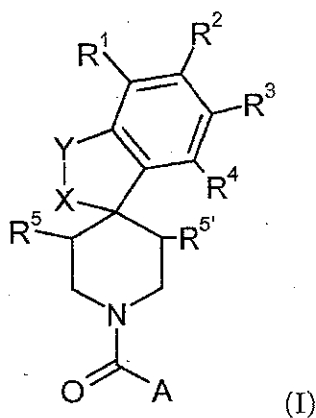


SPIRO-PIPERIDINE DERIVATIVES

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.

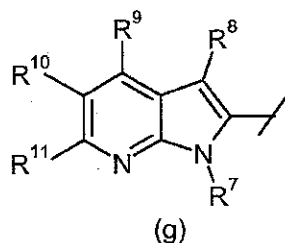
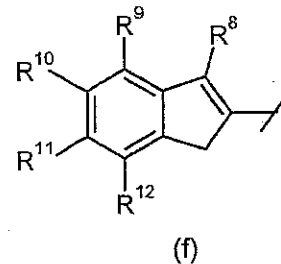
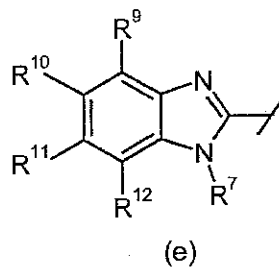
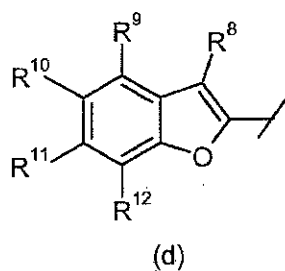
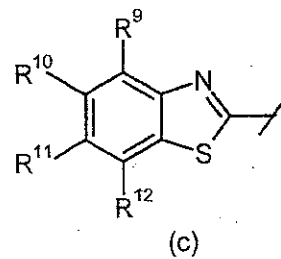
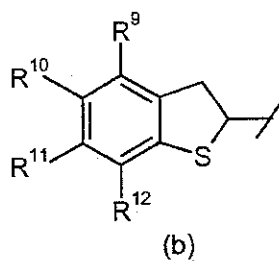
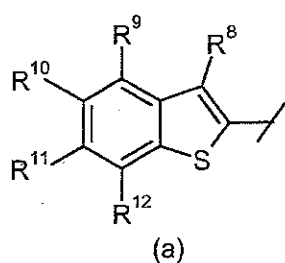
- 5 In particular, the present invention is concerned with compounds of the general formula (I)



wherein

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

A is selected from the group consisting of



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

hydrogen,

halo,

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

halo- C_{1-6} -alkyl,

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

halo- C_{1-6} -alkoxy;

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

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

R^7 is hydrogen,

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

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

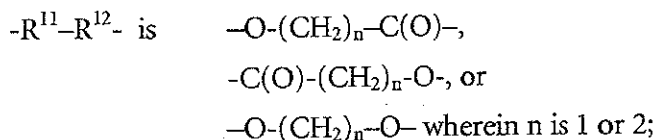
R^8 is hydrogen,

15 C_{1-6} -alkyl,

C_{1-6} -alkoxy,

- $-(C_{1-6}\text{-alkylene})-NR^cR^d$,
 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 benzyl, 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
 5 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;
 R^9 is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 R^{10} 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;
 10 R^{11} is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 or R^{10} and R^{11} are bound together to form a ring with the benzo moiety, wherein
 $-R^{10}-R^{11}-$ is $-O-(CH_2)_n-O-$ wherein n is 1 or 2;
 R^{12} is hydrogen,
 C_{1-6} -alkyl, optionally substituted by CN or OH,
 15 $-(C_{1-6}\text{-alkylene})-NR^gR^h$,
 $-(C_{1-6}\text{-alkylene})-C(O)-NR^iR^j$
 $-O$ -benzyl, 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,
 nitro,
 20 halo,
 cyano,
 C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy,
 halo- C_{1-6} -alkyl,
 25 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 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,
 $-(C_{1-3}\text{-alkylene})-R^m$,
 wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered
 30 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
 $-NR^nR^o$;

or R^{11} and R^{12} are bound together to form a ring with the benzo moiety, wherein



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

hydrogen,

C_{1-6} -alkyl,

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

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

10 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, R^h, R^n and R^o are each independently

hydrogen,

15 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

20 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^n and R^o 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;

25 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,

30 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.

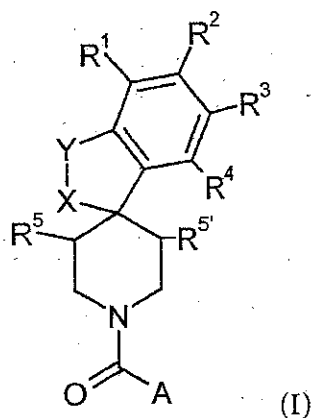
In the periphery vasopressin acts as a neurohormone and stimulates vasoconstriction, glycogenolysis and antidiuresis. In the brain vasopressin acts as a neuromodulator and is elevated in the amygdala during stress (Ebner, K., C. T. Wotjak, et al. (2002). "Forced swimming triggers vasopressin release 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 embodiments disclosed herein 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 disclosure are the treatment of anxiety and depressive disorders.

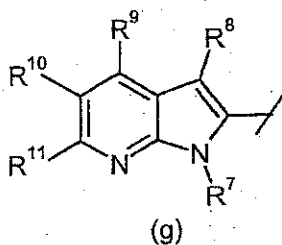
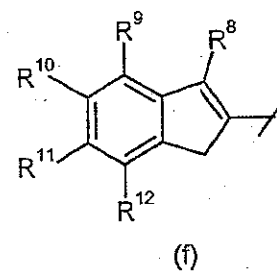
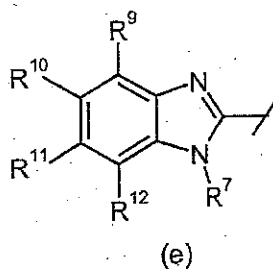
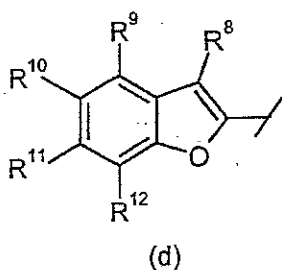
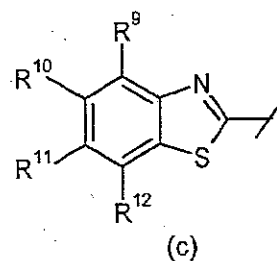
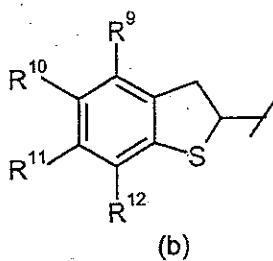
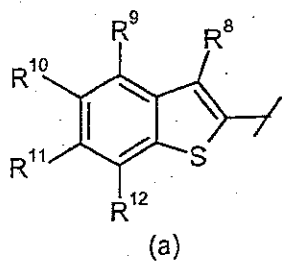
In a first aspect, there is provided a compound of the general formula (I)



wherein

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

A is selected from the group consisting of



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

hydrogen,

halo,

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

halo- C_{1-6} -alkyl,

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

halo- C_{1-6} alkoxy;

