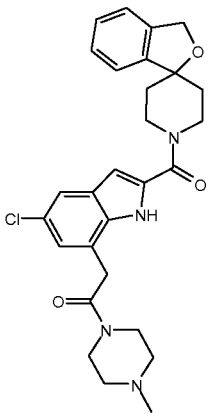
To a solution of 100 mg (0.25 mmol) of [5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetonitrile in acetic acid (5 ml) at RT was added 3 ml of H_2O and 3 ml of H_2SO_4 conc. The reaction mixture was heated at 80 °C for one hour and at 80 °C over night. The product was extracted with EtOAc and concentrated under vacuo to afford 94 mg (90%) of [5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetic acid as a white solid. ES-MS m/e (%): 422.9 ($M-H^+$).

b) 2-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N-[2-(dimethylamino)ethyl]acetamide

To a stirred solution of 30 mg (0.070 mmol) of [5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetic acid in 3 ml CH_2Cl_2 were added 31 mg (0.07 mmol) of BOP and 24 µL of Huenig's base. After 30 minutes 6 mg of N,N-dimethyl-methanediamine were added. 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. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) afforded 10 mg (28%) of 2-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N-[2-(dimethylamino)ethyl]acetamide as a white solid. ES-MS m/e (%): 495.4 ($M+H^+$).

Example 14

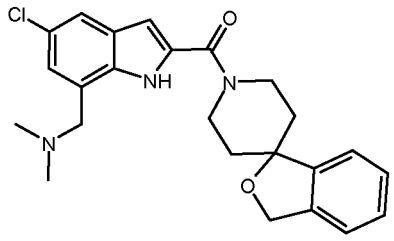
1'-({5-chloro-7-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



To a stirred solution of 60 mg (0.14 mmol) of [5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetic acid in 6 ml CH_2Cl_2 were added 25 mg of HOBt, 35 mg of EDC and 25 mL of Et_3N. After 30 minutes 24 µL of 1-methyl-piperazine was added. 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. Flash chromatography (SiO_2, CH_2Cl_2/MeOH 9/1) afforded 10 mg (14%) of 1'-({5-chloro-7-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]
as a white solid. ES-MS m/e (%): 508.1 ($M+H^+$).

Example 15

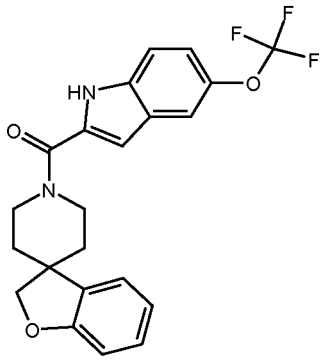
1-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N,N-dimethylmethanamine



Amide coupling according to general procedure I:
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (described in J. Org. Chem. 1976, 41, 2628),
- Acid: 5-chloro-7-dimethylaminomethyl-1H-indole-2-carboxylic acid
ES-MS m/e (%): 424.2 ($M+H^+$).

Example 16

1'-{[5-(trifluoromethoxy)-1H-indol-2-yl]carbonyl}spiro[1-benzofuran-3,4'-piperidine]



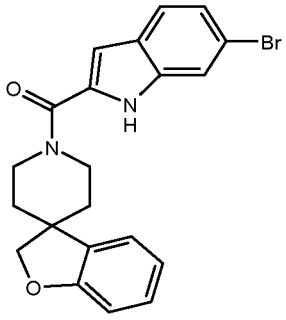
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Trifluoromethoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 415.5 ($M-H^+$).

Example 17

1'-[(6-bromo-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



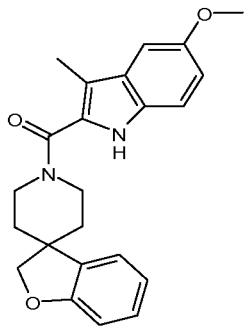
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)- Acid: 6-Bromo-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 409.4 ($M-H^+$).

Example 18

1'-[(5-methoxy-3-methyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



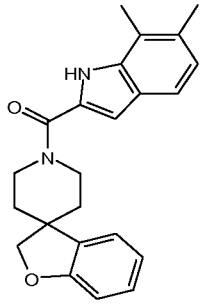
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Methoxy-3-methyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 377.4 ($M+H^+$).

