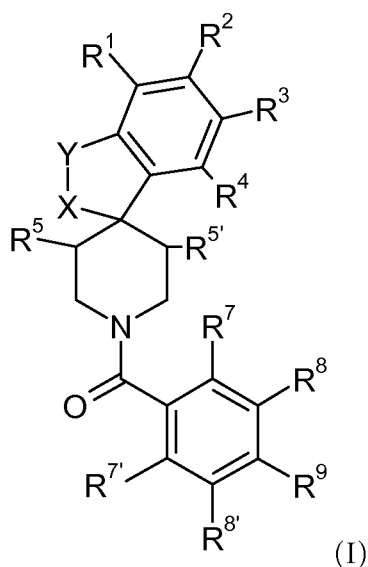


SPIRO-PIPERIDINE DERIVATIVES

The present invention is concerned with novel 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.

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



wherein

- 10 X is O and Y is C=O,
 X is O and Y is CH₂,
 X is C=O and Y is NR⁶,
 X is CH₂ and Y is O, or
 X-Y is CH=CH, or
 15 X-Y is CH₂-CH₂, or
 X is C=O and Y is O, or
 X is CH₂ and Y is NR⁶;

R¹, R², R³ and R⁴ are each independently
 hydrogen,

20 halo,

C₁₋₆-alkyl, optionally substituted by OH,
halo-C₁₋₆-alkyl,
C₁₋₆-alkoxy, optionally substituted by OH, or
halo-C₁₋₆-alkoxy;

5 R⁵ and R^{5'} are each independently hydrogen or methyl;

R⁶ is hydrogen or C₁₋₆-alkyl;

R⁷, R^{7'}, R⁸, R^{8'}, and R⁹ are each independently selected from

hydrogen,

halo,

10 halo-C₁₋₆-alkyl,

C₁₋₆-alkyl,

C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy,

nitro, or

15 cyano,

or R⁷ and R⁸, R^{7'} and R^{8'}, R⁸ and R⁹, or R^{8'} and R⁹ are bound together to form a ring

with the phenyl moiety, wherein

-R⁷-R⁸- or -R^{7'}-R^{8'}- is

-N(R¹⁰)-N=CH-, or -CH=N-N(R¹⁰)-,

20 wherein R¹⁰ is hydrogen, or C₁₋₆-alkyl,

-N(R¹¹)-CH=CH-, or -CH=CH-N(R¹¹)-,

wherein R¹¹ is hydrogen, or C₁₋₆-alkyl,

-C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,

wherein R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from

25 hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy, nitro, or cyano,

-O-(CR¹⁶R^{16'})_n-O-,

wherein n is 1 or 2, and R¹⁶ and R^{16'} are each independently

hydrogen, halo or C₁₋₆-alkyl,

30 -N(R¹⁷)-CH=N-, or -N=CH-N(R¹⁷)-,

wherein R¹⁷ is hydrogen, or C₁₋₆-alkyl, or

-N(R¹⁸)-C(O)-CH₂-, or -CH₂-C(O)-N(R¹⁸)-,

wherein R¹⁸ is hydrogen or C₁₋₆-alkyl,

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.

- 5 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
10 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
15 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
20 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
25 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
30 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 "C₁₋₆-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 C₁₋₆-alkyl is C₁₋₄-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, "C₁₋₆-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 "C₁₋₆-alkoxy" refers to the group R'-O-, wherein R' is alkyl or C₁₋₆-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 C₁₋₆-alkoxy, and still more preferred alkoxy groups are methoxy and/or ethoxy.

In the present description, the term “thioalkyl” and “C₁₋₆-thioalkyl” refers to the group R'-S-, wherein R' is alkyl or C₁₋₆-alkyl as defined above.

The term “C₁₋₆-hydroxyalkyl” or “C₁₋₆-alkyl substituted by OH” denotes a C₁₋₆-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is
5 replaced by a hydroxyl group.

The term “C₁₋₆-cyanoalkyl” or “C₁₋₆-alkyl substituted by CN” denotes a C₁₋₆-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
10 iodine (I) with fluorine, chlorine and bromine being preferred.

The term “halo-C₁₋₆-alkyl” is synonymous with “C₁₋₆-haloalkyl” or “C₁₋₆-alkyl substituted by halo” and means a C₁₋₆-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-C₁₋₆-alkyl include but are not limited to
15 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-C₁₋₆-alkyl groups are difluoro- or trifluoro-methyl or -ethyl.

The term “halo-C₁₋₆-alkoxy” is synonymous with “C₁₋₆-haloalkoxy” or “C₁₋₆-alkoxy substituted by halo” and means a C₁₋₆-alkoxy group as defined above wherein at least one
20 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 “C₂₋₁₂-alkenyl”, alone or in combination, denotes a straight-chain or
25 branched hydrocarbon residue of 2 to 12 carbon atoms comprising at least one double bond. A preferred sub-group of C₂₋₁₂-alkenyl is C₂₋₆-alkenyl. 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
30 below.

The term “one or more” substituents preferably means one, two or three optional substituents per ring.

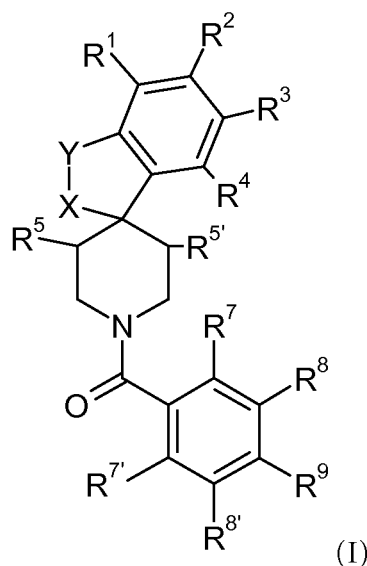
The term "pharmaceutically acceptable acid addition salts" embraces salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid and the like.

- 5 The term "bound together to form a ring with the phenyl moiety" means that the residues of the phenyl ring, which are located in ortho-position to each other, may form an annellated ring to the phenyl moiety.

The invention further comprises individual optical isomers of the compounds herein as well as racemic and non-racemic mixtures thereof.

10

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



wherein

- 15 X is O and Y is C=O,
 X is O and Y is CH₂,
 X is C=O and Y is NR⁶,
 X is CH₂ and Y is O, or
 X-Y is CH=CH, or
 X-Y is CH₂-CH₂, or

20 X is C=O and Y is O, or
 X is CH₂ and Y is NR⁶;

R¹, R², R³ and R⁴ are each independently
 hydrogen,

halo,

C₁₋₆-alkyl, optionally substituted by OH,

halo-C₁₋₆-alkyl,

C₁₋₆-alkoxy, optionally substituted by OH, or

5 halo-C₁₋₆-alkoxy;

R⁵ and R^{5'} are each independently hydrogen or methyl;

R⁶ is hydrogen or C₁₋₆-alkyl;

R⁷, R^{7'}, R⁸, R^{8'}, and R⁹ are each independently selected from

hydrogen,

10 halo,

halo-C₁₋₆-alkyl,

C₁₋₆-alkyl,

C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy,

15 nitro, or

cyano,

or R⁷ and R⁸, R^{7'} and R^{8'}, R⁸ and R⁹, or R^{8'} and R⁹ are bound together to form a ring

with the phenyl moiety, wherein

-R⁷-R⁸- or -R^{7'}-R^{8'}- is

20 -N(R¹⁰)-N=CH-, or -CH=N-N(R¹⁰)-,

wherein R¹⁰ is hydrogen, or C₁₋₆-alkyl,

-N(R¹¹)-CH=CH-, or -CH=CH-N(R¹²)-,

wherein R¹¹ is hydrogen, or C₁₋₆-alkyl,

-C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,

25 wherein R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from

hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy, nitro, or cyano,

-O-(CR¹⁶R^{16'})_n-O-,

wherein n is 1 or 2, and R¹⁶ and R^{16'} are each independently

30 hydrogen, halo or C₁₋₆-alkyl,

-N(R¹⁷)-CH=N-, or -N=CH-N(R¹⁷)-,

wherein R¹⁷ is hydrogen, or C₁₋₆-alkyl, or

-N(R¹⁸)-C(O)-CH₂-, or -CH₂-C(O)-N(R¹⁸)-,

wherein R¹⁸ is hydrogen or C₁₋₆-alkyl,

or a pharmaceutically acceptable salt thereof.

In certain embodiments of the invention, R^1 , R^2 , R^3 and R^4 are each independently hydrogen, halo, C_{1-6} -alkyl or C_{1-6} -alkoxy, optionally substituted by OH.

5 In certain embodiments of the invention, R^1 is hydrogen or halo, preferably hydrogen or fluoro.

In certain embodiments of the invention, R^2 is hydrogen, halo or C_{1-6} -alkoxy; preferably hydrogen, fluoro, bromo or methoxy.

10 In certain embodiments of the invention, R^3 is hydrogen, halo, or C_{1-6} -alkoxy, optionally substituted by OH; preferably hydrogen, chloro, bromo, methoxy or – $O(CH_2)_2OH$.

In certain embodiments of the invention, R^4 is hydrogen or C_{1-6} -alkyl; preferably hydrogen or methyl.

In certain embodiments all R^1 to R^4 are hydrogen.

In certain embodiments, one residue of R^1 to R^4 is halo and the others are hydrogen.

15 In certain embodiments, one residue of R^1 to R^4 is C_{1-6} -alkyl, preferably methyl, and the others are hydrogen.

In certain embodiments, one residue of R^1 to R^4 is C_{1-6} -alkoxy, optionally substituted by OH, preferably methoxy or $-O(CH_2)_2OH$, and the others are hydrogen.

20 In certain embodiments of the invention, R^5 and $R^{5'}$ are both hydrogen, in other embodiments of the invention, R^5 and $R^{5'}$ are both methyl, in other embodiments of the invention, R^5 is hydrogen and $R^{5'}$ is methyl.

In certain embodiments of the invention, R^5 is hydrogen, $R^{5'}$ is methyl, X is O and Y is C=O.

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

In certain embodiments of the invention, both R^7 and $R^{7'}$ are hydrogen.

In certain embodiments of the invention, one of R^7 and $R^{7'}$ is hydrogen and the other is 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^7 and $R^{7'}$ are each independently hydrogen, or halo.

In certain embodiments of the invention, one of R^7 and $R^{7'}$ is hydrogen and the other is halo, preferably chloro.

5 In certain embodiments of the invention, each of R^8 and $R^{8'}$ are independently hydrogen, 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^8 and $R^{8'}$ are each independently hydrogen, halo, or C_{1-6} -alkoxy, preferably hydrogen, chloro, ethoxy or methoxy.