R^5 and R^5 are each independently hydrogen or methyl;

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

R^7 is hydrogen,

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

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

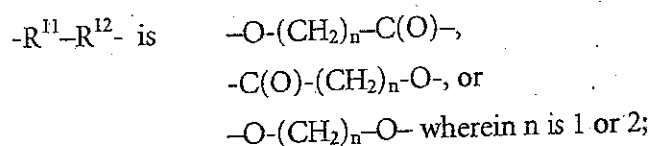
R^8 is hydrogen,

15 C_{1-6} -alkyl,

C_{1-6} -alkoxy,

- $-(C_{1-6}\text{-alkylene})-NR^eR^d$,
 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 benzyl, 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
 5 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;
 R^9 is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 R^{10} 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;
 10 R^{11} is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 or R^{10} and R^{11} are bound together to form a ring with the benzo moiety, wherein
 $-R^{10}-R^{11}-$ is $-O-(CH_2)_n-O-$ wherein n is 1 or 2;
 R^{12} is hydrogen,
 C_{1-6} -alkyl, optionally substituted by CN or OH,
 15 $-(C_{1-6}\text{-alkylene})-NR^gR^h$,
 $-(C_{1-6}\text{-alkylene})-C(O)-NR^iR^j$
 $-O$ -benzyl, 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,
 nitro,
 20 halo,
 cyano,
 C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy,
 halo- C_{1-6} -alkyl,
 25 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 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,
 $-(C_{1-3}\text{-alkylene})-R^m$,
 wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered
 30 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
 $-NR^nR^o$;

or R¹¹ and R¹² are bound together to form a ring with the benzo moiety, wherein



5 R^a, R^b, Rⁱ and R^j are each independently

hydrogen,

C₁₋₆-alkyl,

-(C₁₋₆-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C₁₋₆-alkyl,

10 or R^a and R^b, or Rⁱ 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, R^h, Rⁿ and R^o are each independently

hydrogen,

15 C₁₋₆-alkyl,

-C(O)R^e, or -S(O)₂R^e

wherein R^e is selected from the group of

hydrogen,

C₁₋₆-alkyl, and

20 phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,

C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

or R^c and R^d, or Rⁿ and R^o 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;

25 R^f is selected from the group of

hydrogen,

C₁₋₆-alkyl,

C₁₋₆-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

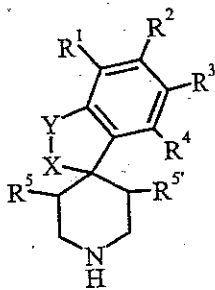
30 C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

or a pharmaceutically acceptable salt thereof.

In a second aspect, there is provided the compound of formula (I), which is selected from

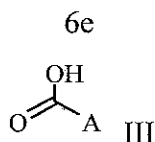
1'-[(1-Benzothien-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
 1'-[(7-Methoxy-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
 1'-[(5-Methoxy-2,3-dihydro-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
 1'-[(5-Bromo-7-ethyl-1-benzofuran-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
 1'-[(5-Chloro-1H-benzimidazol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
 (1RS,3'SR)-3'-Methyl-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one, or
 6-Methoxy-1'-[(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one.

In a third aspect, there is provided a process for the preparation of compounds of formula (I) as defined above, comprising the step of reacting a compound of formula (II):



II

with a carboxylic acid of the formula III



wherein R¹ to R^{5'}, X, Y and A are as defined above.

In a fourth aspect, there is provided a compound of formula (I) as defined above 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.

In a fifth aspect, there is provided a pharmaceutical composition comprising a compound of formula (I), as defined above.

In a sixth aspect, there is provided the use of a compound of formula (I), as defined above for the preparation of a medicament for the treatment of a disease selected from the group consisting of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, 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 and the isomeric pentyls. 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 and 2-methylpropylene.

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 and *sec*-butoxy. 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 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.

5 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-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 methyl, ethyl, propyl,
10 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
15 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
20 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
25 below.

The term "5 or 6 membered heteroaryl" means a monovalent 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
30 independently be selected from the group consisting of hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, C₁₋₆-thioalkyl, halo, cyano, nitro, halo-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl, C₁₋₆-alkoxycarbonyl, amino, C₁₋₆-alkylamino, di(C₁₋₆)alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Preferred substituents are halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, hydroxy or cyano. Examples of heteroaryl moieties

include pyrrolyl, pyrazolyl, imidazolyl, furanyl (synonymous to furyl), thiophenyl (synonymous to thienyl), oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, each of which is optionally substituted as described herein.

- 5 The term "heterocycloalkyl" means a monovalent saturated ring, consisting of one ring of 3 to 7, preferably from 4 to 6 atoms as ring members, including one, two, or three heteroatoms chosen from nitrogen, oxygen or sulfur, the rest being carbon atoms. 3 to 7 membered heterocycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, C₁₋₆-alkyl, C₁₋₆-alkoxy, 10 C₁₋₆-thioalkyl, halo, cyano, nitro, halo-C₁₋₆-alkyl, C₁₋₆-hydroxyalkyl, C₁₋₆-alkoxycarbonyl, amino, C₁₋₆-alkylamino, di(C₁₋₆)alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Preferred substituents are halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, hydroxy or cyano. Examples of heterocyclic moieties include oxiranyl, thiiranyl, oxetanyl, tetrahydro-furanyl, tetrahydro-thiophenyl 15 (synonymous to tetrahydro-thienyl), pyrrolidinyl, pyrazolidinyl, imidazolidinyl, oxazolidinyl, isoxazolidinyl, thiazolidinyl, isothiazolidinyl, piperidinyl, piperazinyl, morpholinyl, or tetrahydropyranyl, each of which is optionally substituted as described herein.

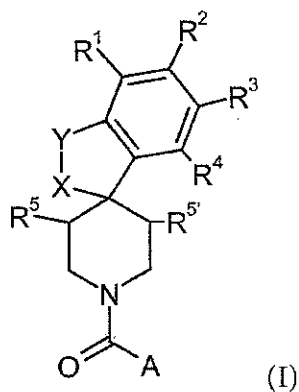
- The term "heterocycle" in the definition "R^a and R^b, R^c and R^d, Rⁱ and R^j, or Rⁿ and R^o, together with the nitrogen to which they are bound form a five- or six-membered 20 heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur" means either heterocycloalkyl 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-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano. Preferred heterocycles are 25 optionally substituted piperazine, N-methylpiperazine, morpholin, piperidine and pyrrolidine.