Example 19

1'-[(6,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



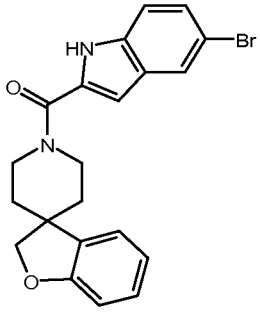
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 6,7-Dimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 361.5 ($M+H^+$).

Example 20

1'-[(5-bromo-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



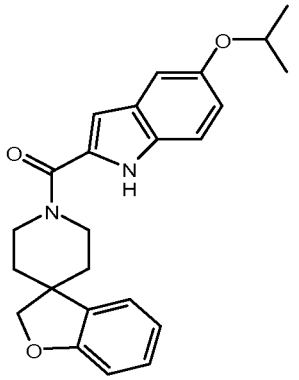
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Bromo-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 409.4 ($M-H^+$).

Example 21

1'-[(5-isopropoxy-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



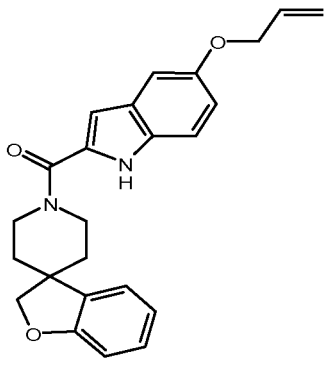
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Isopropoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 391.4 ($M+H^+$).

Example 22

1'-{[5-(allyloxy)-1H-indol-2-yl]carbonyl}spiro[1-benzofuran-3,4'-piperidine]



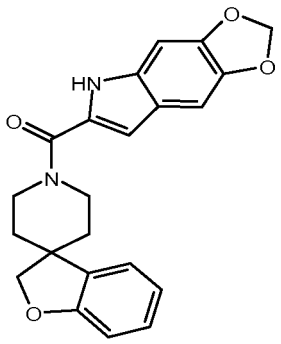
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Allyloxy-1H-indole-2-carboxylic acid (described in US 2004157841),

ES-MS m/e (%): 389.4 ($M+H^+$).

Example 23

1'-(5H-[1,3]dioxolo[4,5-f]indol-6-ylcarbonyl)spiro[1-benzofuran-3,4'-piperidine]



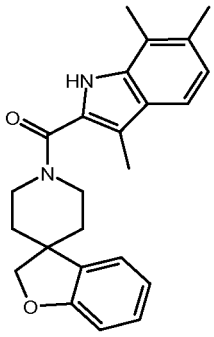
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5H-[1,3]Dioxolo[4,5-f]indole-6-carboxylic acid,

ES-MS m/e (%): 377.4 ($M+H^+$).

Example 24

1'-[(3,6,7-trimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



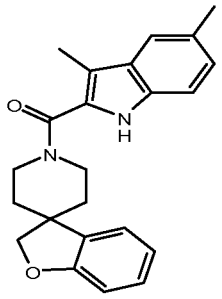
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 3,6,7-Trimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 375.4 ($M+H^+$).

Example 25

1'-[(3,5-dimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



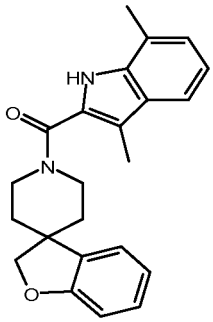
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 3,5-Dimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 361.4 ($M+H^+$).

Example 26

1'-[(3,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



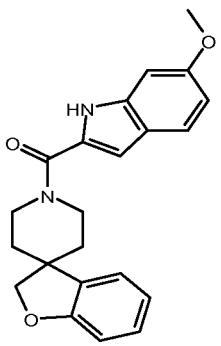
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 3,5-Dimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 361.4 ($M+H^+$).

Example 27

1'-[(6-methoxy-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



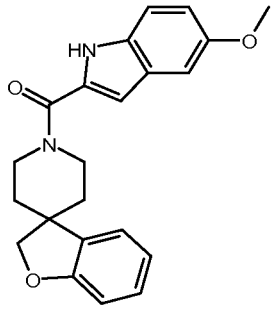
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 6-Methoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 363.4 ($M+H^+$).

Example 28

1'-[(5-methoxy-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



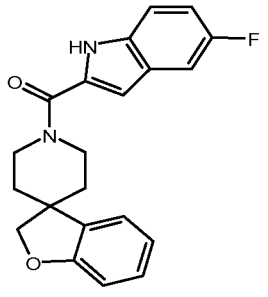
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Methoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 363.4 ($M+H^+$).