10 In certain embodiments of the invention, R^7 and R^8 or $R^{7'}$ and $R^{8'}$ are bound together to form a ring with the phenyl moiety, wherein

$-R^7-R^8-$ or $-R^{7'}-R^{8'}-$ is

$-N(R^{10})-N=CH-$, or $-CH=N-N(R^{10})-$,

wherein R^{10} is hydrogen, or C_{1-6} -alkyl,

$-N(R^{11})-CH=CH-$, or $-CH=CH-N(R^{12})-$,

15 wherein R^{11} is hydrogen, or C_{1-6} -alkyl,

$-C(R^{12})=C(R^{13})-C(R^{14})=C(R^{15})-$,

wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from hydrogen, halo, halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkoxy, nitro, or cyano,

20 $-O-(CR^{16}R^{16'})_n-O-$,

wherein n is 1 or 2, and R^{16} and $R^{16'}$ are each independently hydrogen, halo or C_{1-6} -alkyl, or

$-N(R^{17})-CH=N-$, or $-N=CH-N(R^{17})-$,

wherein R^{17} is hydrogen, or C_{1-6} -alkyl.

25

In certain embodiments of the invention, R^7 and R^8 are bound together to form a ring with the phenyl moiety as described above, and

R^9 , $R^{8'}$ and $R^{7'}$ are hydrogen, or

R^9 and $R^{7'}$ are hydrogen, and $R^{8'}$ is halo, preferably chloro, or

30 R^9 and $R^{7'}$ are hydrogen, and $R^{8'}$ is C_{1-6} -alkoxy, preferably ethoxy or methoxy.

In certain embodiments of the invention, $R^{7'}$ and $R^{8'}$ are bound together to form a ring with the phenyl moiety as described above, and

R^9 , R^8 and R^7 are hydrogen, or

R^9 and R^7 are hydrogen, and R^8 is halo, preferably chloro, or

R^9 and R^7 are hydrogen, and R^8 is C_{1-6} -alkoxy, preferably ethoxy or methoxy.

In certain embodiments of the invention, R^7 and R^8 are halo, preferably chloro, and
 5 R^9 , R^7 and R^8 are hydrogen.

In certain embodiments of the invention, R^9 is hydrogen, 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^9 is hydrogen, halo, or C_{1-6} -alkyl, preferably hydrogen, chloro or tert-butyl.

10 In certain embodiments of the invention,

R^8 and R^9 or $R^{8'}$ and R^9 are bound together to form a ring with the phenyl moiety, wherein
 $-R^8-R^9-$ or $-R^{8'}-R^9-$ is

$-C(R^{12})=C(R^{13})-C(R^{14})=C(R^{15})-$,

wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from

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

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

$-N(R^{18})-C(O)-CH_2-$, or $-CH_2-C(O)-N(R^{18})-$,

wherein R^{18} is hydrogen or C_{1-6} -alkyl.

In certain embodiments of the invention, R^8 and R^9 are bound together to form a
 20 ring with the phenyl moiety as described above, and
 R^7 , $R^{8'}$ and R^7 are hydrogen.

In certain embodiments of the invention, $R^{8'}$ and R^9 are bound together to form a
 ring with the phenyl moiety as described above, and

R^7 , R^8 and R^7 are hydrogen.

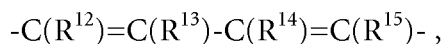
25 In certain embodiments of the invention, R^8 and R^9 are halo, preferably chloro, and
 R^7 , $R^{7'}$ and R^8 are hydrogen.

In certain embodiments of the invention, $R^{8'}$ and R^9 are halo, preferably chloro, and
 R^7 , $R^{7'}$ and $R^{8''}$ are hydrogen.

In certain embodiments of the invention, R^9 is C_{1-6} -alkyl or halo, preferably tert-butyl or chloro, and R^7 , $R^{7'}$, R^8 , and $R^{8'}$ are hydrogen.

Preferred compounds of the invention are those of formula (I) wherein R^8 and R^9 are halo, or wherein

- 5 R^8 and R^9 are bound together to form a ring with the phenyl moiety, wherein
 $-R^8-R^9-$ is

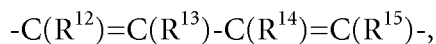


- wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from
hydrogen, halo, halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{1-6} -alkoxy,
10 halo- C_{1-6} -alkoxy, nitro, or cyano,

and R^7 , $R^{7'}$ and $R^{8'}$ are hydrogen.

Preferred compounds of the invention are those of formula (I) wherein $R^{8'}$ and R^9 are halo, or wherein

- $R^{8'}$ and R^9 are bound together to form a ring with the phenyl moiety, wherein
15 $-R^{8'}-R^9-$ is

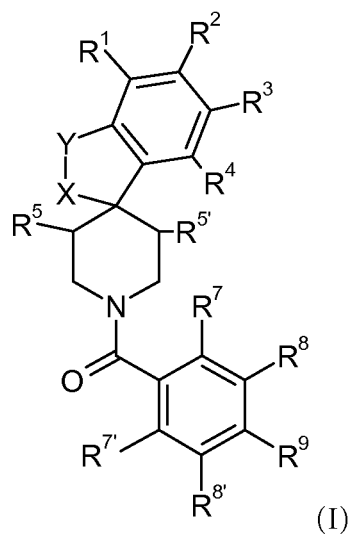


- wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from
hydrogen, halo, halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{1-6} -alkoxy,
halo- C_{1-6} -alkoxy, nitro, or cyano,

- 20 and R^7 , $R^{7'}$ and R^8 are hydrogen.

Preferably, R^7 , $R^{7'}$, R^8 , $R^{8'}$ and R^9 are not simultaneously hydrogen.

A certain embodiment of the invention relates to a compound of the general formula
(I)



wherein

X is O and Y is C=O,

X is O and Y is CH₂,

5 X is C=O and Y is NR⁶,

X is CH₂ and Y is O; or

X-Y is CH=CH, or

X-Y is CH₂-CH₂, or

X is C=O and Y is O, or

10 X is CH₂ and Y is NR⁶;

R¹, R², R³ and R⁴ are each independently

hydrogen,

halo,

C₁₋₆-alkyl, optionally substituted by OH,

15 halo-C₁₋₆-alkyl,

C₁₋₆-alkoxy, optionally substituted by OH, or

halo-C₁₋₆-alkoxy;

R⁵ and R^{5'} are each independently hydrogen or methyl;

R⁶ is hydrogen or C₁₋₆-alkyl;

20 R⁷ and R^{7'} are each independently selected from

hydrogen,

halo,

halo-C₁₋₆-alkyl,

C₁₋₆-alkyl,

25 C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy,

nitro, or

cyano;

R⁸ and R^{8'} are each independently selected from

5 hydrogen,

halo,

C₁₋₆-alkoxy,

halo-C₁₋₆-alkyl,

C₁₋₆-alkyl,

10 halo-C₁₋₆-alkoxy,

nitro, or

cyano;

R⁷ and R⁸ or R^{7'} and R^{8'} are bound together to form a ring with the phenyl moiety, wherein

-R⁷-R⁸- or -R^{7'}-R^{8'}- is

15 -N(R¹⁰)-N=CH- , or -CH=N-N(R¹⁰)-,

wherein R¹⁰ is hydrogen, or C₁₋₆-alkyl,

-N(R¹¹)-CH=CH- , or -CH=CH-N(R¹¹)-,

wherein R¹¹ is hydrogen, or C₁₋₆-alkyl,

-C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,

20 wherein R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from

hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy, nitro, or cyano,

-O-(CR¹⁶R^{16'})_n-O-,

wherein n is 1 or 2, and R¹⁶ and R^{16'} are each independently

25 hydrogen, halo or C₁₋₆-alkyl,

-N(R¹⁷)-CH=N- , or -N=CH-N(R¹⁷)-,

wherein R¹⁷ is hydrogen, or C₁₋₆-alkyl,

R⁹ is hydrogen,

halo,

30 C₁₋₆-alkyl,

halo-C₁₋₆-alkyl,

C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy,

nitro, or

35 cyano;

R^8 and R^9 or $R^{8'}$ and R^9 are bound together to form a ring with the phenyl moiety, wherein

$-R^8-R^9-$ or $-R^{8'}-R^9-$ is

$-C(R^{12})=C(R^{13})-C(R^{14})=C(R^{15})-$,

wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from

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

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

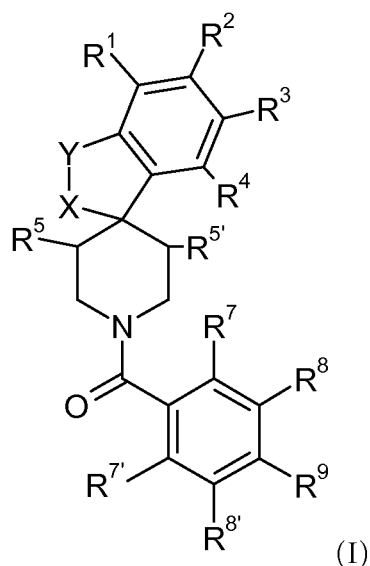
$-N(R^{18})-C(O)-CH_2-$, or $-CH_2-C(O)-N(R^{18})-$,

wherein R^{18} is hydrogen or C_{1-6} -alkyl,

or a pharmaceutically acceptable salt thereof.

10

A certain embodiment of the invention relates to compounds of formula (I)



wherein

X is O and Y is C=O,

15 X is O and Y is CH₂,

X is C=O and Y is NR⁶,

X is CH₂ and Y is O, or

X-Y is CH=CH, or

X-Y is CH₂-CH₂, or

20 X is C=O and Y is O, or

X is CH₂ and Y is NR⁶;

R^1 , R^2 , R^3 and R^4 are each independently

hydrogen,

halo, or

C₁₋₆-alkoxy, optionally substituted by OH,

R⁵ and R^{5'} are each independently hydrogen or methyl;

R⁶ is hydrogen or C₁₋₆-alkyl;

5 R⁷ and R^{7'} are each independently hydrogen, or halo;

R⁸ and R^{8'} are each independently hydrogen, halo, or C₁₋₆-alkoxy;

R⁷ and R⁸ or R^{7'} and R^{8'} are bound together to form a ring with the phenyl moiety, wherein

-R⁷-R⁸- or -R^{7'}-R^{8'}- is

-N(R¹⁰)-N=CH- , or -CH=N-N(R¹⁰)-,

10 wherein R¹⁰ is hydrogen, or C₁₋₆-alkyl,

-N(R¹¹)-CH=CH- , or -CH=CH-N(R¹¹)-,

wherein R¹¹ is hydrogen, or C₁₋₆-alkyl,

-C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,

15 wherein R¹², R¹³, R¹⁴ and R¹⁵ are each independently selected from

hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy, nitro, or cyano,

-O-(CR¹⁶R^{16'})_n-O- ,

wherein n is 1 or 2, and R¹⁶ and R^{16'} are each independently

hydrogen, halo or C₁₋₆-alkyl,

20 -N(R¹⁷)-CH=N- , or -N=CH-N(R¹⁷)- ,

wherein R¹⁷ is hydrogen, or C₁₋₆-alkyl,

R⁹ is hydrogen, halo, or C₁₋₆-alkyl;

R⁸ and R⁹ or R^{8'} and R^{9'} are bound together to form a ring with the phenyl moiety, wherein