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

- The term "pharmaceutically acceptable acid addition salts" embraces salts with 30 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 and p-toluenesulfonic acid.

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

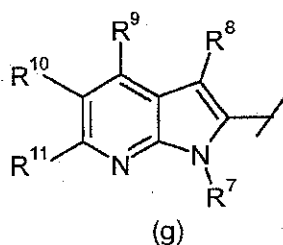
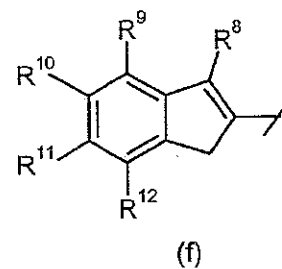
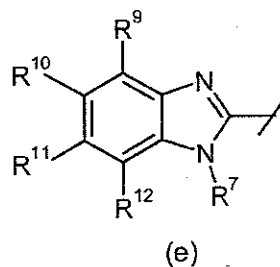
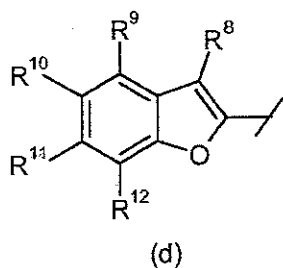
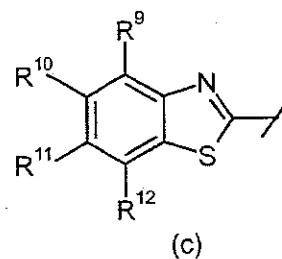
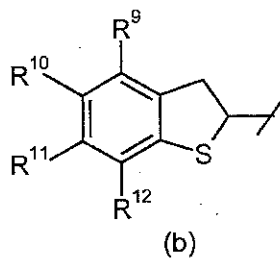
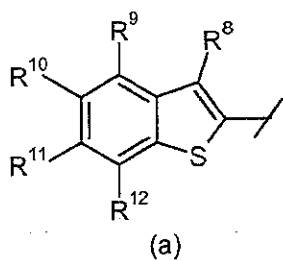
In detail, the present invention relates to compounds of the general formula (I)



wherein

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

A is selected from the group consisting of



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

hydrogen,

halo,

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

halo- C_{1-6} -alkyl,

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

halo- C_{1-6} alkoxy;

R^5 and R^5 are each independently hydrogen or methyl;

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

R^7 is hydrogen,

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

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

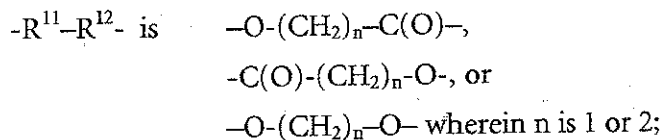
R^8 is hydrogen,

15 C_{1-6} -alkyl,

C_{1-6} -alkoxy,

- $-(C_{1-6}\text{-alkylene})-NR^cR^d$,
 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 benzyl, 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
 5 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;
 R^9 is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 R^{10} 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;
 10 R^{11} is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 or R^{10} and R^{11} are bound together to form a ring with the benzo moiety, wherein
 $-R^{10}-R^{11}-$ is $-O-(CH_2)_n-O-$ wherein n is 1 or 2;
 R^{12} is hydrogen,
 C_{1-6} -alkyl, optionally substituted by CN or OH,
 15 $-(C_{1-6}\text{-alkylene})-NR^gR^h$,
 $-(C_{1-6}\text{-alkylene})-C(O)-NR^iR^j$
 $-O$ -benzyl, 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,
 nitro,
 20 halo,
 cyano,
 C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy,
 halo- C_{1-6} -alkyl,
 25 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 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,
 $-(C_{1-3}\text{-alkylene})-R^m$,
 wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered
 30 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
 $-NR^nR^o$;

or R¹¹ and R¹² are bound together to form a ring with the benzo moiety, wherein



5 R^a, R^b, Rⁱ and R^j are each independently

hydrogen,

C₁₋₆-alkyl,

-(C₁₋₆-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C₁₋₆-alkyl,

10 or R^a and R^b, or Rⁱ 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, R^h, Rⁿ and R^o are each independently

hydrogen,

15 C₁₋₆-alkyl,

-C(O)R^e, or -S(O)₂R^e

wherein R^e is selected from the group of

hydrogen,

C₁₋₆-alkyl, and

20 phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

or R^c and R^d, or Rⁿ and R^o 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;

25 R^f is selected from

hydrogen,

C₁₋₆-alkyl,

C₁₋₆-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

30 C₁₋₆-alkoxy, halo-C₁₋₆-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, Rⁱ and R^j, or Rⁿ and R^o together with the nitrogen to which they are bound may form piperazine, 4-(C₁₋₆-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^n and R^o together with the nitrogen to which they are bound may form 4-methylpiperazine, or morpholine, in particular morpholine.

In certain embodiments of the invention, wherein R^m is a 5- to 6-membered
5 heteroaryl, the preferred heteroaryl is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, imidazole, pyrazole, oxazole, and isoxazole. All these residues are optionally substituted as described herein.

In embodiments of the invention, wherein R^m is a 4- to 6-membered
10 heterocycloalkyl, the preferred heterocycloalkyl is selected from the group consisting of pyrrolidine, oxethane, tetrahydropyran, piperidine, morpholine, and piperazine. All these residues are optionally substituted as described herein.

In certain embodiments of the invention,

R^1 , R^2 , R^3 and R^4 are each independently
15 hydrogen,
halo, or
 C_{1-6} -alkoxy, optionally substituted by OH.

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

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.

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.

25 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.

In certain embodiments of the invention, R⁶ is hydrogen or C₁₋₆-alkyl, preferably hydrogen.

In certain embodiments of the invention,

R⁷ is hydrogen,

5 C₁₋₆-alkyl, optionally substituted by CN or OH, or
-(C₁₋₆-alkylene)-C(O)-NR^aR^b,

wherein R^a and R^b are each independently hydrogen or C₁₋₆-alkyl.

Preferably, R⁷ is hydrogen.

In certain embodiments of the invention,

10 R⁸ is hydrogen,

C₁₋₆-alkyl, or

C₁₋₆-alkoxy,

-(C₁₋₆-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently

15 hydrogen,

-C(O)R^e, or -S(O)₂R^e

wherein R^e is selected from the group of

hydrogen,

C₁₋₆-alkyl, or

20 phenyl, optionally substituted by one or more halo,

halo-C₁₋₆-alkyl, C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano,

-(C₁₋₆-alkylene)-C(O)R^f,

wherein R^f is

25 hydrogen,

C₁₋₆-alkyl,

C₁₋₆-alkoxy, or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,

C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

30 benzyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano, or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano.

