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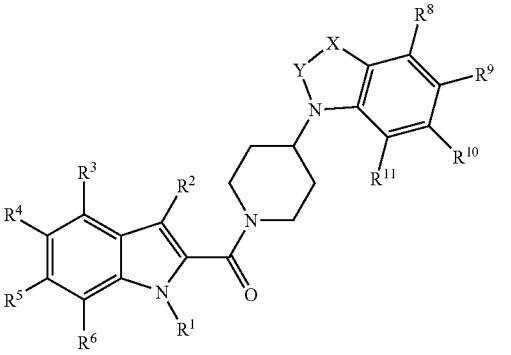
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(57) **ABSTRACT**

The present invention is concerned with novel indol-2-yl-carbonyl-piperidin-benzoimidazolon and indol-2-yl-carbonyl-piperidin-benzoxazolon derivatives as V1a receptor antagonists, their manufacture, pharmaceutical compositions containing them and their use for the treatment of anxiety and depressive disorders and other diseases. In particular, the present invention concerns compounds of formula (I)

(I)



wherein R^1 to R^{11}, X and Y are as defined in the specification.

INDOLES

PRIORITY OF RELATED APPLICATION(S)

[0001] This application claims the benefit of European Patent Application No. 06125663.2, filed Dec. 8, 2006, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] 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.

[0003] 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).

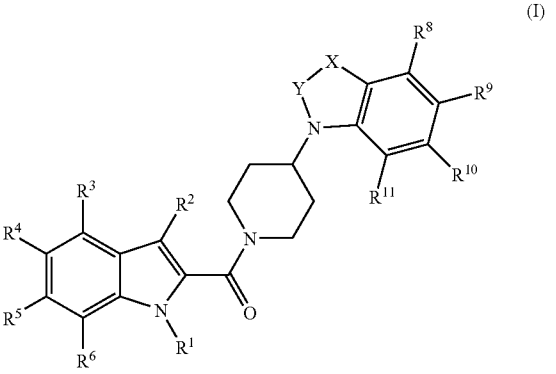
[0004] The V1a receptor is also mediating the cardiovascular effects of vasopressin in the brain by centrally regulating blood pressure and heart rate in the solitary tract nucleus (Michelini, L. C. and M. Morris (1999). "Endogenous vasopressin modulates the cardiovascular responses to exercise." *Ann 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).

SUMMARY OF THE INVENTION

[0005] The present invention provides novel indol-2-yl-carbonyl-piperidin-benzoimidazolon and indol-2-yl-carbonyl-piperidin-benzoxazolon derivatives, their manufacture, pharmaceutical compositions containing them. The compounds of formula (I) are V1a receptor modulators, and in particular are V1a receptor antagonists. The present invention provides methods for the treatment of such conditions as 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.

[0006] In particular, the present invention provides compounds of formula (I)

(I)



wherein

[0007] X and Y are selected from the combinations of:

[0008] X is NR^7 and Y is C═O,

[0009] X is CH_2 and Y is C═O,

[0010] X—Y is N═N, and

[0011] X is O and Y is C═O;

[0012] R^1 is hydrogen,

[0013] C_{1-6}-alkyl, optionally substituted by CN or OH, or

[0014] —(C_{1-6}-alkylene)—C(O)—NR^aR^b;

[0015] R^2 is hydrogen,

[0016] C_{1-6}-alkyl,

[0017] C_{1-6}-alkoxy,

[0018] —(C_{1-6}-alkylene)-NR^cR^d,

[0019] —(C_{1-6}-alkylene)-C(O)R^f,

[0020] 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

[0021] 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;

[0022] R^3 is hydrogen, halo, or C_{1-6}-alkyl;

[0023] R^4 is hydrogen,

[0024] halo,

[0025] C_{1-6}-alkyl,

[0026] halo-C_{1-6}-alkyl,

[0027] C_{1-6}-alkoxy,

[0028] halo-C_{1-6}-alkoxy, or

[0029] —O—C_{2-10}-alkenyl;

[0030] R_5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

[0031] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

[0032] —R^4—R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2;

[0033] R^6 is hydrogen,

[0034] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0035] —(C_{1-6}-alkylene)-NR^gR^h,

[0036] —(C_{1-6}-alkylene)-C(O)—NR^iR^j,

[0037] —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,

[0038] nitro,

[0039] halo,

[0040] cyano,
[0041] C_{1-6}-alkoxy,
[0042] halo-C_{1-6}-alkoxy,
[0043] halo-C_{1-6}-alkyl,
[0044] —(C_{1-6}-alkylene)-C(O)R^f,
[0045] 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,
[0046] —(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,
[0047] 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;

[0048] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein
[0049] —R^5-R^6— is —O—(CH_2)$_n$—C(O)—,
[0050] —C(O)—(CH_2)$_n$—O—, or
[0051] —O—(CH_2)$_n$—O— wherein n is 1 or 2;

[0052] R^7 is hydrogen or C_{1-6}-alkyl;
[0053] R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}-alkoxy;
[0054] R^a, R^b, R^i and R^j are each independently
[0055] hydrogen,
[0056] C_{1-6}-alkyl,
[0057] —(C_{1-6}-alkylene)-NR^kR^l,
[0058] wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,
[0059] 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;

[0060] R^c, R^d, R^g and R^h are each independently
[0061] hydrogen,
[0062] C_{1-6}-alkyl,
[0063] —C(O)R^e, or —S(O)$_2R^e$
[0064] wherein R^e is selected from the group of
[0065] hydrogen,
[0066] C_{1-6}-alkyl, and
[0067] 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;
[0068] or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
[0069] or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;

[0070] R^f is selected from
[0071] hydrogen,
[0072] C_{1-6}-alkyl,
[0073] C_{1-6}-alkoxy; and
[0074] 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;

[0075] or a pharmaceutically acceptable salt thereof.

[0076] 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.

DETAILED DESCRIPTION OF THE INVENTION

[0077] The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination. It must be noted that, as used in the specification and the appended claims, the singular forms "a", "an," and "the" include plural forms unless the context clearly dictates otherwise.

[0078] In the present description, the term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated hydrocarbon radical. The term "C_{1-6}-alkyl" denotes a saturated straight- or branched-chain hydrocarbon group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, the isomeric pentyls and the like. A preferred sub-group of C_{1-6}-alkyl is C_{1-4}-alkyl, i.e. with 1-4 carbon atoms.

[0079] In the present invention, the term "alkylene" refers to a linear or branched saturated divalent hydrocarbon radical. In particular, "C_{1-6}-alkylene" means a linear saturated divalent hydrocarbon radical of one to six carbon atoms or a branched saturated divalent hydrocarbon radical of three to six carbon atoms, e.g. methylene, ethylene, 2,2-dimethylethylene, n-propylene, 2-methylpropylene, and the like.