-R⁸-R⁹- or -R^{8'}-R^{9'}- is

25 -C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,

wherein R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from

hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,

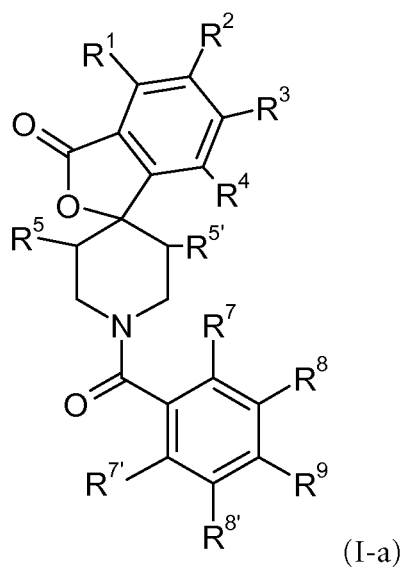
halo-C₁₋₆-alkoxy, nitro, or cyano,

-N(R¹⁸)-C(O)-CH₂- , or -CH₂-C(O)-N(R¹⁸)-,

30 wherein R¹⁸ is hydrogen or C₁₋₆-alkyl,

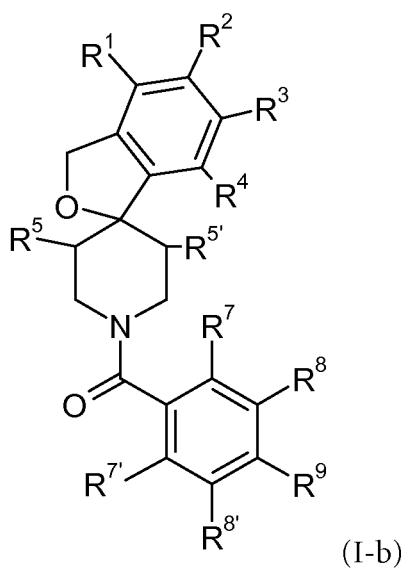
or a pharmaceutically acceptable salt thereof.

An embodiment of the invention relates to compounds of formula (I-a)



wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

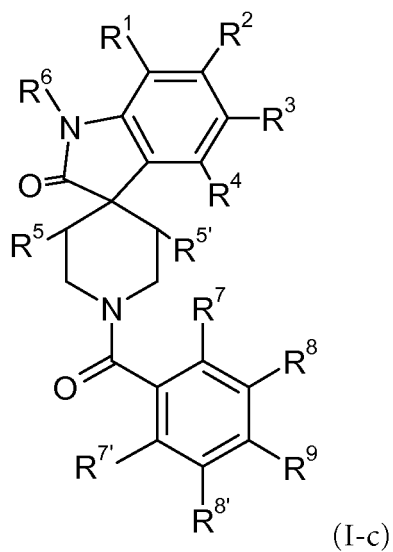
An embodiment of the invention relates to compounds of formula (I-b)



wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

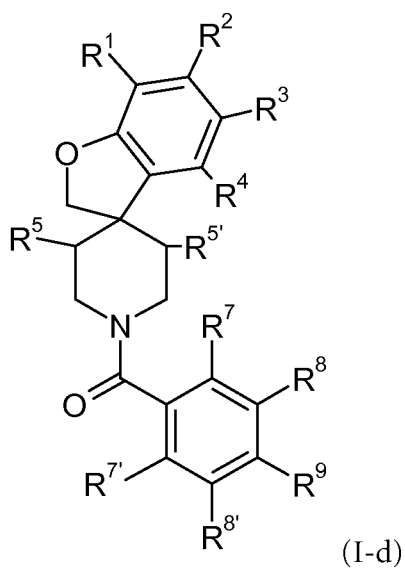
An embodiment of the invention relates to compounds of formula (I-c)

- 17 -



wherein R^1 to R^9 are as defined in any combination as described above.

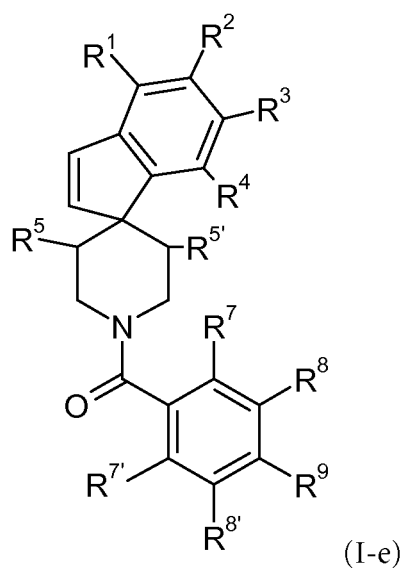
An embodiment of the invention relates to compounds of formula (I-d)



5 wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

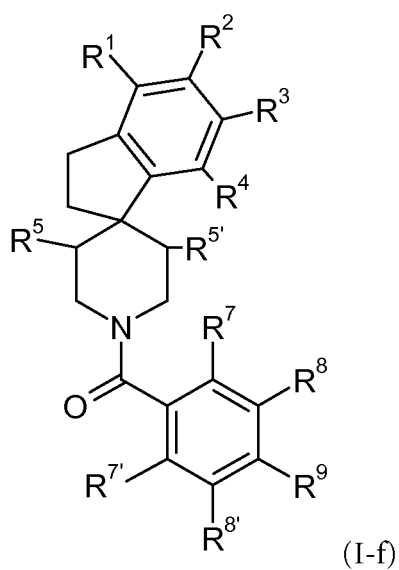
An embodiment of the invention relates to compounds of formula (I-e)

- 18 -



wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

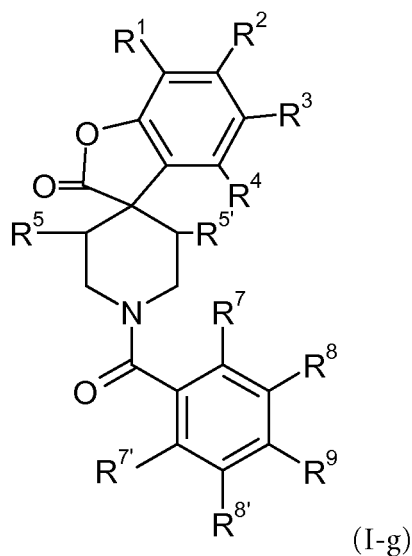
An embodiment of the invention relates to compounds of formula (I-f)



5 wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

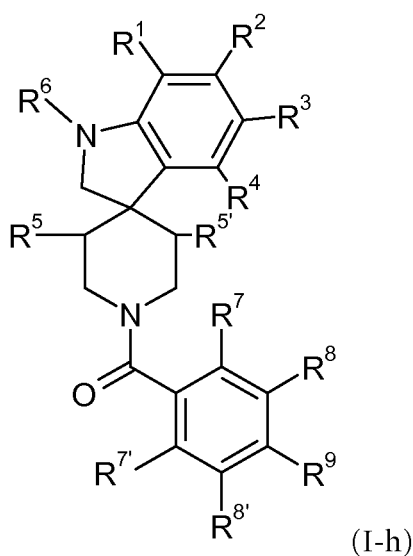
An embodiment of the invention relates to compounds of formula (I-g)

- 19 -



wherein R^1 to $R^{5'}$ and R^7 to R^9 are as defined in any combination as described above.

An embodiment of the invention relates to compounds of formula (I-h)



5 wherein R^1 to R^9 are as defined in any combination as described above.

Any compound of formula (I-a) to (I-h) may be combined with any residue or combination of residues R^1 to R^9 as defined above.

Preferred compounds are those of formula (I-a) to (I-f).

Preferred compounds of the invention are those of the examples. More preferred are the
10 following compounds:

- 6-Methoxy-1'-(2-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-(3,4-Dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-(3,4-Dichlorobenzoyl)-6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-(3,4-Dichlorobenzoyl)-5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
5 1'-(3,4-Dichlorobenzoyl)-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-(3,4-Dichlorobenzoyl)-6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
1'-(4-tert-Butylbenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(5-Methoxy-1H-indol-7-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
10 5-Bromo-1'-(2-naphthoyl)spiro[indole-3,4'-piperidin]-2(1H)-one,
1'-(2-Naphthoyl)spiro[indene-1,4'-piperidine], and
1'-(3,4-Dichlorobenzoyl)-2,3-dihydrospiro[indene-1,4'-piperidine].

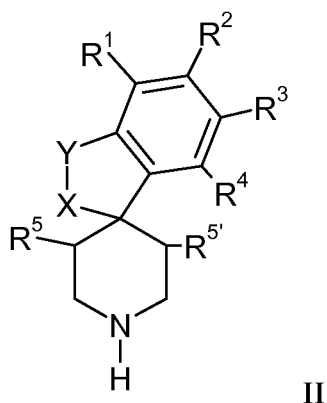
The invention also encompasses the compounds of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h) for a use in the prevention or treatment of dysmenorrhea,
15 hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders.

The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h) which
20 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.

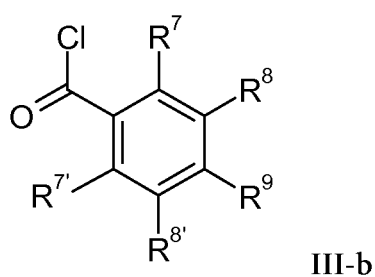
The invention further encompasses the use of a compound of formula (I), (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g) or (I-h) for the preparation of a medicament which is
25 useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic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

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

- 21 -

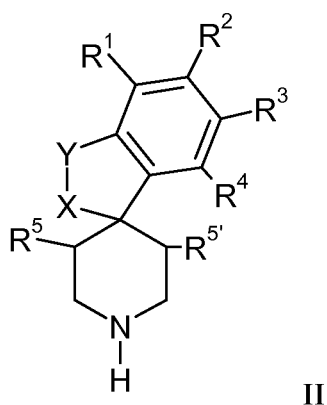


with an acid chloride of formula (III-b)



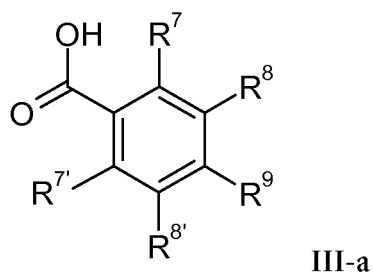
to obtain the compound according to formula (I) wherein R^1 to R^{10} and X and Y are as
5 defined above.

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 (II):



10 with an acid of formula (III-a)

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to obtain the compound of formula (I) wherein R^1 to R^{10} and X and Y are as defined above.

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

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

10

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
15 present invention to the human V1a receptor binding studies were performed. Cell membranes were prepared from HEK293 cells transiently transfected with the expression vector and grown in 20 liter fermenters with the following protocol.