Preferably, R^8 is hydrogen; C_{1-6} -alkyl, preferably methyl; or C_{1-6} -alkoxy, preferably methoxy or $-O$ -*iso*-propyl.

In a certain embodiment of the invention, R^9 is hydrogen, halo or C_{1-6} -alkoxy. Preferably, R^9 is hydrogen or C_{1-6} -alkoxy.

- 5 In certain embodiments of the invention, R^9 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^{10} is hydrogen; halo, preferably bromo or chloro; C_{1-6} -alkyl, preferably methyl; or C_{1-6} -alkoxy, preferably methoxy.

- 10 In certain embodiments of the invention, R^{11} is hydrogen; halo, preferably bromo or chloro; C_{1-6} -alkyl, preferably methyl; or C_{1-6} -alkoxy, preferably methoxy. More preferably, R^{11} is hydrogen.

In certain embodiments of the invention
 R^{12} is hydrogen,

- 15 C_{1-6} -alkyl, optionally substituted by CN or OH,
 $-(C_{1-6}\text{-alkylene})-NR^gR^h$, wherein 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
20 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;
 $-(C_{1-6}\text{-alkylene})-C(O)-NR^iR^j$, wherein R^i and R^j are each independently
25 hydrogen,
 C_{1-6} -alkyl,
 $-(C_{1-6}\text{-alkylene})-NR^kR^l$,
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
30 five or six membered heterocycle comprising one or two heteroatoms
selected from the group of nitrogen, oxygen and sulfur;

-O-benzyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano,

nitro,

halo,

5 cyano,

C₁₋₆-alkoxy,

halo-C₁₋₆-alkoxy,

halo-C₁₋₆-alkyl,

-(C₁₋₆-alkylene)-C(O)R^f, wherein R^f is

10 C₁₋₆-alkyl,

C₁₋₆-alkoxy, or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,

C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano,

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

15 C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano,

-(C₁₋₃-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-C₁₋₆-alkyl,

20 C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano, or

-NRⁿR^o,

wherein Rⁿ and R^o are each independently

hydrogen,

C₁₋₆-alkyl,

25 or Rⁿ and R^o 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.

In certain embodiments of the invention,

R¹² is hydrogen,

30 C₁₋₆-alkyl, optionally substituted by CN or OH,

C₁₋₆-alkoxy, or

-NRⁿR^o,

wherein Rⁿ and R^o are each independently

hydrogen,

C₁₋₆-alkyl,

or Rⁿ and R^o 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.

5 In certain embodiments of the invention, namely in combination with any embodiment described herein, R⁷, R⁸, R⁹, R¹⁰, R¹¹ and R¹² are not simultaneously hydrogen.

In certain embodiments of the invention, X is O and Y is CH₂, A is selected from the group consisting of (a), (b), (c), (d) and (e); and R¹ to R⁵ and R⁷ to R¹² are as defined above.

10 In certain embodiments of the invention, X is O and Y is C=O, A is (f) or (g), and R¹ to R⁵ and R⁷ to R¹² are as defined above.

In certain embodiments of the invention, X is C=O and Y is NR⁶, A is (f), and R¹ to R¹² are as defined above.

15 In certain embodiments of the invention, X-Y is CH=CH, and A is (f) or (g), and R¹ to R⁵ and R⁷ to R¹² are as defined above.

Preferred X and Y are:

X is O and Y is CH₂, or

X is O and Y is C=O, or

20 X is C=O and Y is NR⁶, or

X-Y is CH=CH, or

X-Y is CH₂-CH₂.

Preferred compounds of the invention are:

25 1'-(1-Benzothien-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],

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

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

1'-[(5-Methoxy-2,3-dihydro-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],

30 1'-[(4-Methoxy-7-morpholin-4-yl-1,3-benzothiazol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],

- 1'-[(5-Bromo-7-ethyl-1-benzofuran-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-(1H-Benzimidazol-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(5-Methyl-1H-benzimidazol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(5-Chloro-1H-benzimidazol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
5 (1RS,3'SR)-3'-Methyl-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-
piperidin]-3-one,
6-Methoxy-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-
3-one,
5-Methoxy-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-
10 3-one,
1'-(1H-Pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one,
6-Methoxy-1'-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-
piperidin]-3-one,
6-(2-Hydroxyethoxy)-1'-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-
15 1,4'-piperidin]-3-one,
5-Bromo-1'-[(3-methyl-1H-inden-2-yl)carbonyl]spiro[indole-3,4'-piperidin]-2(1H)-one,
1'-[(3-Methyl-1H-inden-2-yl)carbonyl]spiro[indene-1,4'-piperidine], or
1'-(1H-Pyrrolo[2,3-b]pyridin-2-ylcarbonyl)spiro[indene-1,4'-piperidine].

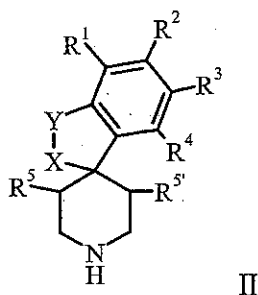
The invention also encompasses the compounds of formula (I) for a use in the
20 prevention or treatment of dysmenorrhea, hypertension, chronic heart failure, inappropriate
secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive
disorder, anxiety and depressive disorders.

The invention also encompasses a pharmaceutical composition comprising a
compound of formula (I), which pharmaceutical composition is useful against
25 dysmenorrhea, hypertension, chronic heart failure,

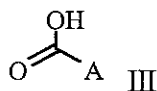
inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders. The pharmaceutical composition may further comprise at least one pharmaceutically acceptable excipient.

5 The invention further encompasses the use of a compound of formula (I) 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 of general formula (I) can be manufactured according to a process comprising the step of reacting a compound of
10 formula (II):



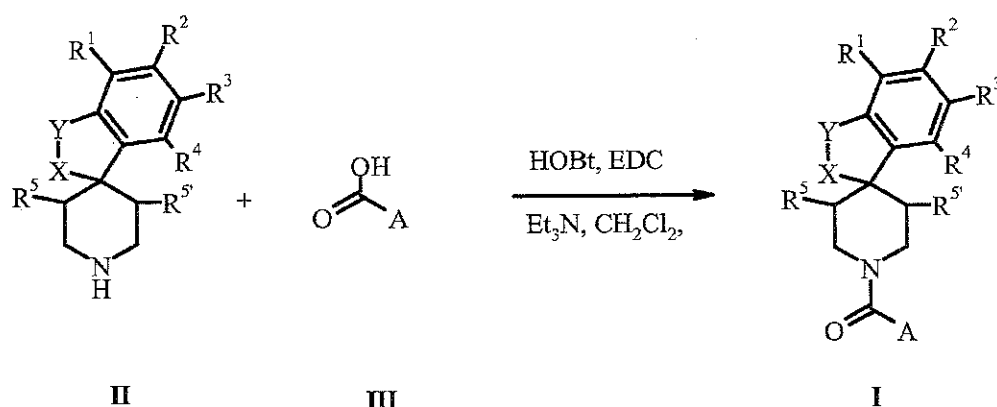
with a carboxylic acid of the formula III



15

wherein R^1 to $R^{5'}$, X, Y and A are as defined above.