Example 29

1'-[(5-fluoro-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



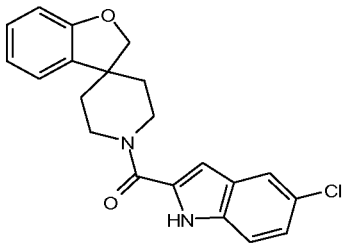
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Fluoro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 351.4 ($M+H^+$).

Example 30

1'-[(5-chloro-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



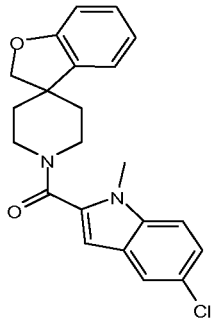
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Chloro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 367.4 ($M+H^+$).

Example 31

1'-[(5-chloro-1-methyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine]



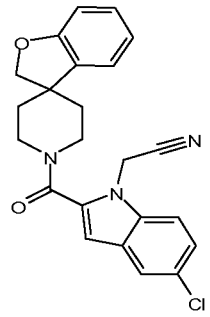
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Chloro-1-methyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 381.4 ($M+H^+$).

Example 32

[5-chloro-2-(1'H-spiro[1-benzofuran-3,4'-piperidin]-1'-ylcarbonyl)-1H-indol-1-yl]acetonitrile



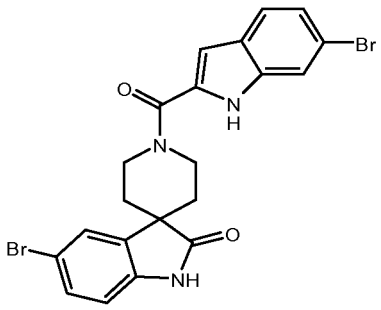
Amide coupling according to general procedure I:

- Amine: Spiro[benzofuran-3(2H),4'-piperidine] (prepared as in WO 2006092731)
- Acid: 5-Chloro-1-cyanomethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 406.4 ($M+H^+$).

Example 33

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

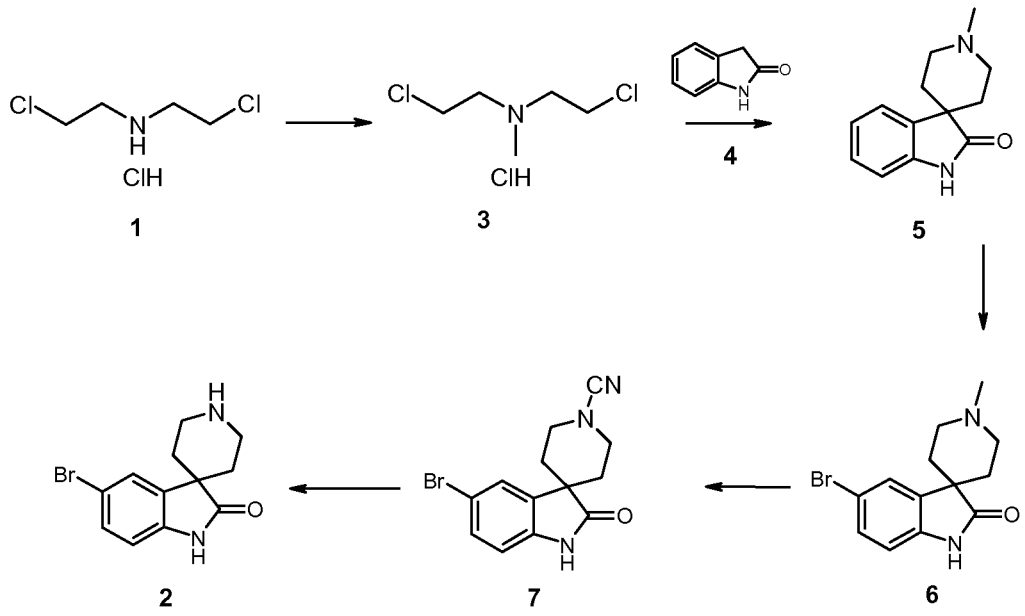


Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein below)
- Acid: 6-Bromo-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 504.3 ($M+H^+$).