50g of cells are resuspended in 30ml freshly prepared ice cold Lysis buffer (50mM HEPES, 1mM EDTA, 10mM $MgCl_2$ adjusted to pH= 7.4 + complete cocktail of protease inhibitor
20 (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
25 by the Bradford method and aliquots are stored at -80°C until use. For binding studies 60mg Yttrium silicate SPA beads (Amersham) are mixed with an aliquot of membrane in binding buffer (50 mM Tris, 120mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 10 mM $MgCl_2$) for 15 minutes with mixing. 50ul of bead/membrane mixture is then added to each well of a 96

well plate, followed by 50ul of 4 nM 3H-Vasopressin (American Radiolabeled Chemicals). For total binding measurement 100ul of binding buffer are added to the respective wells, for non-specific binding 100ul of 8.4mM cold vasopressin and for compound testing 100ul of a serial dilution of each compound in 2%DMSO. The plate is incubated 1h at room temperature, centrifuged 1 min at 1000g and counted on a Packard Top-Count. Non-specific binding counts are subtracted from each well and data is normalized to the maximum specific binding set at 100%. To calculate an IC 50 the curve is fitted using a non-linear regression model (XLfit) and the Ki is calculated using the Cheng-Prusoff equation.

Ex	pKi hV1a	Ex	pKi hV1a
1	8.08	25	7.2
6	7.72	27	7.3
7	7.54	33	6.96
9	7.32	36	7.05
11	7.53	42	6.95
12	7.66		

10

The compounds of formula (I), and (Ia) to (If) 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.

25

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.

15 Example A

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

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

Example B

25 Capsules of the following composition are manufactured:

mg/capsule

	Active substance	10
	Lactose	155
	Corn starch	30
	Talc	5
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

10 Suppositories of the following composition are manufactured:

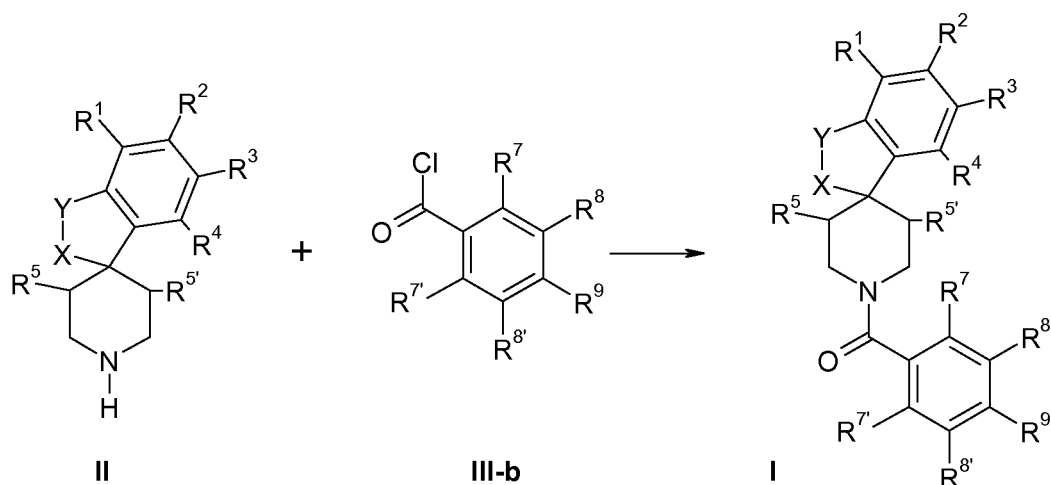
	<u>mg/supp.</u>
Active substance	15
Suppository mass	1285
Total	1300

15 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.

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

The following general scheme A is an example of the preparation of the compounds of the invention according to general procedure 1:

General Scheme A

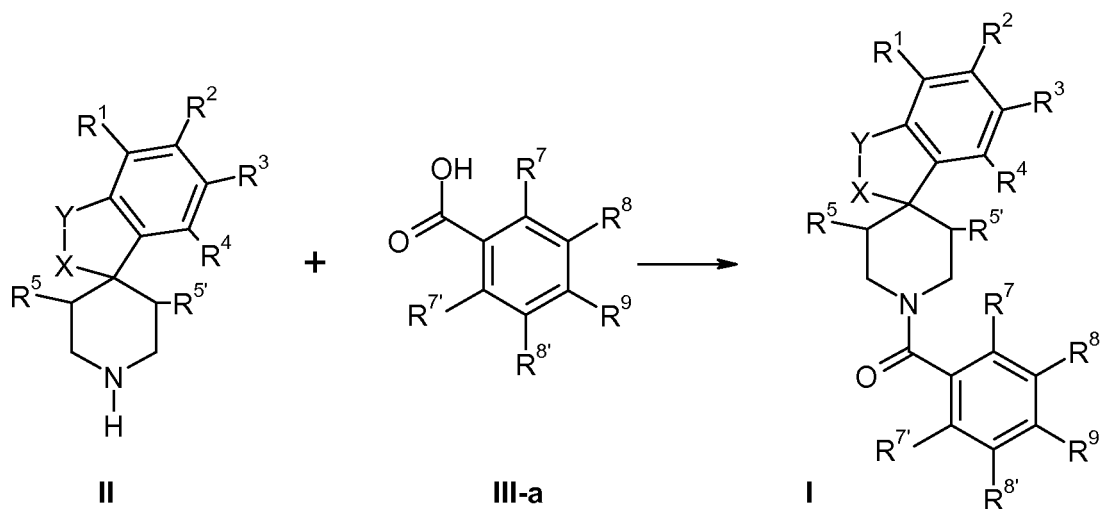


5 General Procedure I - amide coupling with acid chlorides:

A solution of the amine (1 eq), the acid chloride (1 eq) and DIPEA (1.5 eq) in DMF is stirred at RT for 14h. The mixture is concentrated and purified by preparative HPLC to yield the desired product.

The following general scheme B is an example of the preparation of the compounds of the
 10 invention according to general procedure 2:

General scheme B:



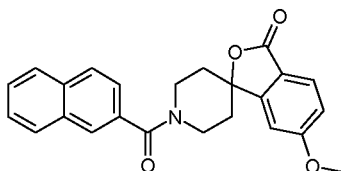
General Procedure 2 - amide coupling with carboxylic acids:

A solution of the acid (1 eq) and HATU (1eq) in DMF is shaken for 30 min at RT and then a solution of the amine (1 eq) and DIPEA (2 eq) in DMF is added and the mixture shaken at RT for 2h. The mixture is concentrated and purified by preparative HPLC to yield the

5 desired product.

Examples**Example 1**

6-Methoxy-1'-(2-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one:



10

Amide coupling according to general procedure I:

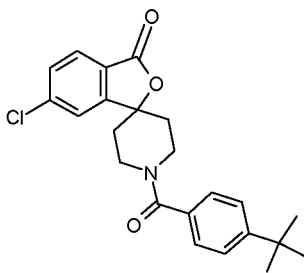
- Amine: 6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

- Acid chloride: Naphthalene-2-carbonyl chloride

15 ES-MS m/e (%): 388.4 (M+H⁺).

Example 2

1'-(4-tert-Butylbenzoyl)-6-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure I:

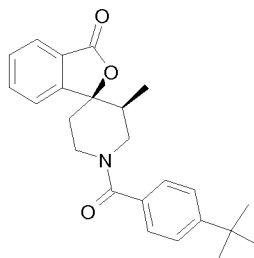
20 - Amine: 6-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

- Acid chloride: 4-tert-Butyl-benzoyl chloride

ES-MS m/e (%): 398.4 (M+H⁺).

Example 3

Rac-(1R,3'S)-1'-(4-tert-butylbenzoyl)-3'-methyl-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



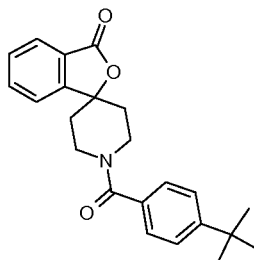
Amide coupling according to general procedure I:

- 5 - Amine: rac-(1R,3'S)-3'-methyl-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in WO 9929696)
 - Acid chloride: 4-tert-Butyl-benzoyl chloride
 ES-MS m/e (%): 378.5 (M+H⁺).

10

Example 4

1'-(4-tert-Butylbenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



15

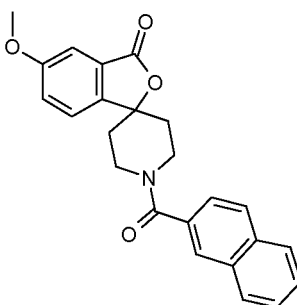
Amide coupling according to general procedure I:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in Journal of Organic Chemistry (1976), 41(15), 2628-33)
 - Acid chloride: 4-tert-Butyl-benzoyl chloride
 20 ES-MS m/e (%): 364.5 (M+H⁺).

Example 5

5-Methoxy-1'-(2-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one

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Amide coupling according to general procedure I:

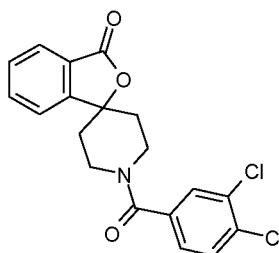
- Amine: 5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

5 - Acid chloride: Naphthalene-2-carbonyl chloride

ES-MS m/e (%): 388.5 ($M+H^+$).

Example 6

1'-(3,4-Dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



10 Amide coupling according to general procedure 2:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in Journal of Organic Chemistry (1976), 41(15), 2628-33)

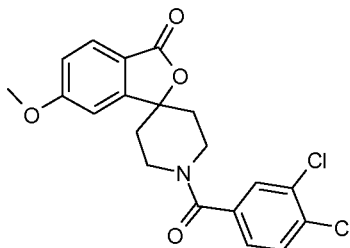
- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 376.4 ($M+H^+$).

15

Example 7

1'-(3,4-Dichlorobenzoyl)-6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure 2:

- Amine: 6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

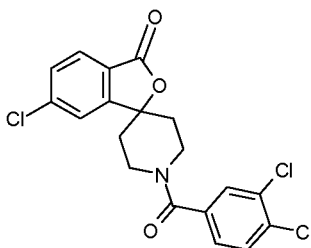
- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 406.4 (M+H⁺).

5

Example 8

6-Chloro-1'-(3,4-dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure 2:

- Amine: 6-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP

10 722941)

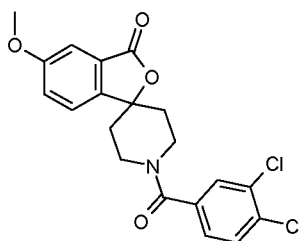
- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 410.3 (M+H⁺).