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



General scheme A

Compounds of formula (I) can be prepared via an amide coupling between a spirocyclic derivative of formula (II) and a carboxylic acid A-CO₂H (III), wherein A is defined as hereinabove. The usual reagents and protocols known in the art can be used to effect the amide coupling. Spiropiperidine derivatives of formula (II) and carboxylic acids (III) are either commercially available or readily prepared using procedures described hereinafter or using methods known in the art starting from commercially available materials. General scheme A is hereinafter further illustrated with general procedure I.

General procedure I: Amide coupling:

To a 0.1 M stirred solution of a carboxylic acid derivative in CH₂Cl₂ are added EDC (1.3 eq), HOBT (1.3 eq), Et₃N (1.3 eq) and the spirocyclic derivative (1 eq). The mixture is stirred over night at RT and then poured onto water and extracted with CH₂Cl₂. The combined organic phases are dried over Na₂SO₄ and concentrated in vacuo. Flash chromatography or preparative HPLC affords the title compound.

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 K_i is calculated using the Cheng-Prusoff equation.

Example	pK _i hV1a
1	7.6
2	7.3
4	7.2
6	7.3
9	7.5
10	7.2
14	6.7

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

The compounds of formula (I) and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragees and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients
5 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.

10 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,
15 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
20 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. All temperatures are given in degrees Celsius.

Example A

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

	<u>mg/tablet</u>
Active substance	5
Lactose	45

Corn starch	15
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

5 Example B

Capsules of the following composition are manufactured:

	<u>mg/capsule</u>
Active substance	10
Lactose	155
10 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:

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

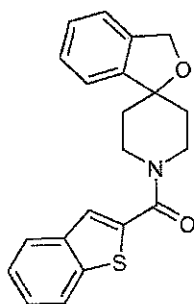
The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of
25 suitable size, left to cool; the suppositories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

Example 1

5 1'-(1-Benzothien-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidine]

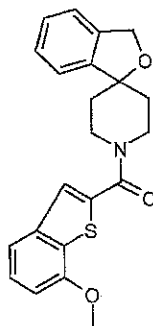


Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
- 10 - Acid: Benzo[b]thiophene-2-carboxylic acid,
ES-MS m/e (%): 350.2 (M+H⁺).

Example 2

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

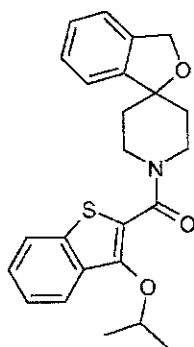


Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
- 20 - Acid: 7-Methoxy-benzo[b]thiophene-2-carboxylic acid,
ES-MS m/e (%): 380.1 (M+H⁺).

Example 3

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



5 Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),

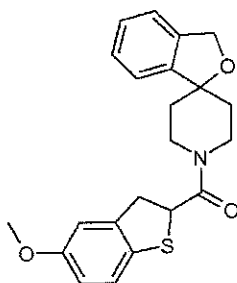
- Acid: 3-Isopropoxy-benzo[b]thiophene-2-carboxylic acid (described in *J. Med. Chem.* 1992, 35, 958),

10 ES-MS m/e (%): 408.2 (M+H⁺).

15

Example 4

1'-[(5-Methoxy-2,3-dihydro-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



20

Amide coupling according to general procedure I:

- 26 -

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),

- Acid: 5-Methoxy-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid

ES-MS m/e (%): 381.0 (M+H⁺).

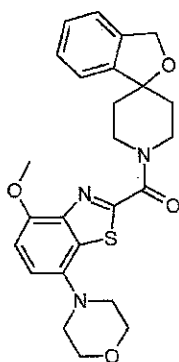
5 5-Methoxy-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid

From the commercially available 5-methoxy-benzo[b]thiophene-2-carboxylic acid was prepared 5-methoxy-2,3-dihydro-benzo[b]thiophene-2-carboxylic acid by reduction using known procedures. One example is Mg/MeOH.

10

Example 5

1'-[(4-Methoxy-7-morpholin-4-yl)-1,3-benzothiazol-2-yl]carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]



Amide coupling according to general procedure I:

15 - Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),

- Acid: 4-Methoxy-7-morpholin-4-yl-benzothiazole-2-carboxylic acid (described in patent WO2003045385)

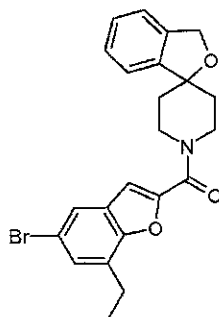
ES-MS m/e (%): 466.6 (M+H⁺).

20

Example 6

1'-[(5-Bromo-7-ethyl-1-benzofuran-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine]

- 27 -

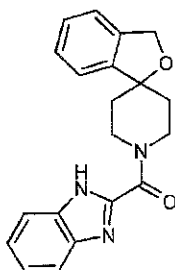


Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
 - 5 - Acid: 5-Bromo-7-ethyl-benzofuran-2-carboxylic acid
- ES-MS m/e (%): 442.0 (M+H⁺).

Example 7

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



10

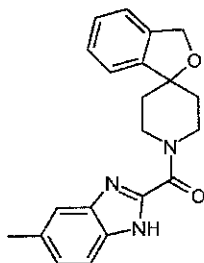
Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
- Acid: 1H-Benzoimidazole-2-carboxylic acid,
- 15 ES-MS m/e (%): 334.2 (M+H⁺).

Example 8

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

- 28 -

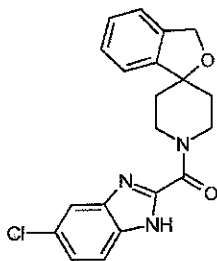


Amide coupling according to general procedure I:

- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
- 5 - Acid: 5-Methyl-1H-benzimidazole-2-carboxylic acid,
ES-MS m/e (%): 348.1 (M+H⁺).

Example 9

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

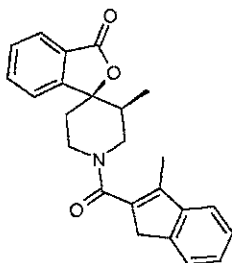


- 10 Amide coupling according to general procedure I:
- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidine] (described in *J. Org. Chem.* 1976, 41, 2628),
- Acid: 5-Chloro-1H-benzimidazole-2-carboxylic acid,
ES-MS m/e (%): 368.0 (M+H⁺).