[0080] In the present description, the terms "alkoxy" and "C_{1-6}-alkoxy" refer to the group R'—O—, wherein R' is C_{1-6}-alkyl as defined above. Examples of alkoxy groups are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, tert-butoxy, sec-butoxy and the like. A preferred sub-group of C_{1-6}-alkoxy, and still more preferred alkoxy groups are methoxy and/or ethoxy.

[0081] In the present description, the term "thioalkyl" and "C_{1-6}-thioalkyl" refers to the group R'—S—, wherein R' is C_{1-6}-alkyl as defined above.

[0082] The terms "C_{1-6}-hydroxyalkyl" and "C_{1-6}-alkyl substituted by OH" denote a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a hydroxyl group.

[0083] The terms "C_{1-6}-cyanoalkyl" and "C_{1-6}-alkyl substituted by CN" denote a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a CN group.

[0084] The terms "halo" and "halogen" refer to fluorine (F), chlorine (Cl), bromine (Br) and iodine (I) with fluorine, chlorine and bromine being preferred.

[0085] The term "halo-C_{1-6}-alkyl" denotes a C_{1-6}-alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Examples of halo-C_{1-6}-alkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Among the preferred halo-C_{1-6}-alkyl groups are difluoro- or trifluoro-methyl or -ethyl.

[0086] The term "halo-C_{1-6}-alkoxy" denotes a C_{1-6}-alkoxy group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom,

preferably fluoro or chloro, most preferably fluoro. Among the preferred halogenated alkoxy groups are difluoro- or trifluoro-methoxy or -ethoxy.

[0087] The term "C_{2-12}-alkenyl", alone or in combination, denotes a straight-chain or branched hydrocarbon residue of 2 to 12 carbon atoms comprising at least one double bond. A preferred sub-group of C_{2-12}-alkenyl is C_{2-6}-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 below.

[0088] The term "5 or 6 membered heteroaryl" means an aromatic ring of 5 or 6 ring atoms as ring members containing one, two, or three ring heteroatoms selected from N, O, and S, the rest being carbon atoms. 5 or 6 membered heteroaryl can optionally be substituted with one, two, three or four substituents, wherein each substituent may independently be selected from the group consisting of hydroxy, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, halo, cyano, nitro, halo-C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-alkoxycarbonyl, amino, C_{1-6}-alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, and carbonylamino, unless otherwise specifically indicated. Preferred substituents are halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano. Examples of heteroaryl moieties include, but are not limited to, optionally substituted imidazolyl, optionally substituted oxazolyl, optionally substituted thiazolyl, optionally substituted pyrazinyl, optionally substituted pyrrolyl, optionally substituted pyrazinyl, optionally substituted pyridinyl, optionally substituted pyrimidinyl, optionally substituted furanyl, and those which are specifically exemplified herein.

[0089] The term "heterocycloalkyl" means a monovalent saturated moiety, consisting of one ring of 3 to 7, preferably from 4 to 6 atoms as ring members, including one, two, or three heteroatoms 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, C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-thioalkyl, halo, cyano, nitro, halo-C_{1-6}-alkyl, C_{1-6}-hydroxyalkyl, C_{1-6}-alkoxycarbonyl, amino, C_{1-6}-alkylamino, di(C_{1-6})alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated.

[0090] Preferred substituents are halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano. Examples of heterocyclic moieties include, but are not limited to, optionally substituted tetrahydro-furanyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted morpholinyl, optionally substituted piperazinyl, and the like or those which are specifically exemplified herein.

[0091] The term "heterocycle" in the definition "R^a and R^b, R^c and R^d, R^g and R^h, R^i and R^j, together with the nitrogen to which they are bound form a five- or six-membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur"means either heterocycloalkyl or heteroaryl in the above-given sense which may optionally be substituted as described above. Preferably, the "heterocycle" may optionally be substituted with one, two or three substituents selected from halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, and cyano. Preferred heterocycles are piperazine, N-methylpiperazine, morpholin, piperidine and pyrrolidine.

[0092] The term "one or more" substituents preferably means one, two or three substituents per ring.

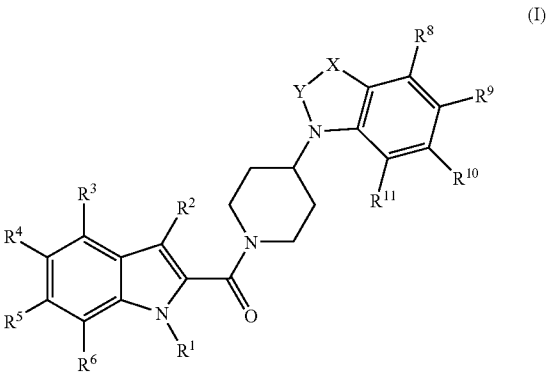
[0093] The term "cycloalkyl" means a cycloalkyl group containing 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Cycloalkyl containing 3 to 4 carbon atoms are the most preferred.

[0094] "Pharmaceutically acceptable," such as pharmaceutically acceptable carrier, excipient, etc., means pharmacologically acceptable and substantially non-toxic to the subject to which the particular compound is administered.

[0095] The term "pharmaceutically acceptable acid addition salt" 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.

[0096] "Therapeutically effective amount" means an amount that is effective to prevent, alleviate or ameliorate symptoms of disease or prolong the survival of the subject being treated.

[0097] In detail, the present invention relates to compounds of the general formula (I)



wherein

[0098] X and Y are selected from the combinations of:

[0099] X is NR^7 and Y is C═O,

[0100] X is CH_2 and Y is C═O,

[0101] X—Y is N—N, and

[0102] X is O and Y is C═O;

[0103] R^1 is hydrogen,

[0104] C_{1-6}-alkyl, optionally substituted by CN or OH, or

[0105] —(C_{1-6}-alkylene)-C(O)—NR^aR^b;

[0106] R^2 is hydrogen,

[0107] C_{1-6}-alkyl,

[0108] C_{1-6}-alkoxy,

[0109] —(C_{1-6}-alkylene)-NR^cR^d,

[0110] —(C_{1-6}-alkylene)-C(O)R^f,

[0111] benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

[0112] phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

[0113] R^3 is hydrogen, halo, or C_{1-6}-alkyl;