15

Example 9

20 1'-(3,4-Dichlorobenzoyl)-5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure 2:

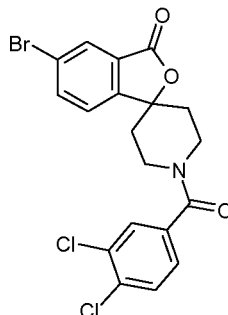
- Amine: 5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

25 - Acid: 3,4-Dichloro-benzoic acid

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

Example 10

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



5 Amide coupling according to general procedure 2:

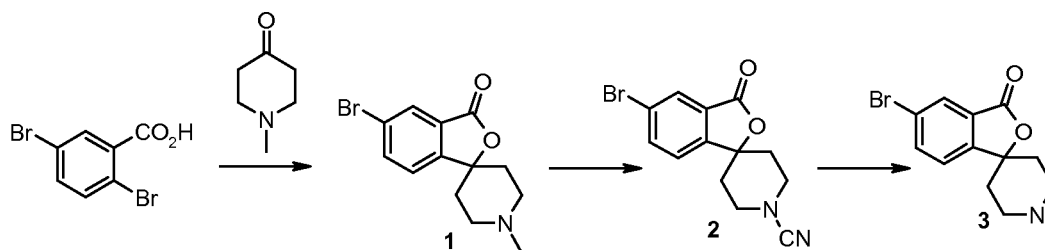
- Amine: 5-bromo-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described herein)

- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 456.3 ($M+H^+$).

The synthesis of 5-bromo-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one is described

10 below (3):



Preparation of 1: 1'-methyl-(5-bromo-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one):

Butyllithium (97.2 ml of 1.47 M solution in hexane, 143 mmol) was added dropwise to a solution of 2,5-Dibromo-benzoic acid (20 g, 72 mmol) in dry THF (300 ml) at -78°C over
 15 a period of 3.5 h under a nitrogen atmosphere. The reaction mixture was stirred at -78°C for 2 h. A solution of N-methyl piperidone (11.31 g, 99 mmol) in hexane (40 mL) was added dropwise during 30 min to the reaction mixture at 78°C . The reaction mixture was allowed to come to room temperature and stirring was continued for overnight. The reaction mixture was added to a mixture of water (500 ml) and ether (300 mL). The
 20 aqueous layer was extracted with ether (5 X 150 mL) and acidified with concentrated HCl (to pH 2-3) and extracted with ether (2 X 150 ml). The acidic solution was boiled for 1 h and then cooled to $0-5^{\circ}\text{C}$ and made alkaline (to pH 9-10) with aqueous NaOH. The cold

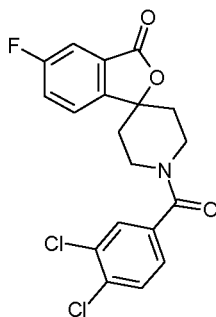
solution was rapidly extracted with chloroform (5 X 300 mL). The combined chloroform extracts were washed with water (150 ml), dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel (100-200) column chromatography eluting with methanol in dichloromethane (0.5% to 2.5%) to afford 1 (4.2 g, 20%). ¹H-NMR (400MHz, CDCl₃): δ 1.71 (d, J = 14.2 Hz, 2H), 2.15-2.24 (m, 2H), 2.37 (s, 3H), 2.45-2.52 (m, 2H), 2.83-2.87 (m, 2H), 7.26 (d, J = 8.25 Hz, 1H), 7.75 (dd, J = 7.8, 1.7 Hz, 1H). ¹³C-NMR (100MHz, CDCl₃): δ 35.95, 46.05, 51.42, 84.00, 122.54, 122.97, 127.52, 128.64, 137.06, 152.24, 167.77.

Preparation of 2: 1'-cyano-(5-bromo-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one): A solution of 1 (3.0 g, 10 mmol) in chloroform (50 ml) was added dropwise to a stirred boiling solution of cyanogens bromide (12.16 g, 120 mmol) in chloroform (100 ml) under a nitrogen atmosphere and the resulting solution was refluxed for overnight. The reaction mixture was cooled and washed with 25 mL of 5% HCl and then with 20 ml of water. The organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (100-200) eluting with methanol in dichloromethane (0.5% to 1.0%) to get the pure product (1.6 g, 51%). ¹H-NMR (400MHz, CDCl₃): δ 1.72 (d, J = 14.2Hz, 2H), 2.24-2.32 (m, 2H), 3.37-3.59 (m, 4H), 7.32 (d, J = 8.2 Hz, 1H), 7.83 (dd, J = 8.0, 1.7Hz, 1H), 8.03 (d, J = 1.7Hz, 1H).

Preparation of 3: (5-bromo-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one): A mixture of 2 (1.0 g, 3.2 mmol) and 20%HCl (12 ml) was heated under reflux under a nitrogen atmosphere for 6 h. The reaction mixture was cooled to 0-5°C and pH was adjusted to 9-10 with aqueous NaOH solution and rapidly extracted with chloroform (3 X 50 ml). The combined extracts were washed with water, the organic layer was dried over sodium sulfate and evaporated under reduced pressure. The residue was washed with distilled hexane and dried under high vacuum to get the pure product (0.64 g, 70%). IR (KBr) 3333.84, 290.53, 2835.25, 2811.07, 2749.38, 1756.04, 1470.28, 1415.14, 1271.03, 1196.28, 1083.84, 929.07, 831.50, 792.35, 734.78, 691.24, 548.46, 534.50 cm⁻¹. ¹H-NMR (400MHz, CDCl₃): δ 1.66-1.72 (m, 2H), 2.02-2.09 (m, 2H), 3.07-3.18 (m, 4H), 7.29 (d, J = 7.8 Hz, 1H), 7.77 (dd, J = 7.8, 1.7 Hz, 1H), 7.99 (d, J = 1.7Hz, 1H). ¹³C-NMR (100MHz, CDCl₃): δ 6.33, 42.49, 85.23, 122.61, 122.93, 127.39, 128.64, 137.07, 152.44, 167.91. FIA-MS: 282.1 and 284.1; C₁₂H₁₂BrNO₂ [MH⁺] requires 282.1. mp: 162-163 °C.

Example 11

1'-(3,4-Dichlorobenzoyl)-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure 2:

- Amine: 5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in WO

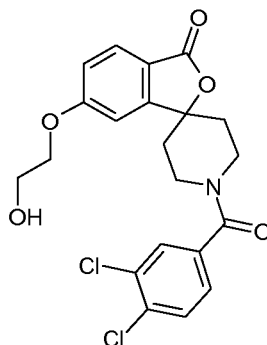
5 2001014376)

- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 394.3 (M+H⁺).

Example 12

1'-(3,4-Dichlorobenzoyl)-6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



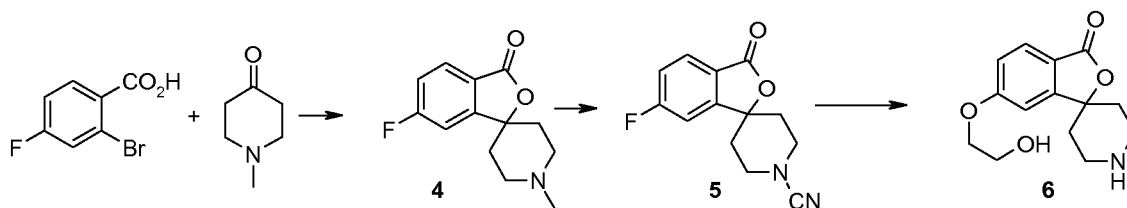
Amide coupling according to general procedure 2:

- Amine: 6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in WO 2001014376)

15 - Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 436.4 (M+H⁺).

Preparation of (6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one): 6



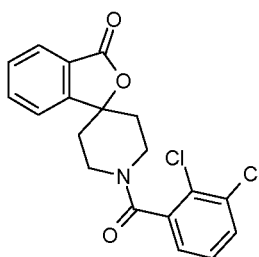
Preparation of 4: 1'-methyl-6-(2-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one: To a solution of the substituted 2-bromo-4-fluoro-benzoic acid (10.9 g, 50 mmol) in dry THF (200 ml) at -78°C n-butyllithium (1.6 M in hexanes) (100mmol) was added drop wise (3 h) and the resulting solution was stirred for an additional 2 h at the same temperature. Freshly distilled N-methyl 4- piperidone 6 (7.91 g, 70mmol) in dry hexane (25 ml) was added over 30 min at the same temperature. The mixture was then allowed to stir at rt and was finally added to ether (200 ml) and water (300 ml). The basic (aqueous) layer was extracted with ether (5 X 100 ml) and the aqueous layer was acidified with concentrated hydrochloric acid (pH 2-3) and extracted with ether. The aqueous solution was boiled for 1 h and was then cooled to $0-5^{\circ}\text{C}$ and made alkaline (pH 9-10) with cold aqueous sodium hydroxide. The cold solution was rapidly extracted with chloroform (5 X 200 ml). The combined chloroform extracts were washed with water, dried, concentrated to give light yellow solid which was purified over neutral alumina eluting with a gradient of 30-50% ethyl acetate-hexane to obtain 1.75 g (15%) of 9 as white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.68-1.75 (m, 2H), 2.18-2.19 (m, 1H), 2.38 (s, 3H), 2.44-2.52 (m, 2H), 2.68-2.84 (m, 2H), 2.84-2.85 (m, 1H), 7.02-7.05 (m, 1H), 7.19-7.22 (m, 1H), 7.84-7.87 (m, 1H); FIA-MS: 236 ($\text{M} + 1$).

Preparation of 5: 1'-cyano-6-(2-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one: To a solution of the N-methylated lactone 9 (1.17 g, 5 mmol) in dry chloroform (10 ml) was added cyanogenbromide (60 mmol) and the resulting solution was refluxed for 36 h. The reaction mixture was extracted with 5% HCl (5 ml) and then with water (2.5 ml). The chloroform solution was dried (anhydrous MgSO_4) and concentrated to give a pale yellow solid which was chromatographed over SiO_2 eluting with 1% MeOH- CH_2Cl_2 to give 858 mg (70%) 5 as white solid. $^1\text{H-NMR}$ (CDCl_3 , 400 MHz): δ 1.72-1.76 (m, 2H), 2.22-2.30 (m, 1H), 3.48-3.60 (m, 4H), 7.09-7.11 (m, 1H), 7.11-7.28 (m, 1H), 7.89-7.92 (m, 1H); IR (KBr): 3492, 3043, 2216, 1760, 1602, 1478 cm^{-1} .

Preparation of 6: 6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one): N-cyano lactone 5 (1.23 g, 5 mmol) was heated with ethylene glycol (5 ml) and sodium hydroxide (0.82 g, 20.5 mmol) for 15-20 min at 130 °C. Most of the ethylene glycol was removed by distillation under high vacuum. The residual reaction mixture was diluted with water and extracted repeatedly with chloroform. The combined organics was dried and concentrated to give a semi solid material which was purified over Al₂O₃ column upon elution with 5-7% MeOH/CH₂Cl₂ containing NH₃ (aqueous) to yield 789 mg (60%) of CRI 1072 as pale yellow solid. ¹H-NMR (d₆-DMSO, 400 MHz): δ 1.47-1.50 (m, 2H), 2.03-2.10 (m, 2H), 2.79-2.85 (m, 2H), 2.95-2.97 (m, 2H), 3.73-3.76 (m, 2H), 4.12-4.14 (m, 2H), 7.09 (d, J = 8.4 Hz, 1H), 7.20 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H); ¹³C-NMR (d₆-DMSO, 100 MHz): δ 35.9, 42.3, 59.3, 70.4, 84.6, 106.4, 116.6, 117.0, 126.8, 156.9, 163.9, 168.5; FIA-MS: 264.3 (M + 1).