15

Example 10

(1RS,3'SR)-3'-Methyl-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



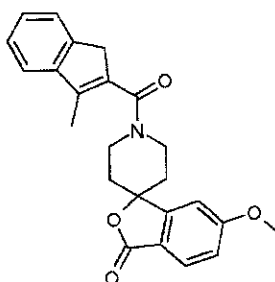
Amide coupling according to general procedure I:

- Amine: (1RS,3'SR)-3'-Methyl-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (prepared according to WO 9929696)
- Acid: 3-Methyl-1H-indene-2-carboxylic acid,
ES-MS m/e (%): 374.5 (M+H⁺).

5

Example 11

6-Methoxy-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



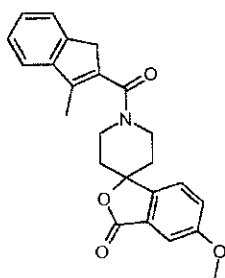
Amide coupling according to general procedure I:

- 10 - Amine: 6-Methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (prepared according to EP 722941)
- Acid: 3-Methyl-1H-indene-2-carboxylic acid,
ES-MS m/e (%): 390.5 (M+H⁺).

15

Example 12

5-Methoxy-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



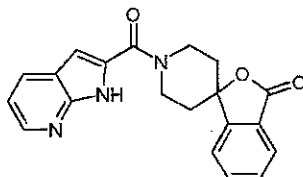
Amide coupling according to general procedure I:

- 20 - Amine: 5-Methoxy-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (described in EP 722941)
- Acid: 3-Methyl-1H-indene-2-carboxylic acid,

ES-MS m/e (%): 390.5 (M+H⁺).

Example 13

1'-(1H-Pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



5

Amide coupling according to general procedure I:

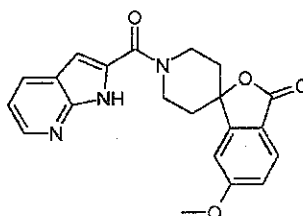
- Amine: 3H-Spiro[2-benzofuran-1,4'-piperidin]-3-one (preparation described in Organic Process Research & Development (2006), 10(4), 822-828.)

- Acid: 1H-Pyrrolo[2,3-b]pyridine-2-carboxylic acid,

10 ES-MS m/e (%): 348.4 (M+H⁺).

Example 14

6-Methoxy-1'-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one



15 Amide coupling according to general procedure I:

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

- Acid: 1H-Pyrrolo[2,3-b]pyridine-2-carboxylic acid,

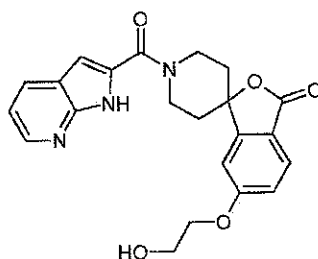
ES-MS m/e (%): 378.4 (M+H⁺).

20

Example 15

6-(2-Hydroxyethoxy)-1'-(1H-pyrrolo[2,3-b]pyridin-2-ylcarbonyl)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one

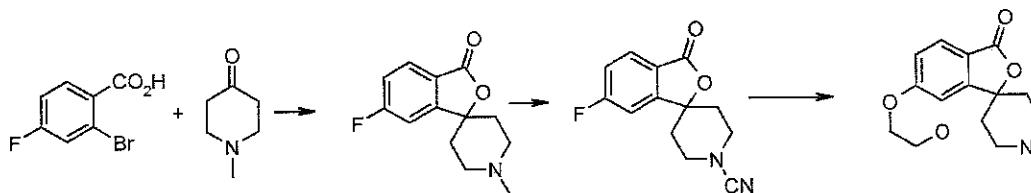
- 31 -



Amide coupling according to general procedure I:

- Amine: 6-(2-Hydroxyethoxy)- 3H-spiro[2-benzofuran-1,4'-piperidin]-3-one (preparation described in EP 722941)
- 5 - Acid: 1H-Pyrrolo[2,3-b]pyridine-2-carboxylic acid,
ES-MS m/e (%): 408.4 (M+H⁺).

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



10 Preparation of N-methylated lactone intermediate:

- To a solution of the substituted ortho-bromo 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 (7.91 g, 70mmol) in dry hexane (25 ml) was
- 15 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 °C and made alkaline (pH 9-10) with cold aqueous sodium
- 20 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 N-methylated lactone as white solid. 1H-NMR (CDCl₃, 400 MHz): δ1.68-1.75 (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 (M + 1).

Preparation of cyano-piperidine intermediate:

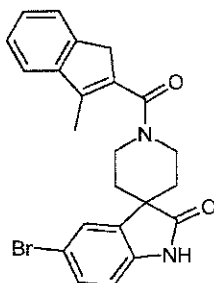
To a solution of the N-methylated lactone from above (1.17 g, 5 mmol) in dry chloroform (10 ml) was added cyanogenbromide (60 mmol) and the resulting solution was refluxed for 36 h. The reaction mixture was extracted with 5% HCl (5 ml) and then with water (2.5 ml). The chloroform solution was dried (anhydrous MgSO₄) and concentrated to give a pale yellow solid which was chromatographed over SiO₂ eluting with 1% MeOH-CH₂Cl₂ to give 858 mg (70%) of the desired Cyano-piperidine as white solid. ¹H-NMR (CDCl₃, 400 MHz): δ1.72-1.76 (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-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one:

The above cyano-piperidine (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 were 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 6-(2-hydroxyethoxy)-3H-spiro[2-benzofuran-1,4'-piperidin]-3-one as pale yellow solid. ¹H-NMR (d₆-DMSO, 400 MHz): δ1.47-1.50 (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): 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 16

5-Bromo-1'-[(3-methyl-1H-inden-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 described herein below)

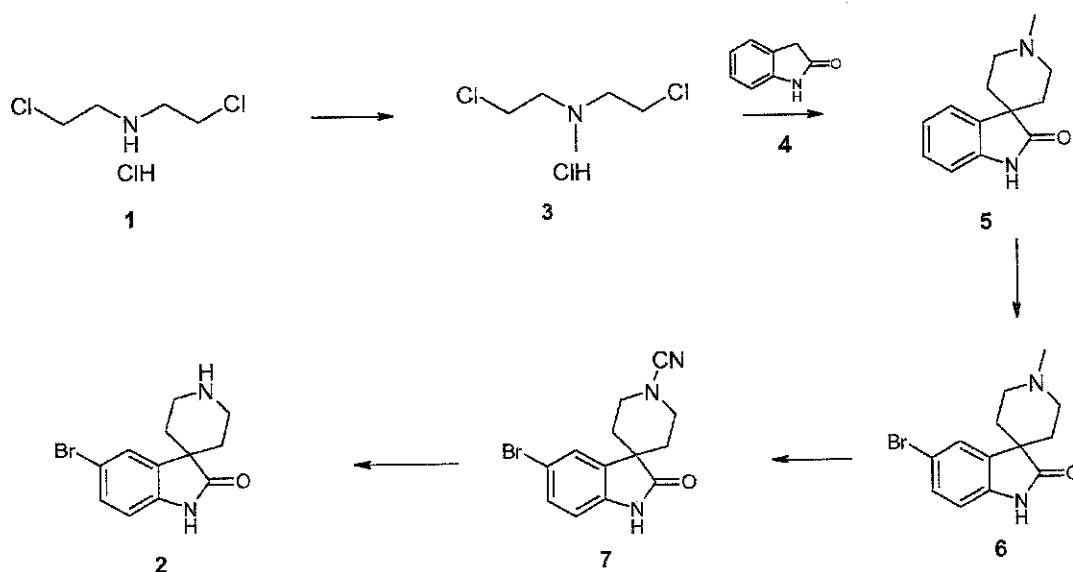
- Acid: 3-Methyl-1H-indene-2-carboxylic acid,

ES-MS m/e (%): 437.4 (M+H⁺).