[0114] R^4 is hydrogen,

[0115] halo,
[0116] C_{1-6}-alkyl,
[0117] halo-C_{1-6}-alkyl,
[0118] C_{1-6}-alkoxy,
[0119] halo-C_{1-6}-alkoxy, or
[0120] —O—C_{2-10}-alkenyl;
[0121] R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;
[0122] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein —R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2;
[0123] $R^6$is hydrogen,
[0124] C_{1-6}-alkyl, optionally substituted by CN or OH,
[0125] —(C_{1-6}-alkylene)-NR^gR^h,
[0126] —(C_{1-6}-alkylene)-C(O)—NR^iR^j,
[0127] —O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
[0128] nitro,
[0129] halo,
[0130] cyano,
[0131] C_{1-6}-alkoxy,
[0132] halo-C_{1-6}-alkoxy,
[0133] halo-C_{1-6}-alkyl,
[0134] —(C_{1-6}-alkylene)-C(O)R^f,
[0135] 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,
[0136] —(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,
[0137] 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;
[0138] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein
[0139] —R^5-R^6— is —O—$(CH_2)_n$—C(O)—,
[0140] —C(O)—$(CH_2)_n$—O—, or
[0141] —O—$(CH_2)_n$—O— wherein n is 1 or 2;
[0142] R^7 is hydrogen or C_{1-6}-alkyl;
[0143] R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}-alkoxy;
[0144] R^a, R^b, R^i and R^j are each independently
[0145] hydrogen,
[0146] C_{1-6}-alkyl, or
[0147] —(C_{1-6}-alkylene)-NR^kR^l,
[0148] wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,
[0149] 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;
[0150] R^c, R^d, R^g and R^h are each independently
[0151] hydrogen,
[0152] C_{1-6}-alkyl,
[0153] —C(O)R^e, or —$S(O)_2R^e$
[0154] wherein R^e is selected from the group of
[0155] hydrogen,
[0156] C_{1-6}-alkyl, and
[0157] 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;
[0158] or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
[0159] or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;
[0160] R^f is selected from
[0161] hydrogen,
[0162] C_{1-6}-alkyl,
[0163] C_{1-6}-alkoxy; and
[0164] 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;
[0165] or a pharmaceutically acceptable salt thereof.
[0166] In certain embodiments of the invention, R^a and R^b, R^c and R^d, R^i and R^j, or R^g and R^h together with the nitrogen to which they are bound may form piperazine, 4-(C_{1-6}-alkyl)-piperazine, 4-methylpiperazine, morpholine, piperidine or pyrrolidine.
[0167] In certain embodiments of the invention, R^a and R^b, R^c and R^d, R^i and R^j, or R^g and R^h together with the nitrogen to which they are bound may form 4-methylpiperazine, or morpholine.
[0168] In certain embodiments of the invention, wherein R^m is a 5- to 6-membered heteroaryl, the preferred heteroaryl is selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, imidazole, pyrazole, oxazole, and isoxazole.
[0169] In embodiments of the invention, wherein R^m is a 4- to 6-membered heterocycloalkyl, the preferred heterocycloalkyl is selected from the group consisting of pyrrolidine, oxethane, tetrahydropyrane, piperidine, morpholine, and piperazine.
[0170] In certain embodiments of the invention, R^1 is hydrogen or C_{1-6}-alkyl, optionally substituted by CN or OH.
[0171] In certain embodiments of the invention,
[0172] R^2 is hydrogen,
[0173] C_{1-6}-alkyl,
[0174] C_{1-6}-alkoxy,
[0175] —(C_{1-6}-alkylene)-NR^cR^d,
[0176] wherein R^c and R^d are each independently
[0177] hydrogen,
[0178] —C(O)R^e, or —$S(O)_2R^e$
[0179] wherein R^e is selected from the group of hydrogen,
C_{1-6}-alkyl, and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or
[0180] R^c and R^d together with the nitrogen to which they are bound form isoindole-1,3-dione,
[0181] —(C_{1-6}-alkylene)-C(O)R^f,
[0182] wherein R^f is selected from
[0183] hydrogen,
[0184] C_{1-6}-alkyl,
[0185] C_{1-6}-alkoxy, and
[0186] 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;
[0187] benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

[0188] phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

[0189] In certain embodiments of the invention, R^3 is hydrogen or halo.

[0190] In certain embodiments of the invention,

[0191] R^4 is hydrogen,

[0192] halo,

[0193] C_{1-6}-alkyl, or

[0194] C_{1-6}-alkoxy;

[0195] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

[0196] —R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2.

[0197] In certain embodiments of the invention,

[0198] R^5 is hydrogen, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

[0199] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

[0200] —R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2.

[0201] In certain embodiments of the invention,

[0202] R^6 is hydrogen,

[0203] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0204] —(C_{1-6}-alkylene)-NR^gR^h

[0205] wherein R^g and R^h are each independently selected from hydrogen and C_{1-6}-alkyl;

[0206] or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;

[0207] —(C_{1-6}-alkylene)-C(O)—NR^iR^j

[0208] wherein R^i and R^j are each independently

[0209] hydrogen;

[0210] C_{1-6}-alkyl;

[0211] —(C_{1-6}-alkylene)-NR^kR^l;

[0212] wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

[0213] 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;

[0214] —O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

[0215] nitro;

[0216] halo;

[0217] cyano;

[0218] C_{1-6}-alkoxy;

[0219] halo-C_{1-6}-alkoxy;

[0220] halo-C_{1-6}-alkyl;

[0221] —(C_{1-6}-alkylene)-C(O)R^f;

[0222] wherein R^f is selected from

[0223] hydrogen;

[0224] C_{1-6}-alkyl;

[0225] C_{1-6}-alkoxy; and

[0226] phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl,

[0227] C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

[0228] —(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,

[0229] 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

[0230] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

[0231] —R^5-R^6— is —O—$(CH_2)_n$—C(O)—,

[0232] —C(O)—$(CH_2)_n$—O—, or

[0233] —O—$(CH_2)_n$—O— wherein n is 1 or 2;

[0234] In certain embodiments of the invention,

[0235] $R^6$is hydrogen,

[0236] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0237] —O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

[0238] nitro;

[0239] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

[0240] —R^5-R^6— is —O—$(CH_2)_n$—C(O)—, or —C(O)—$(CH_2)_n$—O—, wherein n is 1 or 2.

[0241] In certain embodiments, R^7 is hydrogen.

[0242] In certain embodiments all R^8 to R^{11} are hydrogen.

[0243] In certain embodiments, R^8 to R^{11} are independently hydrogen or halo.

[0244] In certain embodiments, R^9 is fluoro, and R^8, R^{10} and R^{11} are hydrogen.

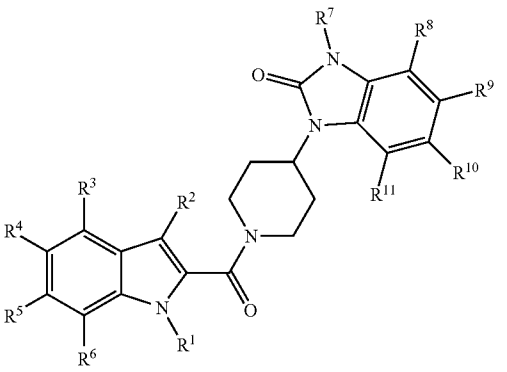
[0245] In certain embodiments, R^8, R^9 and R^{11} are hydrogen and R^{10} is bromo.

[0246] In certain embodiments, R^8 to R^{11} are independently hydrogen or methyl.

[0247] In certain embodiments, R^8 to R^{10} are hydrogen and R^{11} is methyl.