5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one



1,5-Dichloro-3-methyl-3-azapentane, Hydrochloride 3: Formic acid (10.0 g; 0.2 mol) and 37 % formaldehyde (20 ml) were mixed in a 250 ml round-bottom flask equipped with reflux condenser. 1,5-Dichloro-3-azapentane, hydrochloride (17.0 g; 0.1 mol) was added and the solution was heated with magnetic stirring at 100 °C. After 3 h the temperature was increased to 120 °C for 20 min and finally allowed to cool to room temperature before the solvent was evaporated in vacuo to afford 3 as white solid in quantitative yield. 1HNMR (CD3OD, 400MHz) δ 3.0 (s, 3 H); 3.45 (br s, 2 H); 3.62(br s, 2 H); 4.07(br s, 4 H).

1,2-Benzo-8-methyl-3, 8-diazaspiro [4,5] decane-4-one 5:

A solution of oxindole 4 (6.25 g, 47 mmol) in THF (500 ml) was cooled to – 78 °C and to it a solution of sodium hexamethyldisilazide (43 g, 235 mmol) in THF (300 ml) was added drop wise under N2 atmosphere. After stirring at – 78 °C for 45 min, N-methylbis (2-chloromethyl) amine hydrochloride (9 g, 47 mmol) was added, as a solid. The reaction mixture was stirred at – 78 °C for 1 h and at room temperature for 24 h. After quenching with H2O (90 ml), the mixture was extracted with ethyl acetate (3 x 100 ml). The organic extracts were washed with brine (25 ml), dried and the solvent removed in vacuo. Silica gel chromatography (5- 50% MeOH/CH2Cl2, gradient) gave 6g (57%) of 5 as a solid. 1HNMR (CD3OD, 400MHz) δ 1.84(m, 2 H); 2.51(m, 2 H); 2.62 (s, 3H); 3.02(m, 2 H); 3.37(m, 2H); 6.82(d, 1 H, J = 7.68 Hz); 6.94(t, 1 H, J = 7.58 Hz); 7.12 (t, 1 H, J = 7.7 Hz); 7.26 (d, 1 H, J = 9 Hz); 9.27(br s, 1H).

5-Bromo-1,2-dihydro-2-oxospiro [3H-indole-3,4'-piperidine]-1'-methyl 6:

A solution of 1,2-Benzo-8-methyl-3, 8-diazaspiro [4,5] decane-4-one (6.3 g, 29.1 mmol) in CH_3CN (100 ml) and MeOH (5 ml) was cooled to – 50 °C and NBS (7.8 g, 44 mmol) was slowly added with stirring. The reaction mixture was stirred for 3.5 h at 0 °C. Solvent was removed by vacuo. The residue was purified by silica gel chromatography (2 – 20 % $MeOH/CH_2Cl_2$) to give 6 g as a solid. The solid compound was dissolved in ethyl acetate (600 ml) and washed with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4). Evaporation of the solvent in vacuo gave 4.2 g (47%) of 6. 1HNMR (CD3OD, 400MHz) δ 7.51(d, J = 1.8 Hz, 1H), 7.35(dd, J = 1.9 and 8.2 Hz, 1H), 6.81(d, J = 8.2 Hz, 1H), 2.93(m, 2H), 2.67(m, 2H), 2.41(s, 3H), 1.86(m, 4H).

5-Bromo-1,2-dihydro-2-oxospiro [3H-indole-3,4'-piperidine]-1'-cyano 7:

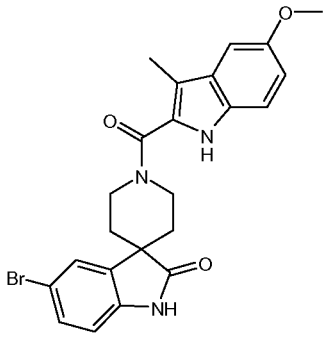
5-Bromo-1, 2-dihydro-2-oxospiro [3H-indole-3, 4'-piperidine]-1'-methyl **6** (4.6 g, 15.6 mmol) was dissolved in chloroform (700 ml) and treated with CNBr (22 g, 209.5 mmol) at room temperature. The mixture was heated to reflux for 24h. The reaction mixture was cooled, diluted with methylene chloride (300 ml) and washed with 10 % aqueous K_2CO_3 solution (2 x 100 ml). After the mixture was dried (Na_2SO_4) and concentrated, the residue was purified by silica gel chromatography (0 – 5% $MeOH/CH_2Cl_2$) to gave 7 as a solid 3.9 g (82%). ^{1}HNMR ($CDCl_3$, 400MHz) δ 7.52 (d, J = 1.8Hz, 1H), 7.37(dd, J = 1.8 and 8.2 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 3.83(m, 2H), 3.41(m, 2H), 2.00(m, 2H), 1.86(m, 4H).