5

10

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



15

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).

20

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 N_2 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 H_2O (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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$, gradient) gave 6g (57%) of 5 as a solid.
- $^1\text{H NMR}$ (CD_3OD , 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 -5°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 % $\text{MeOH}/\text{CH}_2\text{Cl}_2$) 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. $^1\text{H NMR}$ (CD_3OD , 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% $\text{MeOH}/\text{CH}_2\text{Cl}_2$) to gave 7 as a solid 3.9 g (82%). $^1\text{H NMR}$ (CDCl_3 , 400MHz) δ 7.52 (d, $J = 1.8$ Hz, 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).

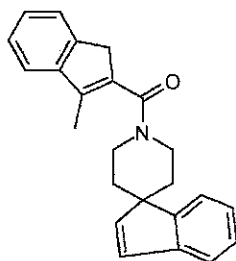
5-Bromo-spiro[indole-3,4'-piperidin]-2(1H)-one 2:

- 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 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 2 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.

15

Example 17

1'-[(3-Methyl-1H-inden-2-yl)carbonyl]spiro[indene-1,4'-piperidine]



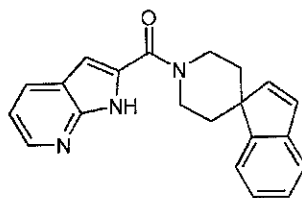
Amide coupling according to general procedure I:

- Amine: Spiro[indene-1,4'-piperidine],
 - 20 - Acid: 3-Methyl-1H-indene-2-carboxylic acid,
- ES-MS m/e (%): 342.5 (M+H⁺).

Example 18

1'-(1H-Pyrrolo[2,3-b]pyridin-2-ylcarbonyl)spiro[indene-1,4'-piperidine]

- 36 -



Amide coupling according to general procedure I:

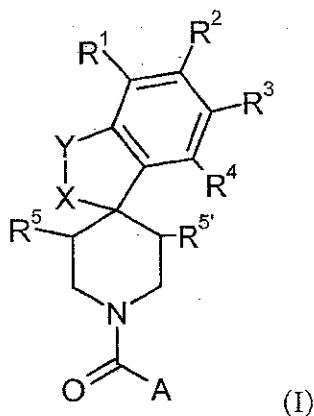
- Amine: Spiro[indene-1,4'-piperidine],

- Acid: 1H-Pyrrolo[2,3-b]pyridine-2-carboxylic acid,

5 ES-MS m/e (%): 330.4 (M+H⁺).

Claims

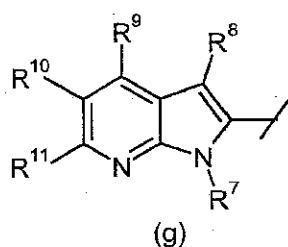
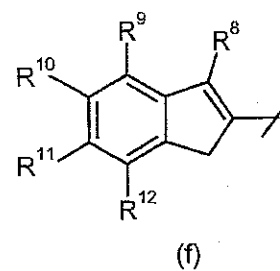
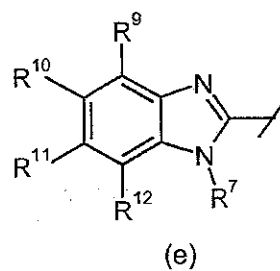
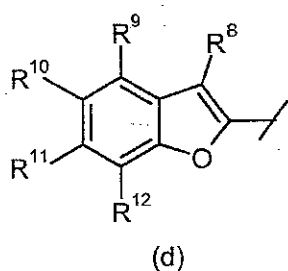
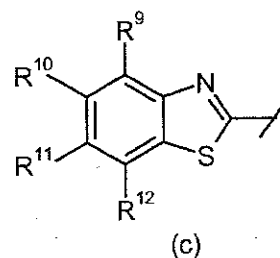
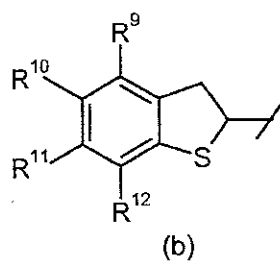
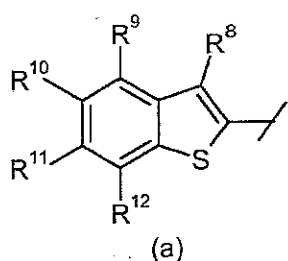
1. A compound of the general formula (I)



wherein

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

A is selected from the group consisting of



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

hydrogen,

halo,

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

halo- C_{1-6} -alkyl,

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

halo- C_{1-6} alkoxy;

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

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

R^7 is hydrogen,

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

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

R^8 is hydrogen,

15 C_{1-6} -alkyl,

C_{1-6} -alkoxy,

- $-(C_{1-6}\text{-alkylene})-NR^cR^d$,
 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 benzyl, 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
 5 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;
 R^9 is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 R^{10} is hydrogen, halo, C_{1-6} -alkyl, halo- C_{1-6} -alkyl, C_{1-6} -alkoxy, halo- C_{1-6} -alkoxy, or
 $-O-C_{2-10}\text{-alkenyl}$;
 10 R^{11} is hydrogen, halo, C_{1-6} -alkyl, or C_{1-6} -alkoxy;
 or R^{10} and R^{11} are bound together to form a ring with the benzo moiety, wherein
 $-R^{10}-R^{11}-$ is $-O-(CH_2)_n-O-$ wherein n is 1 or 2;
 R^{12} is hydrogen,
 C_{1-6} -alkyl, optionally substituted by CN or OH,
 15 $-(C_{1-6}\text{-alkylene})-NR^gR^h$,
 $-(C_{1-6}\text{-alkylene})-C(O)-NR^iR^j$
 $-O$ -benzyl, 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,
 nitro,
 20 halo,
 cyano,
 C_{1-6} -alkoxy,
 halo- C_{1-6} -alkoxy,
 halo- C_{1-6} -alkyl,
 25 $-(C_{1-6}\text{-alkylene})-C(O)R^f$,
 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,
 $-(C_{1-3}\text{-alkylene})-R^m$,
 wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered
 30 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
 $-NR^nR^o$;

or R¹¹ and R¹² are bound together to form a ring with the benzo moiety, wherein

-R¹¹-R¹²- is -O-(CH₂)_n-C(O)-,
 -C(O)-(CH₂)_n-O-, or
 -O-(CH₂)_n-O- wherein n is 1 or 2;