[0248] In certain embodiments of the invention, X is NR^7 and Y is C═O, i.e. compounds of formula (Ia)

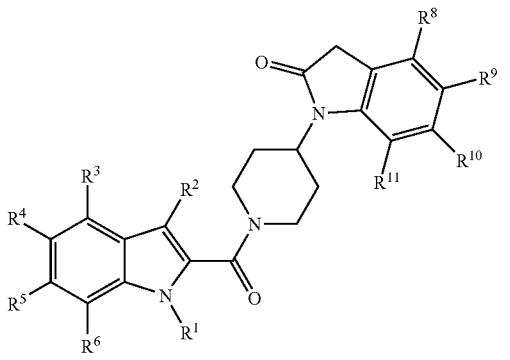
(Ia)



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

[0249] In certain embodiments of the invention, X is CH_2 and Y is C═O, i.e. compounds of formula (Ib)

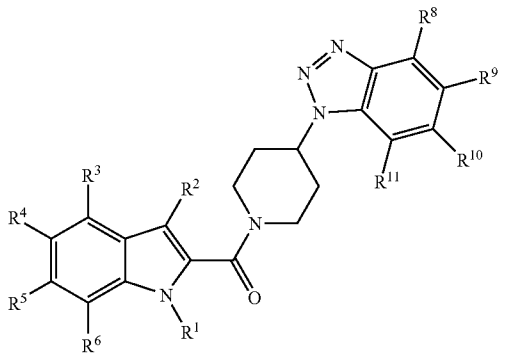
(Ib)



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

[0250] In certain embodiments of the invention, X—Y is N═N, i.e. compounds of formula (Ic)

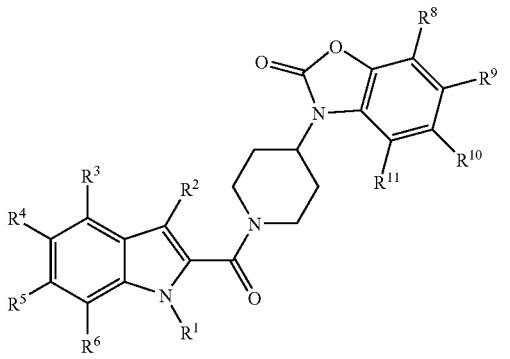
(Ic)



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

[0251] In certain embodiments of the invention, X is O and Y is C═O, i.e. compounds of formula (Id)

(Id)



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

[0252] In certain embodiments of the invention, R^1 to R^6 are not all hydrogen.

[0253] In certain embodiments of the invention, R^1 to R^{11} are not all hydrogen.

[0254] The invention further encompasses an embodiment with the compound of formula (I),

[0255] wherein

[0256] X is NR^7 and Y is C═O; or

[0257] X is CH_2 and Y is C═O; or

[0258] X—Y is N═N;

[0259] R^1 is hydrogen,

[0260] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0261] —(C_{1-6}-alkylene)-C(O)—NR^aR^b,

[0262] wherein R^a and R^b are each independently hydrogen or C_{1-6}-alkyl;

[0263] R^2 is hydrogen,

[0264] C_{1-6}-alkyl,

[0265] C_{1-6}-alkoxy,

[0266] —(C_{1-6}-alkylene)-NR^cR^d,

[0267] wherein R^c and R^d are each independently

[0268] hydrogen,

[0269] —C(O)R^e, or —$S(O)_2R^e$,

[0270] wherein R^e is selected from

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;

[0271] or R^c and R^d together with the nitrogen to which they are bound form isoindole-1,3-dione,

[0272] —(C_{1-6}-alkylene) -C(O)R^f,

[0273] wherein R^f is selected from

[0274] hydrogen,

[0275] C_{1-6}-alkyl,

[0276] C_{1-6}-alkoxy, and

[0277] 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,

[0278] benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

[0279] phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

[0280] R^3 is hydrogen, halo, or C_{1-6}-alkyl;

[0281] R^4 is hydrogen,

[0282] halo,

[0283] C_{1-6}-alkyl,

[0284] halo-C_{1-6}-alkyl,

[0285] C_{1-6}-alkoxy,

[0286] halo-C_{1-6}-alkoxy, or

[0287] —O—C_{2-10}-alkenyl;

[0288] R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

[0289] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

[0290] —R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2;

[0291] $R^6$is hydrogen,

[0292] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0293] —(C_{1-6}-alkylene)-NR^gR^h,

[0294] wherein R^g and R^h are each independently selected from hydrogen and C_{1-6}-alkyl;

[0295] or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six mem-

bered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur,

[0296] —(C_{1-6}-alkylene)-C(O)—NR^iR^j,

[0297] wherein R^i and R^j are each independently

[0298] hydrogen,

[0299] C_{1-6}-alkyl,

[0300] —(C_{1-6}-alkylene)-NR^kR^l,

[0301] wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl;

[0302] 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,

[0303] —O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

[0304] nitro,

[0305] halo,

[0306] cyano,

[0307] C_{1-6}-alkoxy,

[0308] halo-C_{1-6}-alkoxy,

[0309] halo-C_{1-6}-alkyl, —(C_{1-6}-alkylene)-C(O)R^f,

[0310] phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

[0311] —(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,

[0312] 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;

[0313] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

[0314] —R^5-R^6— is —O—(CH_2)$_n$—C(O)—,

[0315] —C(O)—(CH_2)$_n$—O—, or

[0316] —O—(CH_2)$_n$—O— wherein n is 1 or 2;

[0317] R^7 is hydrogen or C_{1-6}-alkyl;

[0318] R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl or halo-C_{1-6}-alkyl.

[0319] The invention further encompasses an embodiment with the compound of formula (I),

[0320] wherein

[0321] X is NR^7 and Y is C═O;

[0322] X is CH_2 and Y is C═O;

[0323] X—Y is N═N;

[0324] X is O and Y is C═O;

[0325] R^1 is hydrogen or C_{1-6}-alkyl, optionally substituted by CN or OH;

[0326] R^2 is hydrogen,

[0327] C_{1-6}-alkyl,

[0328] C_{1-6}-alkoxy,

[0329] —(C_{1-6}-alkylene)-NR^cR^d,

[0330] wherein R^c and R^d are each independently

[0331] hydrogen,

[0332] —C(O)R^e, or —$S(O)_2R^e$,

[0333] wherein R^e is selected from

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;

[0334] or R^c and R^d together with the nitrogen to which they are bound form isoindole-1,3-dione,

[0335] —(C_{1-6}-alkylene)-C(O)R^f,

[0336] wherein R^f is selected from

[0337] hydrogen,

[0338] C_{1-6}-alkyl,

[0339] C_{1-6}-alkoxy, and

[0340] 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,

[0341] benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or

[0342] phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;

[0343] R^3 is hydrogen, halo, or C_{1-6}-alkyl;

[0344] R^4 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

[0345] R^5 is hydrogen, C_{1-6}-alkyl, or C_{1-6}-alkoxy;

[0346] or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein

[0347] —R^4-R^5— is —O—(CH_2)$_n$—O— wherein n is 1 or 2;

[0348] R^6 is hydrogen,

[0349] C_{1-6}-alkyl, optionally substituted by CN or OH,

[0350] —O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano; or

[0351] nitro;

[0352] or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein

[0353] —R^5-R^6— is —O—(CH_2)$_n$—C(O)—; or —C(O)—(CH_2)$_n$—O— and n is 1 or 2;

[0354] R^7 is hydrogen;

[0355] R^8, R^9, R^{10}, and R^{11} are each hydrogen.