Example 13

1'-(2,3-Dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one:



15

Amide coupling according to general procedure 2:

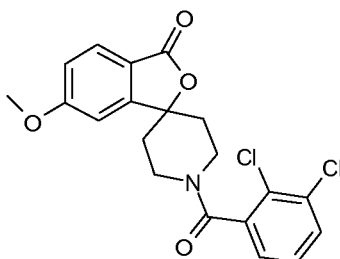
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in Journal of Organic Chemistry (1976), 41(15), 2628-33)

- Acid: 2,3-Dichloro-benzoic acid

20 ES-MS m/e (%): 376.4 (M+H⁺).

Example 14

1'-(2,3-Dichlorobenzoyl)-6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one

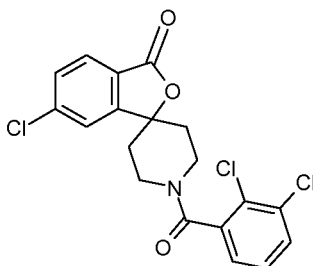


Amide coupling according to general procedure 2:

- Amine: 6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

- Acid: 2,3-Dichloro-benzoic acid
ES-MS m/e (%): 406.4 (M+H⁺).

5

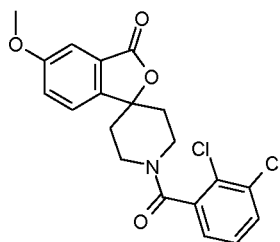
Example 15**6-Chloro-1'-(2,3-dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one**

Amide coupling according to general procedure 2:

- Amine: 6-chloro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

- Acid: 2,3-Dichloro-benzoic acid
ES-MS m/e (%): 410.2 (M+H⁺).

10

Example 16**1'-(2,3-Dichlorobenzoyl)-5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one**

15

Amide coupling according to general procedure 2:

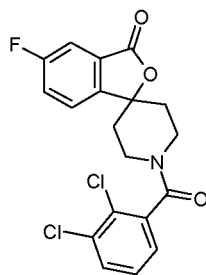
- Amine: 5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

- Acid: 2,3-Dichloro-benzoic acid
ES-MS m/e (%): 406.4 (M+H⁺).

20

Example 17**1'-(2,3-Dichlorobenzoyl)-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one**

- 37 -



Amide coupling according to general procedure 2:

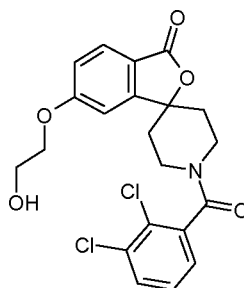
- Amine: 5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in WO 2001014376)

5 - Acid: 2,3-Dichloro-benzoic acid

ES-MS m/e (%): 394.3 (M+H⁺).

Example 18

1'-(2,3-Dichlorobenzoyl)-6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



10

Amide coupling according to general procedure 2:

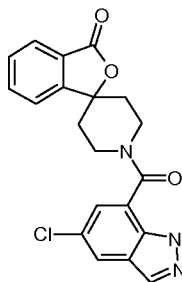
- Amine: 6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described herein)

- Acid: 2,3-Dichloro-benzoic acid

15 ES-MS m/e (%): 436.4 (M+H⁺).

Example 19

1'-[(5-Chloro-1H-indazol-7-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



Amide coupling according to general procedure 2:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in Journal of Organic Chemistry (1976), 41(15), 2628-33)

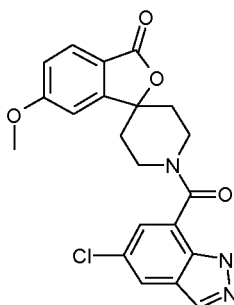
- Acid: 5-Chloro-1H-indazole-7-carboxylic acid (described in WO 2006013048)
ES-MS m/e (%): 382.4 (M+H⁺).

5

Example 20

1'-[(5-Chloro-1H-indazol-7-yl)carbonyl]-6-methoxy-3H-spiro[2-benzofuran-1,4'-
piperidin]-3-one

10



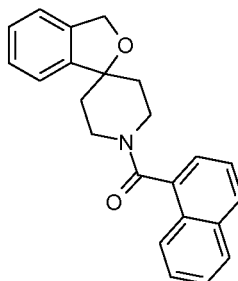
Amide coupling according to general procedure 2:

- Amine: 6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)

15 - Acid: 5-Chloro-1H-indazole-7-carboxylic acid (described in WO 2006013048)
ES-MS m/e (%): 412.4 (M+H⁺).

Example 21

1'-(1-Naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



20 Amide coupling according to general procedure 2:

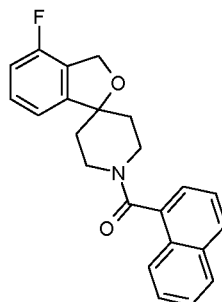
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

- Acid: Naphthalene-1-carboxylic acid

ES-MS m/e (%): 344.4 (M+H⁺).

Example 22

4-Fluoro-1'-(1-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidine]

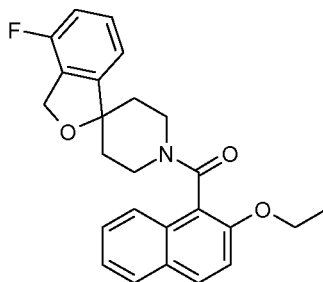


Amide coupling according to general procedure 2:

- 5 - Amine: 4-fluoro-3H-spiro[2-benzofuran-1,4'-piperidine]
(prepared according to Journal of Medicinal Chemistry (1995), 38(11), 2009-17)
- Acid: Naphthalene-1-carboxylic acid
ES-MS m/e (%): 362.3 (M+H⁺).

Example 23

1'-(2-Ethoxy-1-naphthoyl)-4-fluoro-3H-spiro[2-benzofuran-1,4'-piperidine]



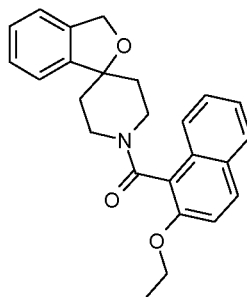
Amide coupling according to general procedure 2:

- Amine: 4-fluoro-3H-spiro[2-benzofuran-1,4'-piperidine] (prepared according to Journal of Medicinal Chemistry (1995), 38(11), 2009-17)
15 - Acid: 2-Ethoxynaphthalene-1-carboxylic acid (CAS 2224-00-2)
ES-MS m/e (%): 406.5 (M+H⁺).

Example 24

1'-(2-Ethoxy-1-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidine]

- 40 -



Amide coupling according to general procedure 2:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

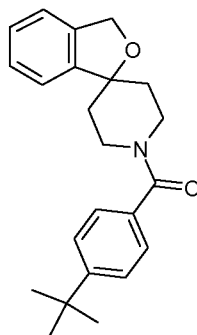
- Acid: 2-Ethoxynaphthalene-1-carboxylic acid (CA 2224-00-2)

5 ES-MS m/e (%): 388.3 (M+H⁺).

10

Example 25

1'-(4-tert-Butylbenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



Amide coupling according to general procedure 1:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

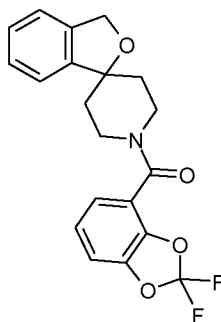
15 - Acid: 4-tert-Butyl-benzoyl chloride

ES-MS m/e (%): 350.5 (M+H⁺).

Example 26

1'-[(2,2-Difluoro-1,3-benzodioxol-4-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]

- 41 -



Amide coupling according to general procedure 1:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

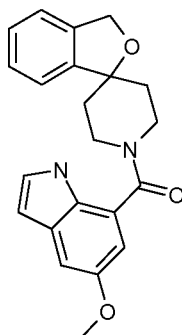
- Acid: 2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl chloride (CAS 143096-86-0)

5 ES-MS m/e (%): 374.4 (M+H⁺).

10

Example 27

15 1'-[(5-Methoxy-1H-indol-7-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



Amide coupling according to general procedure 2:

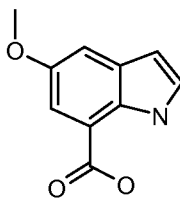
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

- Acid: 5-Methoxy-1H-indole-7-carboxylic acid (prepared herein)

20 ES-MS m/e (%): 363.5 (M+H⁺).

Preparation of 5-Methoxy-1H-indole-7-carboxylic acid:

- 42 -

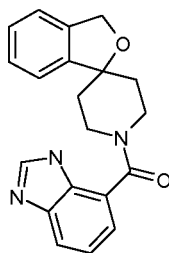


A solution of 7-Bromo-5-methoxy-1H-indole (described in WO 2002028861) in THF was treated with 2eq. of a solution of n-BuLi in n-hexane (1.6M) at 5° and after 30 min at this temperature was cooled to -75°. Dry ice (excess) was added and after 15 mins the mixture
 5 was quenched with H₂O and washed with EtOAc. After acidification of the aqueous layer and extraction into CH₂Cl₂, evaporation gave the desired product.

ES-MS m/e (%): 192.1 (M+H⁺).

Example 28

1'-(1H-Benzimidazol-7-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



10

Amide coupling according to general procedure 2:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

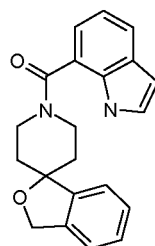
- Acid: 3H-Benzoimidazole-4-carboxylic acid (CAS 46006-36-4)

ES-MS m/e (%): 334.4 (M+H⁺).

15

Example 29

1'-(1H-Indol-7-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



Amide coupling according to general procedure 2:

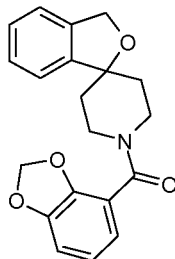
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

20 - Acid: 1H-Indole-7-carboxylic acid (CAS 1670-83-3)

ES-MS m/e (%): 333.5 ($M+H^+$).

Example 30

1'-(1,3-Benzodioxol-4-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]



5 Amide coupling according to general procedure 2:

- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

- Acid: Benzo[1,3]dioxole-4-carboxylic acid (CAS 5768-39-8)

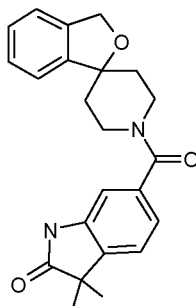
ES-MS m/e (%): 338.4 ($M+H^+$).

10

15

Example 31

3,3-Dimethyl-6-(1'H,3H-spiro[2-benzofuran-1,4'-piperidin]-1'-ylcarbonyl)-1,3-dihydro-2H-indol-2-one



20

Amide coupling according to general procedure 2:

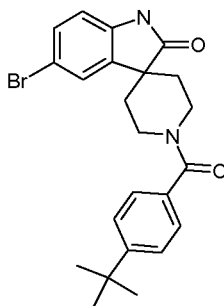
- Amine: 3H-spiro[2-benzofuran-1,4'-piperidine] (CAS 38309-60-3)

- Acid: 3,3-Dimethyl-2-oxo-2,3-dihydro-1H-indole-6-carboxylic acid (described in EP 344634)

ES-MS m/e (%): 377.5 (M+H⁺).