5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one 2:

5-Bromo-1, 2-dihydro-2-oxospiro [3H-indole-3, 4'-piperidine]-1'-cyano 7 (3.3 g, 10.8 mmol) was suspended in ethylene glycol (10 ml). The mixture was treated in NaOH (1.8 g, 45 mmol) and heated to 130 °C for 15 min. It was diluted with methylene chloride (500 ml) and washed with 10% aqueous K_2CO_3 (2 x 100 m). The organic layer was dried (Na_2SO_4) and concentrated and residue purified by silica gel chromatography (30% $MeOH/CH_2Cl_2$) to gave 2 as a light ceramic white solid 1.8 g (60%), mp 256 – 258 °C. ^{1}HNMR (DMSO-d_6, 400MHz) δ 10.6(br s, 1H, NH), 7.57(d, J = 1.84Hz, 1H), 7.36(d, J = 8.2Hz, 1H), 6.79(d, J = 8.2 Hz, 1H), 4.05 (br s, 1H, NH), 3.06(m, 2H), 2.84(m, 2H), 1.64(m, 2H), 1.55(m, 2H), ^{13}C NMR (DMSO-d_6, 100MHz) δ 180.93, 140.64, 137.98, 130.42, 126.75, 113.20, 111.45, 46.24, 40.92, 32.94. Anal.Calcd for $C_{12}H_{13}BrN_2O$: C, 51.26; H, 4.66; N, 9.9. Found: C, 50.87; H, 4.91; N, 9.67.

Example 34

5-Bromo-1'-[(5-methoxy-3-methyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



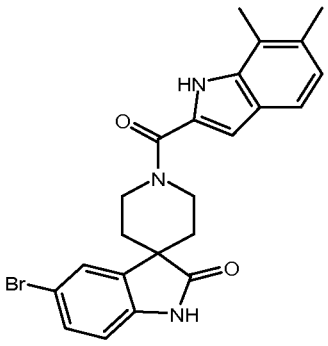
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 5-Methoxy-3-methyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 468.4 ($M+H^+$).

Example 35

5-Bromo-1'-[(6,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



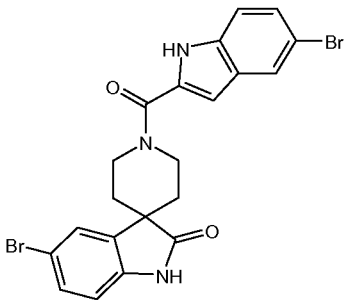
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 6,7-Dimethyl-1H-indole-2-carboxylic acid ,

ES-MS m/e (%): 452.4 ($M+H^+$).

Example 36

5-Bromo-1'-[(5-bromo-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



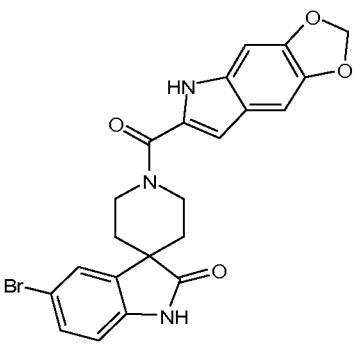
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 5-Bromo-1H-indole-2-carboxylic acid ,

ES-MS m/e (%): 504.3 ($M+H^+$).

Example 37

5-Bromo-1'-(5H-[1,3]dioxolo[4,5-f]indol-6-ylcarbonyl)spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

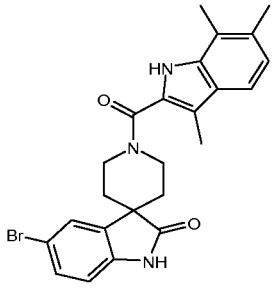
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 5H-[1,3]Dioxolo[4,5-f]indole-6-carboxylic acid,

ES-MS m/e (%): 468.3 ($M+H^+$).

Example 38

5-Bromo-1'-[(3,6,7-trimethyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

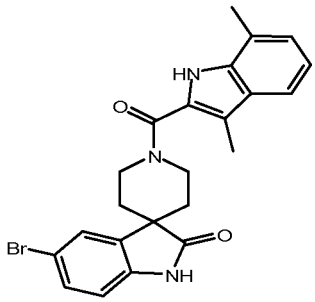
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 3,6,7-Trimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 466.4 ($M+H^+$).