[0356] Preferred compounds of the invention are those as shown in the examples above.

[0357] More preferred compounds of formula Ia are

[0358] 55 5-Bromo-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile,

[0359] N-{5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-2-nitro-benzamide,

[0360] 4-Fluoro-N-{5-methyl-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-benzamide,

[0361] {2-[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl) -piperidine-1-carbonyl]-1H-indol-3-yl}-acetic acid ethyl ester,

[0362] 1-[1-(7-Benzyloxy-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one,

[0363] {5-Chloro-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile, or

[0364] {5-Chloro-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-7-yl}-acetonitrile.

[0365] A preferred compound of formula Ib is

[0366] 1-[1-(5-Chloro-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-indol-2-one.

[0367] A preferred compound of formula Ic is

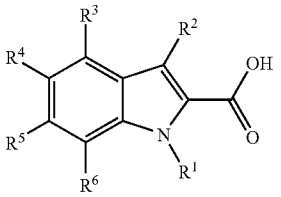
[0368] (4-Benzotriazol-1-yl-piperidin-1-yl)-(5-chloro-1H-indol-2-yl) -methanone.

[0369] The invention also encompasses methods for the treatment of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis,

nephrotic syndrome, obsessive compulsive disorder, anxiety and depressive disorders which comprises administering a therapeutically effective amount of a compound of formula (I), (Ia), (Ib), (Ic), or (Id).

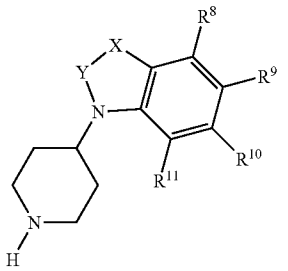
[0370] The invention also encompasses a pharmaceutical composition comprising a compound of formula (I), (Ia), (Ib), (Ic), or (Id) and a pharmaceutically acceptable carrier. The pharmaceutical composition can further comprise at least one pharmaceutically acceptable excipient.

[0371] In a certain embodiment, the compound of the invention can be manufactured according to a process comprising reacting a compound of formula (II):



II

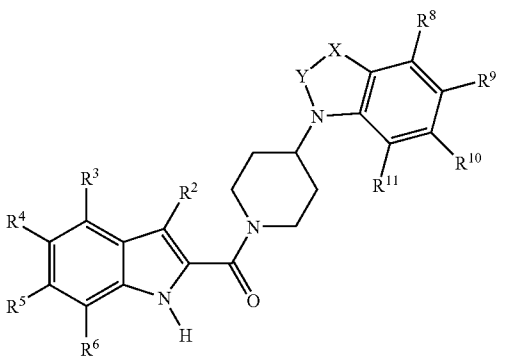
with an amine of formula 1



(1)

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

[0372] In a certain embodiment, the compound of the invention can be manufactured according to a process comprising reacting a compound of formula (I-I):

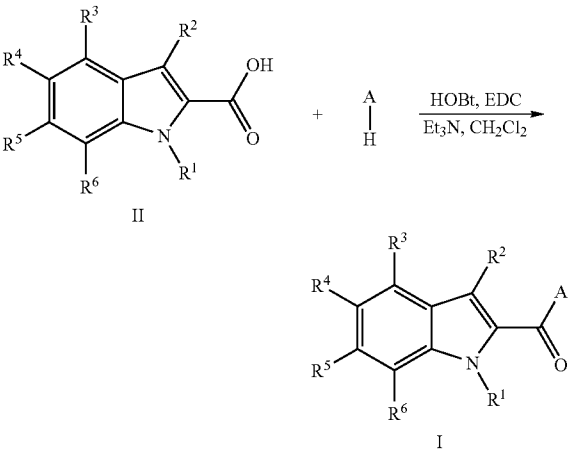


(I-1)

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

[0373] The synthesis of compounds of formula (I) will be described in more detail below and in the examples.

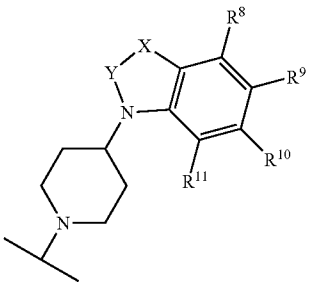
General scheme A



II

I

wherein A is:



wherein

[0374] X and Y are selected from the combinations of:

[0375] X is NR^7 and Y is C═O,

[0376] X is CH_2 and Y is C═O,

[0377] X—Y is N═N, and

[0378] X is O and Y is C═O

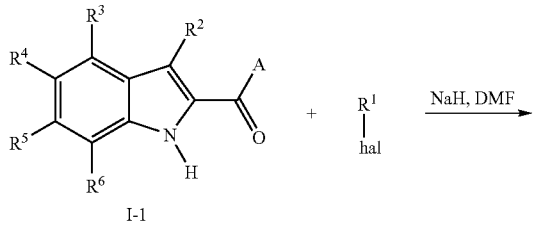
[0379] Compounds of formula (I) can be prepared via an amide coupling between an indole 2-carboxylic acid (II) and a compound of formula (A-H), wherein A is defined as hereinabove. The usual reagents and protocols known in the art can be used to effect the amide coupling. Indole 2-carboxylic acids (II) are either commercially available or readily prepared using procedures described hereinafter. The compounds of formula (A-H) are either commercially available or prepared using methods known in the art starting from commercially available materials. General scheme A is hereinafter further illustrated with general procedure I.

General Procedure I: Amide Coupling:

[0380] To a stirred solution of an indole-2-carboxylic acid derivative (1 mmol) in 10 ml CH_2Cl_2 were added (1.3 mmol) EDC, (1.3 mmol) HOBt, (1.3 mmol) Et_3N and (1 mmol) of the amine derivative A-H. The mixture was stirred overnight at RT and then poured onto water and extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and

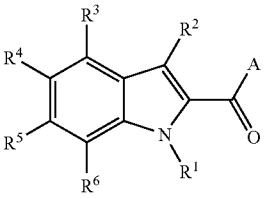
concentrated in vacuo. Flash chromatography or preparative HPLC afforded the title compound.