5 R^a, R^b, Rⁱ and R^j are each independently

hydrogen,

C₁₋₆-alkyl,

-(C₁₋₆-alkylene)-NR^kR^l,

wherein R^k and R^l are each independently hydrogen or C₁₋₆-alkyl,

10 or R^a and R^b, or Rⁱ 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, R^h, Rⁿ and R^o are each independently

hydrogen,

15 C₁₋₆-alkyl,

-C(O)R^e, or -S(O)₂R^e

wherein R^e is selected from the group of

hydrogen,

C₁₋₆-alkyl, and

20 phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,

C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

or R^c and R^d, or Rⁿ and R^o 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;

25 R^f is selected from the group of

hydrogen,

C₁₋₆-alkyl,

C₁₋₆-alkoxy; or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

30 C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

or a pharmaceutically acceptable salt thereof.

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

R¹, R², R³ and R⁴ are each independently
hydrogen,
halo, or
C₁₋₆-alkoxy, optionally substituted by OH.

5

3. The compound of formula (I) according to claim 1 or 2, wherein
R⁷ is hydrogen,

C₁₋₆-alkyl, optionally substituted by CN or OH, or
-(C₁₋₆-alkylene)-C(O)-NR^aR^b,

10 wherein R^a and R^b are each independently hydrogen or C₁₋₆-alkyl.

4. The compound of formula (I) according to any one of claims 1 to 3, wherein

R⁸ is hydrogen,

C₁₋₆-alkyl, or

15 C₁₋₆-alkoxy,

-(C₁₋₆-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently
hydrogen,

-C(O)R^e, or -S(O)₂R^e

20 wherein R^e is selected from the group of

hydrogen,

C₁₋₆-alkyl, or

phenyl, optionally substituted by one or more halo,

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

25 alkoxy, nitro, or cyano,

-(C₁₋₆-alkylene)-C(O)R^f,

wherein R^f is selected from the group of

hydrogen,

C₁₋₆-alkyl,

30 C₁₋₆-alkoxy, or

phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,

C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;

benzyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,

C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano, or
phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl, C₁₋₆-alkyl,
C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano.

- 5 5. The compound of formula (I) according to any one of claims 1 to 4, wherein
R⁸ is hydrogen, C₁₋₆-alkyl, or C₁₋₆-alkoxy.
6. The compound of formula (I) according to any one of claims 1 to 5, wherein
R⁹ is hydrogen, or C₁₋₆-alkoxy.
- 10 7. The compound of formula (I) according to any one of claims 1 to 6, wherein
R¹⁰ is hydrogen, halo, C₁₋₆-alkyl or C₁₋₆-alkoxy.
8. The compound of formula (I) according to any one of claims 1 to 7, wherein
15 R¹¹ is hydrogen.
9. The compound of formula (I) according to any one of claims 1 to 8, wherein
R¹² is hydrogen,
C₁₋₆-alkyl, optionally substituted by CN or OH,
20 -(C₁₋₆-alkylene)-NR^gR^h, wherein R^g and R^h are each independently
hydrogen,
C₁₋₆-alkyl,
-C(O)R^e, or -S(O)₂R^e, wherein R^e is selected from
hydrogen,
25 C₁₋₆-alkyl, and
phenyl, optionally substituted by one or more halo, halo-C₁₋₆-alkyl,
C₁₋₆-alkyl, C₁₋₆-alkoxy, halo-C₁₋₆-alkoxy, nitro, or cyano;
-(C₁₋₆-alkylene)-C(O)-NRⁱR^j, wherein Rⁱ and R^j are each independently
hydrogen,
30 C₁₋₆-alkyl,
-(C₁₋₆-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;

5 -O-benzyl, 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,

nitro,

halo,

cyano,

10 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

C_{1-6} -alkyl,

15 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 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,

20 -(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

25 -NRⁿR^o,

wherein R^n and R^o are each independently

hydrogen,

C_{1-6} -alkyl,

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

10. The compound of formula (I) according to any one of claims 1 to 9, wherein

R^{12} is hydrogen,

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

35 C_{1-6} -alkoxy, or

-NRⁿR^o,

wherein Rⁿ and R^o are each independently

hydrogen,

C₁₋₆-alkyl,

- 5 or Rⁿ and R^o 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.

11. The compound of formula (I) according to any one of claims 1 to 10, wherein
10 X is O and Y is CH₂, and
A is selected from the group consisting of (a), (b), (c), (d) and (e).

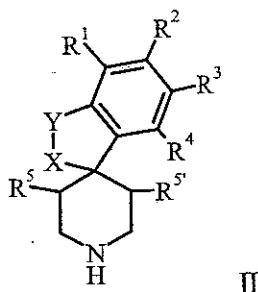
12. The compound of formula (I) according to any one of claims 1 to 10, wherein
X is O and Y is C=O, and A is (f) or (g).

- 15 13. The compound of formula (I) according to any one of claims 1 to 10, wherein
X is C=O and Y is NR⁶, and A is (f).

14. The compound of formula (I) according to any one of claims 1 to 10, wherein
20 X-Y is CH=CH, and A is (f) or (g).

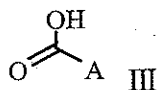
15. The compound of formula (I), which is selected from
1'-[(1-Benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
1'-[(7-Methoxy-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
25 1'-[(5-Methoxy-2,3-dihydro-1-benzothien-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-
piperidine],
1'-[(5-Bromo-7-ethyl-1-benzofuran-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-
piperidine],
1'-[(5-Chloro-1H-benzimidazol-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-piperidine],
30 (1RS,3'SR)-3'-Methyl-1'-[(3-methyl-1H-inden-2-yl)carbonyl]-3H-spiro[2-benzofuran-
1,4'-piperidin]-3-one, or
6-Methoxy-1'-(1H-pyrrolo[2,3-b]pyridin-2-yl)carbonyl]-3H-spiro[2-benzofuran-1,4'-
piperidin]-3-one.

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



5

with a carboxylic acid of the formula III



wherein R¹ to R^{5'}, X, Y and A are as defined in claim 1.

10

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

15

18. A pharmaceutical composition comprising a compound of formula (I), according to any one of claims 1 to 15.

19 Use of a compound of formula (I), according to any one of claims 1 to 15 for
20 the preparation of a medicament for the treatment of a disease selected from the group consisting of

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