Example 32

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



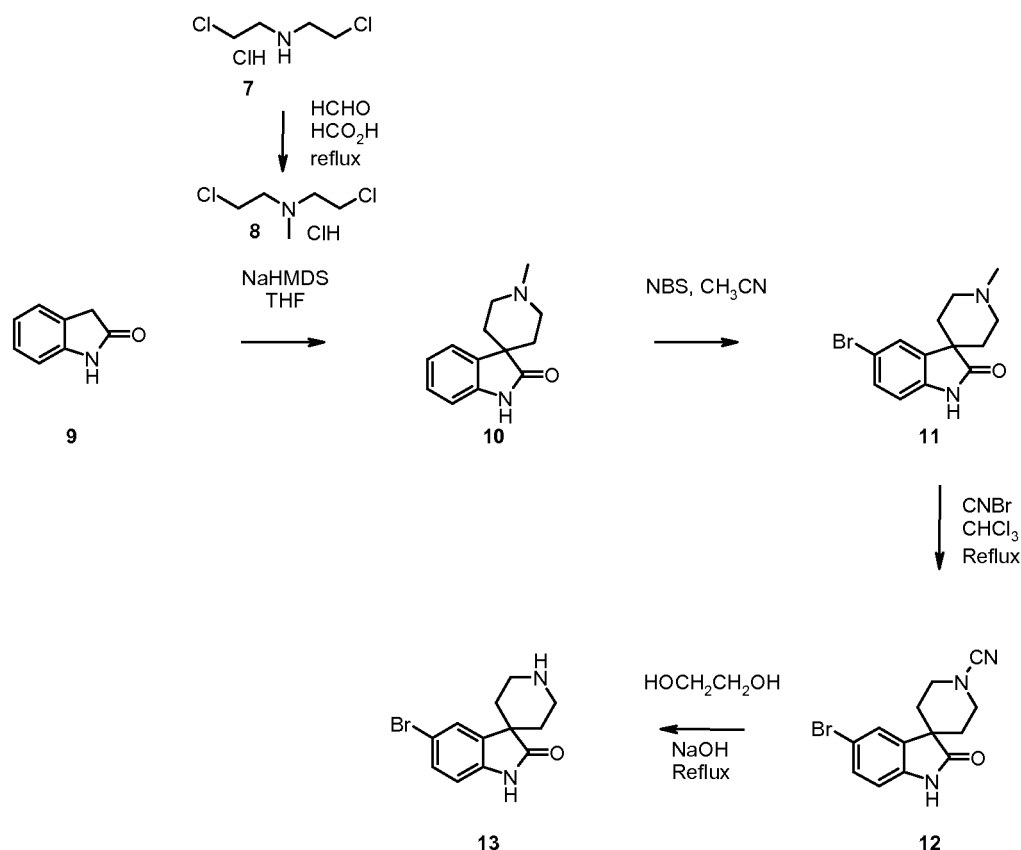
Amide coupling according to general procedure 2:

- Amine: 5-bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (preparation described herein)

- Acid: 4-tert-Butyl-benzoic acid

10 ES-MS m/e (%): 441.5 (M+H⁺).

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



1,5-Dichloro-3-methyl-3-azapentane, hydrochloride **8**: 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 100⁰ C. After 3 h the temperature was increased to 120⁰ C for 20 min and finally allowed to cool to room temperature before the solvent was evaporated in vacuo to afford **8** 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).

10 1'-(Methyl)spiro[indole-3,4'-piperidin]-2(1H)-one **10**:

A solution of oxindole **9** (6.25 g, 47 mmol) in THF (500 ml) was cooled to – 78⁰ 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 – 78⁰ 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 – 78⁰ 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 **10** 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'-(methyl)spiro[indole-3,4'-piperidin]-2(1H)-one (11):

A solution of 1'-(methyl)spiro[indole-3,4'-piperidin]-2(1H)-one (6.3 g, 29.1 mmol) in CH₃CN (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 0⁰C. Solvent was removed by vacuo. The residue was purified by silica gel chromatography (2 – 20 % MeOH/CH₂Cl₂) to give 6 g as a solid. The solid compound was dissolved in ethyl acetate (600 ml) and washed with saturated aqueous NaHCO₃ solution, dried (Na₂SO₄). Evaporation of the solvent in vacuo gave 4.2 g (47%) of 11. 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'-(cyano)spiro[indole-3,4'-piperidin]-2(1H)-one (12):

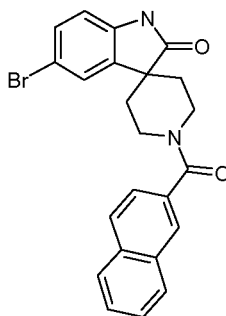
5-bromo-1'-(methyl)spiro[indole-3,4'-piperidin]-2(1H)-one 11 (4.6 g, 15.6 mmol) was dissolved in chloroform (700 ml) and treated with CNBr (22 g, 209.5 mmol) at room temperature. The mixture was heated to reflux for 24h. The reaction mixture was cooled, diluted with methylene chloride (300 ml) and washed with 10 % aqueous K₂CO₃ solution (2 x 100 ml). After the mixture was dried (Na₂SO₄) and concentrated, the residue was purified by silica gel chromatography (0 – 5% MeOH/CH₂Cl₂) to gave 7 as a solid 3.9 g (82%). ¹HNMR (CDCl₃, 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, 2H).

5-bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (13):

5-Bromo-1, 2-dihydro-2-oxospiro [3H-indole-3, 4'-piperidine]-1'-cyano 12 (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 130⁰ C for 15 min. It was diluted with methylene chloride (500 ml) and washed with 10% aqueous K₂CO₃ (2 x 100 m). The organic layer was dried (Na₂SO₄) and concentrated and residue purified by silica gel chromatography (30% MeOH/CH₂Cl₂) to gave 13 as a light ceramic white solid 1.8 g (60%), mp 256 – 258⁰ C. ¹HNMR (DMSO-d₆, 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), ¹³C NMR (DMSO-d₆, 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 C₁₂H₁₃BrN₂O: C, 51.26; H, 4.66; N, 9.9. Found: C, 50.87; H, 4.91; N, 9.67.

Example 33

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



5

Amide coupling according to general procedure 2:

- Amine: 5-bromo-spiro[indole-3,4'-piperidin]-2(1H)-one (preparation described herein)

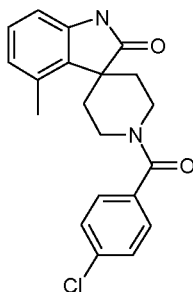
- Acid: Naphthalene-2-carboxylic acid

ES-MS m/e (%): 435.4 (M+H⁺).

10

Example 34

1'-(4-Chlorobenzoyl)-4-methylspiro[indole-3,4'-piperidin]-2(1H)-one



Amide coupling according to general procedure 2:

15 - Amine: 4-methylspiro[indole-3,4'-piperidin]-2(1H)-one (preparation in analogy to 5-bromo-spiro[indole-3,4'-piperidin]-2(1H)-one starting from 1,5-Dichloro-3-methyl-3-azapentane, hydrochloride

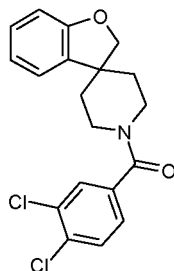
- Acid: 4-Chloro-benzoic acid

ES-MS m/e (%): 355.4 (M+H⁺).

20

Example 35

5 1'-(3,4-Dichlorobenzoyl)spiro[1-benzofuran-3,4'-piperidine]



Amide coupling according to general procedure 2:

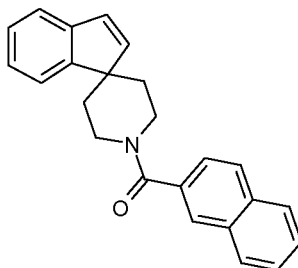
- Amine: Spiro[1-benzofuran-3,4'-piperidine] (CAS 38309-60-3)

- Acid: 3,4-Dichloro-benzoic acid

10 ES-MS m/e (%): 362.4 (M+H⁺).

Example 36

1'-(2-Naphthoyl)spiro[indene-1,4'-piperidine]



Amide coupling according to general procedure 2:

15 - Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

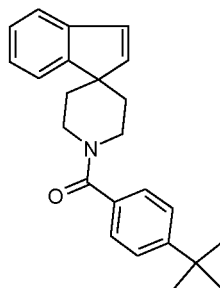
- Acid: Naphthalene-2-carboxylic acid

ES-MS m/e (%): 340.5 (M+H⁺).

Example 37

1'-(4-tert-Butylbenzoyl)spiro[indene-1,4'-piperidine]

- 49 -



Amide coupling according to general procedure 2:

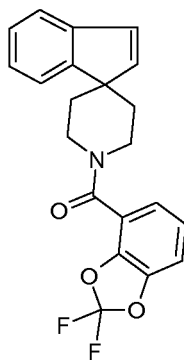
- Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

- Acid: 4-tert-Butyl-benzoic acid

5 ES-MS m/e (%): 346.5 (M+H⁺).

Example 38

1'-[(2,2-Difluoro-1,3-benzodioxol-4-yl)carbonyl]spiro[indene-1,4'-piperidine]



10 Amide coupling according to general procedure 2:

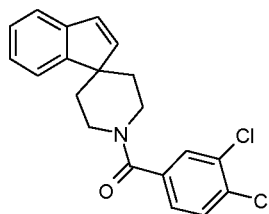
- Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

- Acid: 2,2-Difluoro-benzo[1,3]dioxole-4-carbonyl chloride (CAS 143096-86-0)

ES-MS m/e (%): 370.4 (M+H⁺).

Example 39

15 1'-(3,4-Dichlorobenzoyl)spiro[indene-1,4'-piperidine]



Amide coupling according to general procedure 2:

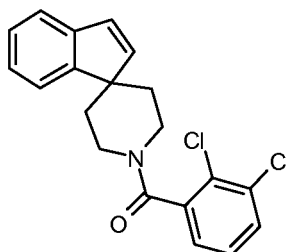
- Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

- Acid: 3,4-Dichloro-benzoic acid

ES-MS m/e (%): 358.4 (M+H⁺).

Example 40

1'-(2,3-Dichlorobenzoyl)spiro[indene-1,4'-piperidine]



5

Amide coupling according to general procedure 2:

- Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

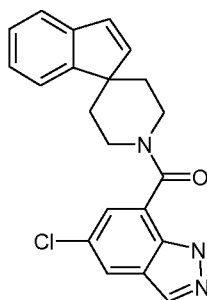
- Acid: 2,3-Dichloro-benzoic acid

ES-MS m/e (%): 358.4 (M+H⁺).