General scheme B



I-1

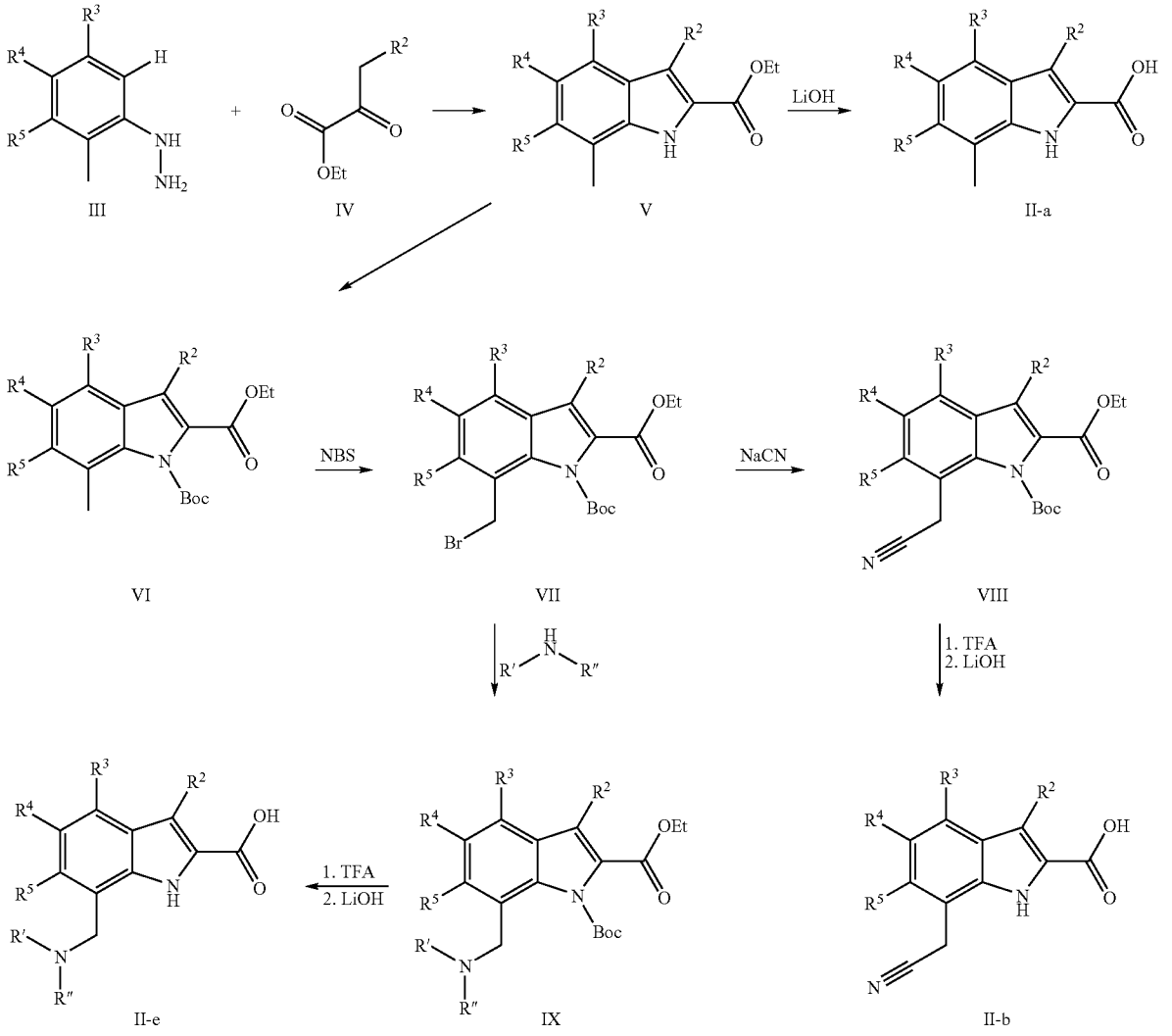
-continued



I-2

[0381] Compounds of formula (I-2) (compounds of formula (I) wherein R^1 is different from H), can be prepared by alkylation of the indole derivative of formula (I-1), with an electrophile of formula R^1-hal (commercially available, wherein hal is halo, preferably Cl or Br) using standard procedures. Derivatives (I-1) are prepared using the amide coupling as described in the general scheme A.

General scheme C: preparation of acids II



[0382] Substituted indole 2-carboxylic acids can be prepared according to the general scheme C. Indoles V are obtained by a Fischer indole synthesis from an aryl hydrazine III and a α-ketoester IV. Saponification gives an acid of formula II-a. Alternatively, Boc protection of the indole nitrogen gives VI. Selective bromination of the methyl group in the 7-position of the indole using NBS affords VII. Subsequent nucleophilic substitution of 7-bromomethyl indole intermediate VII with NaCN or a secondary amine yields intermediates VIII and IX, respectively. After N-deprotection and saponification of the ester moiety, the corresponding carboxylics acids II-b and II-c are obtained.

Abbreviations used:

[0383] NBS N-Bromosuccinimide

[0384] Boc tert-buthoxycarbonyl

V1a Activity

Material & Method:

[0385] 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.

[0386] 50 g of cells were resuspended in 30 ml freshly prepared ice cold Lysis buffer (50 mM HEPES, 1 mM EDTA, 10 mM MgCl2 adjusted to pH=7.4+complete cocktail of protease inhibitor (Roche Diagnostics)), homogenized with Polytron for 1 min, and sonicated on ice for 2×2 minutes at 80% intensity (Vibracell sonicator). The preparation was centrifuged 20 min at 500 g at 4° C., the pellet was discarded, and the supernatant centrifuged 1 hour at 43'000 g at 4° C. (19'000 rpm). The pellet was resuspended in 12.5 ml Lysis buffer+12.5 ml Sucrose 20% and homogenized using a Polytron for 1-2 min. The protein concentration was determined by the Bradford method and aliquots were stored at −80° C. until use. For binding studies, 60 mg Yttrium silicate SPA beads (Amersham) were mixed with an aliquot of membrane in binding buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, 2 mM CaCl2, 10 mM MgCl2) for 15 minutes with mixing. 50 ul of bead/membrane mixture was then added to each well of a 96 well plate, followed by 50 ul of 4 nM 3H-Vasopressin (American Radiolabeled Chemicals). For total binding measurement 100 ul of binding buffer were added to the respective wells, for non-specific binding 100 ul of 8.4 mM cold vasopressin were added, and for compound testing 100 ul of a serial dilution of each compound in 2% DMSO were added. The plate was incubated Ih at room temperature, centrifuged 1 min at 1000 g and counted on a Packard Top-Count. Non-specific binding counts were subtracted from each well and data was normalized to the maximum specific binding set at 100%. To calculate an IC 50, the curve was fitted using a non-linear regression model (XLfit) and the Ki was calculated using the Cheng-Prussoff equation.

Example	pKi
3	7.92
10	7.7

-continued

Example	pKi
11	7.4
14	7.38
37	7.66
45	7.495
46	7.45
47	7.19
48	6.415

[0387] The present invention also provides pharmaceutical compositions containing compounds of the invention, for example compounds of formula I or IA, and their pharmaceutically acceptable acid addition salts, and a pharmaceutically acceptable carrier. Such pharmaceutical compositions can be in the form of tablets, coated tablets, dragees, hard and soft gelatin capsules, solutions, emulsions or suspensions. The pharmaceutical compositions also can be in the form of suppositories or injectable solutions.