Example 39

5-Bromo-1'-[(3,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

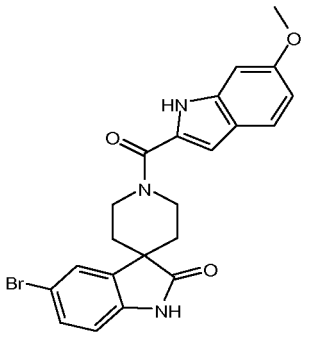
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 3,7-Dimethyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 452.4 ($M+H^+$).

Example 40

5-Bromo-1'-[(6-methoxy-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

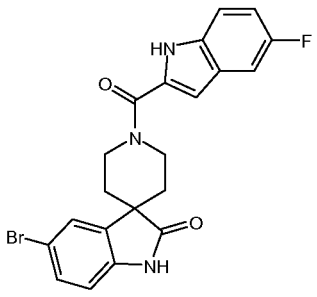
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 6-Methoxy-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 454.4 ($M+H^+$).

Example 41

5-Bromo-1'-[(5-fluoro-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

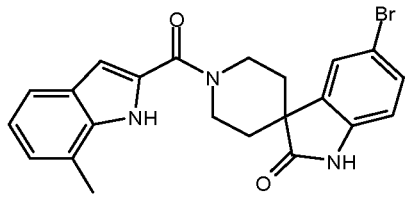
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 5-Fluoro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 442.3 ($M+H^+$).

Example 42

5-Bromo-1'-[(7-methyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure I:

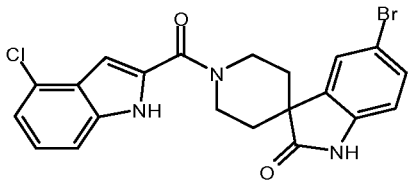
- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)

- Acid: 7-Methyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 438.4 ($M+H^+$).

Example 43

5-Bromo-1'-[(4-chloro-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



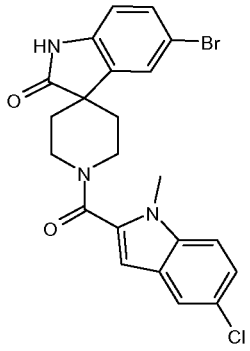
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 4-Chloro-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 458.3 ($M+H^+$).

Example 44

5-Bromo-1'-[(5-chloro-1-methyl-1H-indol-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one



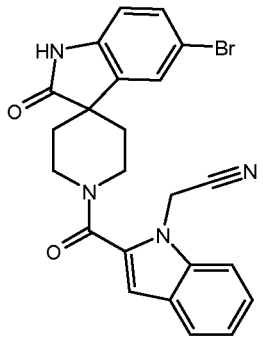
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 5-Chloro-1-methyl-1H-indole-2-carboxylic acid,

ES-MS m/e (%): 472.3 ($M+H^+$).

Example 45

{2-[(5-Bromo-2-oxo-1,2-dihydro-1'H-spiro[indole-3,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}acetonitrile



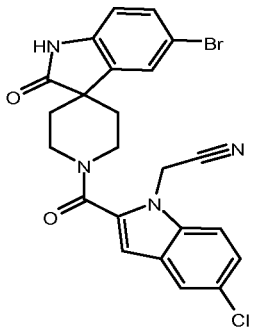
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 1-Cyanomethyl-1H-indole-2-carboxylic acid (prepared herein below),

ES-MS m/e (%): 463.3 ($M+H^+$).

Example 46

{2-[(5-Bromo-2-oxo-1,2-dihydro-1'H-spiro[indole-3,4'-piperidin]-1'-yl)carbonyl]-5-chloro-1H-indol-1-yl}acetonitrile



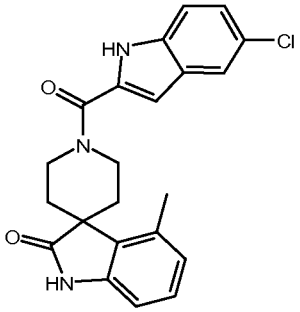
Amide coupling according to general procedure I:

- Amine: 5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (prepared as described herein above)
- Acid: 5-Chloro-1-cyanomethyl-1H-indole-2-carboxylic acid (prepared herein above),

ES-MS m/e (%): 497.3 ($M+H^+$).