10

Example 41

1'-[(5-Chloro-1H-indazol-7-yl)carbonyl]spiro[indene-1,4'-piperidine]



Amide coupling according to general procedure 2:

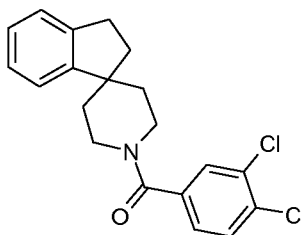
- Amine: Spiro[indene-1,4'-piperidine] (CAS 33042-66-9)

15 - Acid: 5-Chloro-1H-indazole-7-carboxylic acid (described in WO 2006013048)

ES-MS m/e (%): 364.4 (M+H⁺).

Example 42

1'-(3,4-Dichlorobenzoyl)-2,3-dihydrospiro[indene-1,4'-piperidine]



Amide coupling according to general procedure 2:

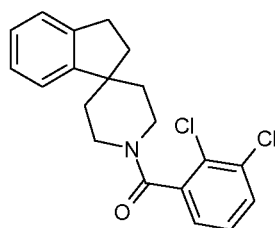
- Amine: 2,3-Dihydrospiro[indene-1,4'-piperidine] (CAS 428-38-6)

- Acid: 3,4-Dichloro-benzoic acid

5 ES-MS m/e (%): 360.4 ($M+H^+$).

Example 43

1'-(2,3-Dichlorobenzoyl)-2,3-dihydrospiro[indene-1,4'-piperidine]



Amide coupling according to general procedure 2:

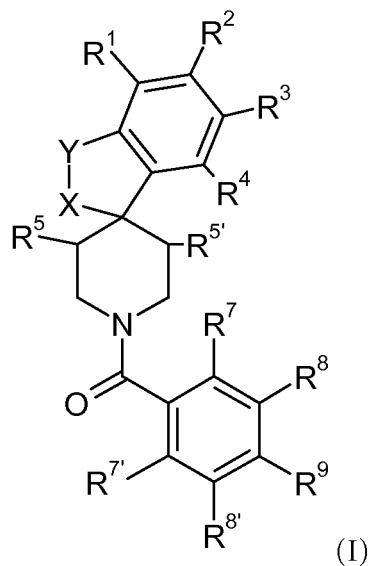
10 - Amine: 2,3-Dihydrospiro[indene-1,4'-piperidine] (CAS 428-38-6)

- Acid: 2,3-Dichloro-benzoic acid

ES-MS m/e (%): 360.4 ($M+H^+$).

Claims

1. A compound of the general formula (I)



wherein

- 5 X is O and Y is C=O,
 X is O and Y is CH₂,
 X is C=O and Y is NR⁶,
 X is CH₂ and Y is O, or
 X-Y is CH=CH, or
 10 X-Y is CH₂-CH₂, or
 X is C=O and Y is O, or
 X is CH₂ and Y is NR⁶;

R¹, R², R³ and R⁴ are each independently
 hydrogen,

- 15 halo,
 C₁₋₆-alkyl, optionally substituted by OH,
 halo-C₁₋₆-alkyl,
 C₁₋₆-alkoxy, optionally substituted by OH, or
 halo-C₁₋₆-alkoxy;

- 20 R⁵ and R^{5'} are each independently hydrogen or methyl;

R⁶ is hydrogen or C₁₋₆-alkyl;

R⁷, R^{7'}, R⁸, R^{8'}, and R⁹ are each independently selected from

- hydrogen,
halo,
halo-C₁₋₆-alkyl,
C₁₋₆-alkyl,
5 C₁₋₆-alkoxy,
halo-C₁₋₆-alkoxy,
nitro, or
cyano,
or R⁷ and R⁸, R^{7'} and R^{8'}, R⁸ and R⁹, or R^{8'} and R⁹ are bound together to form a ring
10 with the phenyl moiety, wherein
-R⁷-R⁸- or -R^{7'}-R^{8'}- is
-N(R¹⁰)-N=CH- , or -CH=N-N(R¹⁰)-,
wherein R¹⁰ is hydrogen, or C₁₋₆-alkyl,
-N(R¹¹)-CH=CH- , or -CH=CH-N(R¹²)-,
15 wherein R¹¹ is hydrogen, or C₁₋₆-alkyl,
-C(R¹²)=C(R¹³)-C(R¹⁴)=C(R¹⁵)-,
wherein R¹², R¹³, R¹⁴, and R¹⁵ are each independently selected from
hydrogen, halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy,
halo-C₁₋₆-alkoxy, nitro, or cyano,
20 -O-(CR¹⁶R^{16'})_n-O-,
wherein n is 1 or 2, and R¹⁶ and R^{16'} are each independently
hydrogen, halo or C₁₋₆-alkyl,
-N(R¹⁷)-CH=N- , or -N=CH-N(R¹⁷)-,
wherein R¹⁷ is hydrogen, or C₁₋₆-alkyl, or
25 -N(R¹⁸)-C(O)-CH₂- , or -CH₂-C(O)-N(R¹⁸)-,
wherein R¹⁸ is hydrogen or C₁₋₆-alkyl,
or a pharmaceutically acceptable salt thereof.

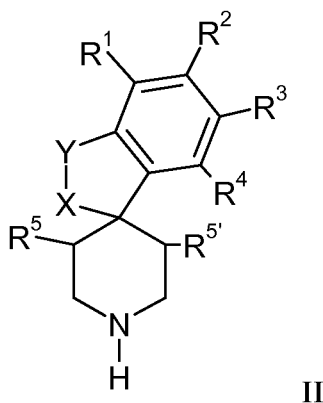
2. The compound of formula (I) according to claim 1, wherein
30 R¹, R², R³ and R⁴ are each independently
hydrogen,
halo,
C₁₋₆-alkyl, or
C₁₋₆-alkoxy, optionally substituted by OH.

3. The compound of formula (I) according to claim 1 or 2, wherein R^7 and $R^{7'}$ are each independently hydrogen, or halo.
- 5 4. The compound of formula (I) according to any one of claims 1 to 3, wherein R^8 and $R^{8'}$ are each independently hydrogen, halo, or C_{1-6} -alkoxy.
5. The compound of formula (I) according to any one of claims 1 to 4, wherein R^7 and R^8 or $R^{7'}$ and $R^{8'}$ are bound together to form a ring with the phenyl moiety, wherein
- 10 $-R^7-R^8-$ or $-R^{7'}-R^{8'}-$ is
- $-N(R^{10})-N=CH-$, or $-CH=N-N(R^{10})-$,
 wherein R^{10} is hydrogen, or C_{1-6} -alkyl,
 $-N(R^{11})-CH=CH-$, or $-CH=CH-N(R^{12})-$,
 wherein R^{11} is hydrogen, or C_{1-6} -alkyl,
- 15 $-C(R^{12})=C(R^{13})-C(R^{14})=C(R^{15})-$,
 wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from
 hydrogen, halo, halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy, nitro, or cyano,
 $-O-(CR^{16}R^{16'})_n-O-$,
- 20 wherein n is 1 or 2, and R^{16} and $R^{16'}$ are each independently
 hydrogen, halo or C_{1-6} -alkyl, or
 $-N(R^{17})-CH=N-$, or $-N=CH-N(R^{17})-$,
 wherein R^{17} is hydrogen, or C_{1-6} -alkyl.
- 25 6. The compound of formula (I) according to any one of claims 1 to 5, wherein R^9 is hydrogen, halo, or C_{1-6} -alkyl.
7. The compound of formula (I) according to any one of claims 1 to 6, wherein R^8 and R^9 or $R^{8'}$ and R^9 are bound together to form a ring with the phenyl moiety, wherein
- 30 $-R^8-R^9-$ or $-R^{8'}-R^9-$ is
- $-C(R^{12})=C(R^{13})-C(R^{14})=C(R^{15})-$,
 wherein R^{12} , R^{13} , R^{14} , and R^{15} are each independently selected from
 hydrogen, halo, halo- C_{1-6} -alkyl, C_{1-6} -alkyl, C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy, nitro, or cyano,

$-N(R^{18})-C(O)-CH_2-$, or $-CH_2-C(O)-N(R^{18})-$,
 wherein R^{18} is hydrogen or C_{1-6} -alkyl.

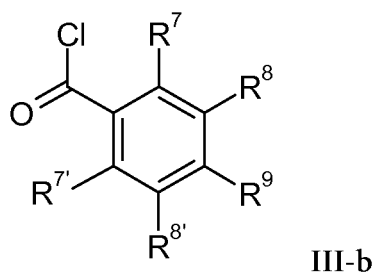
8. The compound of formula (I), which is selected from
- 5 6-Methoxy-1'-(2-naphthoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 1'-(3,4-Dichlorobenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 1'-(3,4-Dichlorobenzoyl)-6-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 1'-(3,4-Dichlorobenzoyl)-5-methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 1'-(3,4-Dichlorobenzoyl)-5-fluoro-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 10 1'-(3,4-Dichlorobenzoyl)-6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
 1'-(4-tert-Butylbenzoyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
 1'-[(5-Methoxy-1H-indol-7-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
 5-Bromo-1'-(2-naphthoyl)spiro[indole-3,4'-piperidin]-2(1H)-one,
 15 1'-(2-Naphthoyl)spiro[indene-1,4'-piperidine], or
 1'-(3,4-Dichlorobenzoyl)-2,3-dihydrospiro[indene-1,4'-piperidine].

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



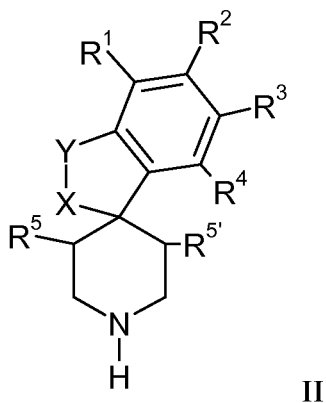
20

with an acid chloride of formula (III-b)

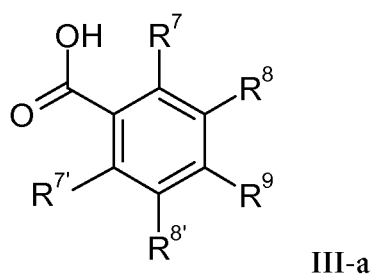


to obtain the compound of formula (I) wherein R^1 to R^{10} and X and Y are as defined in claim 1.

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



with an acid of formula (III-a)



- 10 to obtain the compound of formula (I) wherein R^1 to R^{10} and X and Y are as defined above.

11. A compound formula (I) obtainable by a process according to any one of claims 9 and 10.

- 15 12. A compound of formula (I) according to any one of claims 1 to 8 for 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.

13. A pharmaceutical composition comprising a compound of formula (I)
5 according to any one of claims 1 to 8.

14. A pharmaceutical composition according to claim 13, wherein it is useful
against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of
vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety
10 and depressive disorders.

15 Use of a compound of formula (I), according to any one of claims 1 to 8 for the
preparation of a medicament.

15 16. Use according to claim 15, 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 17. The invention as described herein above.