[0388] The pharmaceutical compounds of the invention, in addition to one or more compounds of the invention, contain a pharmaceutically acceptable carrier. Suitable pharmaceutically acceptable carriers include pharmaceutically inert, inorganic and organic carriers. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragees and hard gelatin capsules. Suitable excipients for soft gelatin capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc. Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc. Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc. Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

[0389] Moreover, the pharmaceutical compositions 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.

[0390] The dosage at which compounds of the invention can be administered 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.

[0391] The following Examples illustrate the present invention without limiting it. All temperatures are given in degrees Celsius.

EXAMPLE A

[0392] Tablets of the following composition can be manufactured in the usual manner:

	mg/tablet
Active substance	5
Lactose	45
Corn starch	15

-continued

	mg/tablet
Microcrystalline cellulose	34
Magnesium stearate	1
Tablet weight	100

EXAMPLE B

[0393] Capsules of the following composition can be manufactured:

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

[0394] The active substance, lactose and corn starch can be firstly mixed in a mixer and then in a comminuting machine. The mixture then can be returned to the mixer, the talc added thereto, and mixed thoroughly. The mixture can be filled by machine into hard gelatin capsules.

EXAMPLE C

[0395] Suppositories of the following composition can be manufactured:

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

[0396] The suppository mass can be melted in a glass or steel vessel, mixed thoroughly and cooled to 45° C. Thereupon, the finely powdered active substance can be added thereto and stirred until it has dispersed completely. The mixture can be poured into suppository moulds of suitable size, left to cool; the suppositories can then be removed from the moulds and packed individually in wax paper or metal foil.

[0397] In the following, the synthesis of compounds of formula (I) is further exemplified. The compounds of formula I may be prepared in accordance with the process variants as described above. The starting materials described in the Example section are either commercially available or otherwise known or derived from the chemical literature, for instance as cited below, or may be prepared as described in the Examples section.

EXAMPLES

General Procedure I—Amide Coupling:

[0398] To a 0.1 M stirred solution of an indole-2-carboxylic acid derivative of type (II) in CH_2Cl_2 are added EDC (1.3 eq), HOBt (1.3 eq), Et_3N (1.3 eq) and the amine derivative (A-H, as defined above, 1 eq). The mixture is stirred overnight at room temperature and then poured onto water and extracted with CH_2Cl_2. The combined organic phases are dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography or preparative HPLC affords a compound of formula (I).

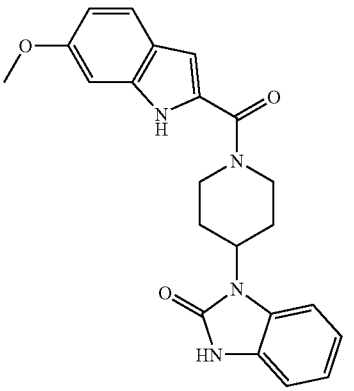
General Procedure II—Alkylation:

[0399] To a 0.1 M stirred solution of a derivative of general formula (I-1) in DMF is added NaH (60% in oil, 2.1 eq.). After stirring the mixture at room temperature for 30 min. the electrophilic reactant R^1-hal (1.1 eq.) is added. The mixture is stirred an additional 14 hours at 60° C. and then poured onto water and extracted with ethyl acetate. The combined organic phases are dried over Na_2SO_4 and concentrated in vacuo. Purification by preparative HPLC affords the corresponding derivatives of general formula (I-2).

Example 1

1-[1-(6-Methoxy-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0400]



[0401] Amide coupling according to general procedure I:

[0402] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

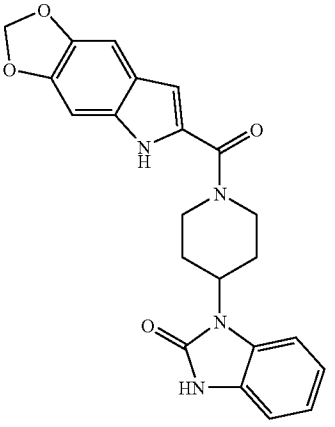
[0403] Acid: 6-Methoxy-1H-indole-2-carboxylic acid,

[0404] ES-MS m/e (%): 391.5 ($M+H^+$).

Example 2

1-[1-(5H-[1,3]Dioxolo[4,5-f]indole-6-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0405]



[0406] Amide coupling according to general procedure I:

[0407] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

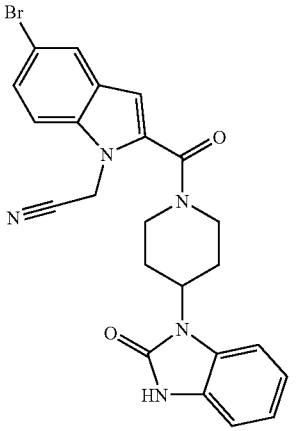
[0408] Acid: 5H-[1,3]Dioxolo[4,5-f]indole-6-carboxylic acid,

[0409] ES-MS m/e (%): 405.5 ($M+H^+$).

Example 3

{5-Bromo-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile

[0410]



[0411] Amide coupling according to general procedure I:

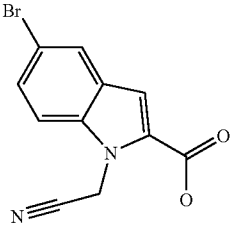
[0412] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

[0413] Acid: 5-Bromo-1-cyanomethyl-1H-indole-2-carboxylic acid (described herein below),

[0414] ES-MS m/e (%): 478.0 ($M+H^+$).

5-Bromo-1-cyanomethyl-1H-indole-2-carboxylic acid

[0415]



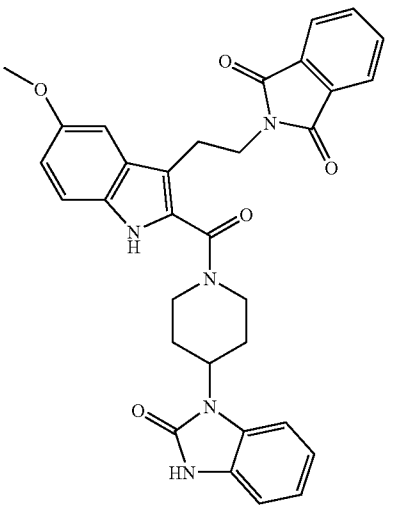
[0416] To a solution of 1.0 eq. of 5-Bromo-1-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester (prepared according to U.S. Pat. No. 5,854,245) in a mixture of THF/H_2O ((9/1) was added $LiOH.H_2O$ (1.0 eq.) and the reaction mixture stirred 6 h at RT, acidified to pH 2 and then partially concentrated until precipitation of the crude product which was filtered off and washed with Et_2O and then dried to give the desired product as a beige solid (86%).

[0417] ES-MS m/e (%):=279.0 ($M-H^+$).