Example 47

1'-[(5-Chloro-1H-indol-2-yl)carbonyl]-4-methylspiro[indole-3,4'-piperidin]-2(1H)-one



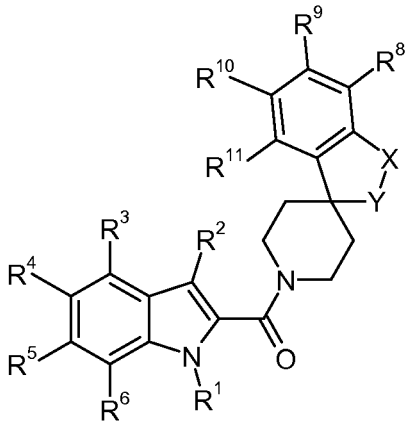
Amide coupling according to general procedure I:

- Amine: 4-methylspiro[indole-3,4'-piperidin]-2(1H)-one
- Acid: 5-Chloro-1H-indole-2-carboxylic acid ,

ES-MS m/e (%): 394.4 ($M+H^+$).

Claims

1. A compound of the general formula (I)



wherein

X and Y are selected from the combinations of:

X is C=O, and Y is O,

X is CH_2, and Y is O,

X is O, and Y is CH_2,

X is NR^7, and Y is C=O,

X is NR^7, and Y is CH_2, or

X-Y is –C=C- or $–CH_2CH_2$-;

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b;

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

-(C_{1-6}-alkylene)-C(O)R^f,

benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

R^3 is hydrogen, halo, or C_{1-6}-alkyl;

R^4 is hydrogen,
halo,
C_{1-6}-alkyl,
halo-C_{1-6}-alkyl,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy, or
-O-C_{2-10}-alkenyl

R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
-R^4–R^5- is –O-$(CH_2)_n$–O– wherein n is 1 or 2;

R^6 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH,
-(C_{1-6}-alkylene)-NR^gR^h,
-(C_{1-6}-alkylene)-C(O)-NR^iR^j,
-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
nitro,
halo,
cyano,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy;,
halo-C_{1-6}-alkyl,
-(C_{1-6}-alkylene)-C(O)R^f,
phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,
each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein
-R^5–R^6- is –O-$(CH_2)_n$–C(O)–,
-C(O)-$(CH_2)_n$-O-, or
–O-$(CH_2)_n$–O– wherein n is 1 or 2;

R^7 is hydrogen or C_{1-6}-alkyl;

R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}alkoxy;

R^a, R^b, R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,

or R^a and R^b, or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

R^c, R^d , R^g and R^h are each independently

hydrogen,

C_{1-6}-alkyl,

-$C(O)R^e$, or -$S(O)_2R^e$

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, and

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

or R^c and R^d , or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;

R^f is selected from

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

or a pharmaceutically acceptable salt thereof.

2. The compound of formula (I) according to claim 1, wherein

R^1 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH, or

-(C_{1-6}-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl.

3. The compound of formula (I) according to claim 1 or 2, wherein

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

-(C_{1-6}-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently

hydrogen,

-C(O)R^e, or -$S(O)_2R^e$

wherein R^e is selected from the group of

hydrogen,

C_{1-6}-alkyl, or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

R^c and R^d together with the nitrogen to which they are bound form

isoindole-1,3-dione,

-(C_{1-6}-alkylene)-C(O)R^f,

wherein R^f is selected from

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy, or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

4. The compound of formula (I) according to any one of claims 1 to 3, wherein R^2 is hydrogen, C_{1-6}-alkyl or C_{1-6}-alkoxy.

5. The compound of formula (I) according to any one of claims 1 to 4, wherein R^3 is hydrogen or halo.

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

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h

wherein R^g and R^h are each independently selected from hydrogen, or

C_{1-6}-alkyl;

or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

-(C_{1-6}-alkylene)-$C(O)-NR^iR^j$

wherein R^i and R^j are each independently

hydrogen;

C_{1-6}-alkyl;

-(C_{1-6}-alkylene)-NR^kR^l;

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

-O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{-1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

nitro;

halo;

cyano;

C_{1-6}-alkoxy;

halo-C_{1-6}-alkoxy;

halo-C_{1-6}-alkyl;

-(C_{1-6}-alkylene)-$C(O)R^f$;

wherein R^f is selected from the group of

hydrogen;

C_{1-6}-alkyl;

C_{1-6}-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

-(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,

each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

7. The compound of formula (I) according to any one of claims 1 to 6, wherein R^6 is hydrogen,

C_{1-6}-alkyl, optionally substituted by CN or OH,

-(C_{1-6}-alkylene)-NR^gR^h,

wherein R^g and R^h are each independently selected from hydrogen, or C_{1-6}-alkyl, or wherein

R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen,

-(C_{1-6}-alkylene)-$C(O)$-NR^iR^j,

wherein R^i and R^j are each independently

hydrogen,

C_{1-6}-alkyl,

-(C_{1-6}-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen and oxygen.

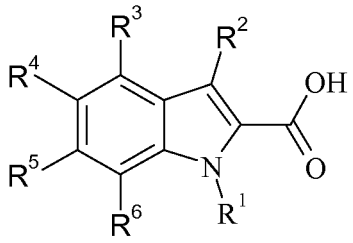
8. The compound of formula (I) according to any one of claims 1 to 7, wherein X is C=O and Y is O.

9. The compound of formula (I) according to any one of claims 1 to 7, wherein X is CH_2 and Y is O.

10. The compound of formula (I) according to any one of claims 1 to 7, wherein X is O and Y is CH_2.

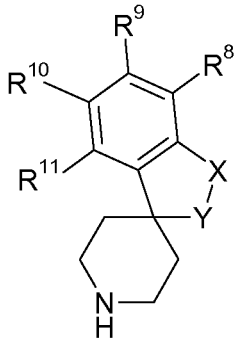
11. The compound of formula (I), which is selected from the group consisting of
{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-7-yl}acetonitrile,
2-{5-chloro-2-[(3-oxo-1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-yl)carbonyl]-1H-indol-1-yl}-N,N-dimethylacetamide,
1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-[(5-chloro-1H-indol-2-yl)carbonyl]-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]acetonitrile,
1'-({5-chloro-7-[2-(4-methylpiperazin-1-yl)-2-oxoethyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
1-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N,N-dimethylmethanamine,
1'-{[5-chloro-7-(morpholin-4-ylmethyl)-1H-indol-2-yl]carbonyl}-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(5-chloro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
2-[5-chloro-2-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1H-indol-7-yl]-N-[2-(dimethylamino)ethyl]acetamide,
1'-[(5-fluoro-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-({5-chloro-7-[(4-methylpiperazin-1-yl)methyl]-1H-indol-2-yl}carbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(4-bromo-3-methoxy-1H-indol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(3,7-dimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine],
1'-[(3,6,7-trimethyl-1H-indol-2-yl)carbonyl]spiro[1-benzofuran-3,4'-piperidine], and
{2-[(5-bromo-2-oxo-1,2-dihydro-1'H-spiro[indole-3,4'-piperidin]-1'-yl)carbonyl]-5-chloro-1H-indol-1-yl}acetonitrile.

12. A process for the preparation of compounds of formula (I) according to claim 1, comprising the step of reacting a compound of formula (II):



II

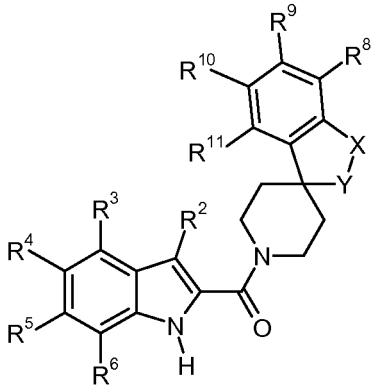
with an amine of the formula 1



(1)

to obtain a compound of formula (I), wherein R^1 to R^6, R^8 to R^{11}, X and Y are as defined in claim 1.

13. A process for the preparation of compounds of formula (I) according to claim 1, comprising the step of reacting a compound of formula (I-1)



(I-1)

with an electrophile of formula R^1-hal, to give a compound of general formula (I), wherein R^1 to R^6, R^8 to R^{11}, X and Y are as defined in claim 1 with the proviso that R^1 is not H.

14. A compound formula (I) obtainable by a process according to any one of claims 12 and 13.

15. A compound of formula (I) according to any one of claims 1 to 11 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.

16. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 11.

17. A pharmaceutical composition according to claim 16, 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.

18. Use of a compound of formula (I) according to any one of claims 1 to 11 for the preparation of a medicament.

19. Use according to claim 18, wherein the medicament is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

20. The invention as described hereinabove.

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