Example 4

2-(2-{5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-ethyl)-isoindole-1,3-dione

[0418]



[0419] Amide coupling according to general procedure I:

[0420] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

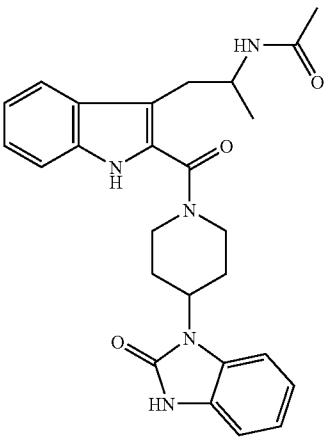
[0421] Acid: 3-[2-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-ethyl]-5-methoxy-1H-indole-2-carboxylic acid,

[0422] ES-MS m/e (%): 564.5 ($M+H^+$).

Example 5

N-(1-Methyl-2-{2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-ethyl)-acetamide

[0423]



[0424] Amide coupling according to general procedure I:

[0425] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

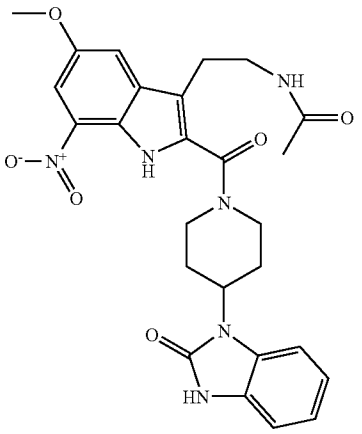
[0426] Acid: 3-(2-Acetylamino-propyl)-1H-indole-2-carboxylic acid,

[0427] ES-MS m/e (%):458.6 ($M-H^+$).

Example 6

N-(2-{5-Methoxy-7-nitro-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-ethyl)-acetamide

[0428]



[0429] Amide coupling according to general procedure I:

[0430] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

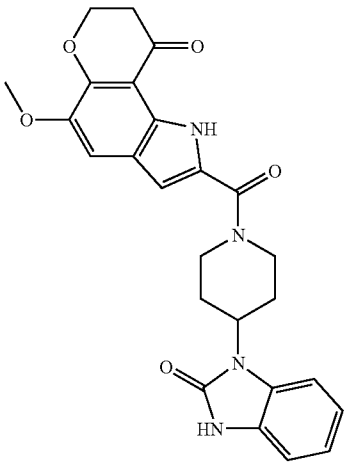
[0431] Acid: 3-(2-Acetylamino-propyl)-1H-indole-2-carboxylic acid,

[0432] ES-MS m/e (%): 519.6 ($M-H^+$).

Example 7

5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl) -piperidine-1-carbonyl]-7,8-dihydro-1H-pyrano[2,3-g]indol-9-one

[0433]



[0434] Amide coupling according to general procedure I:

[0435] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

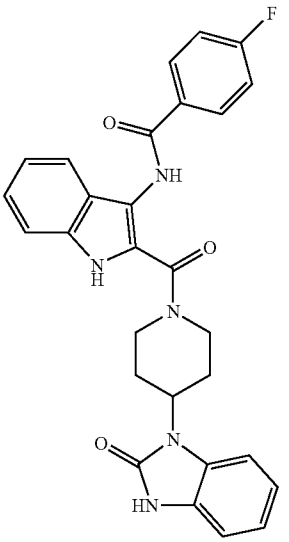
[0436] Acid: 5-Methoxy-9-oxo-1,7,8,9-tetrahydro-pyrano[2,3-g]indole-2-carboxylic acid

[0437] ES-MS m/e (%): 461.5 ($M+H^+$).

Example 8

4-Fluoro-N-{2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-benzamide

[0438]



[0439] Amide coupling according to general procedure I:

[0440] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

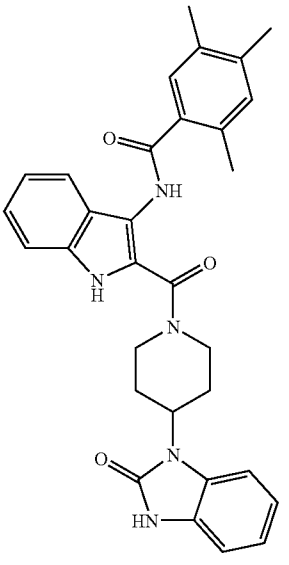
[0441] Acid: 3-(4-Fluoro-benzoylamino)-1H-indole-2-carboxylic acid,

[0442] ES-MS m/e (%): 498.5 ($M+H^+$).

Example 9

2,4,5-Trimethyl-N-{2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-benzamide

[0443]

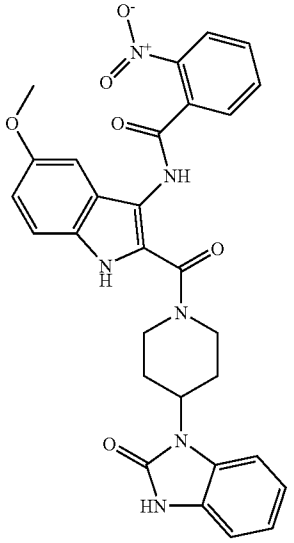


[0444] Amide coupling according to general procedure I:
[0445] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0446] Acid: 3-(2,4,5-Trimethyl-benzoylamino)-1H-indole-2-carboxylic acid,
[0447] ES-MS m/e (%): 522.6 ($M+H^+$).

Example 10

N-{5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-2-nitro-benzamide

[0448]

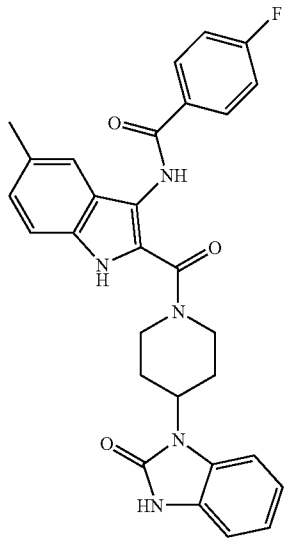


[0449] Amide coupling according to general procedure I:
[0450] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0451] Acid: 5-Methoxy-3-(2-nitro-benzoylamino)-1H-indole-2-carboxylic acid,
[0452] ES-MS m/e (%): 555.5 ($M+H^+$).

Example 11

N-{5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-2-nitro-benzamide

[0453]

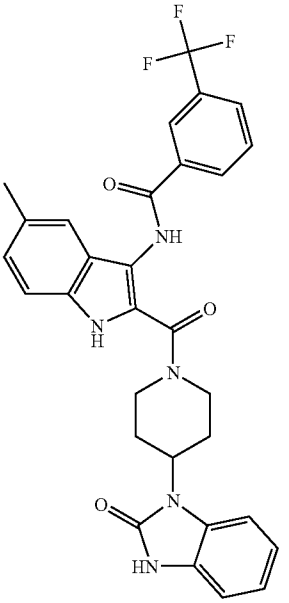


[0454] Amide coupling according to general procedure I:
[0455] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0456] Acid: 3-(4-Fluoro-benzoylamino)-5-methyl-1H-indole-2-carboxylic acid,
[0457] ES-MS m/e (%): 512.5 ($M+H^+$).

Example 12

N-{5-Methoxy-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-2-nitro-benzamide

[0458]

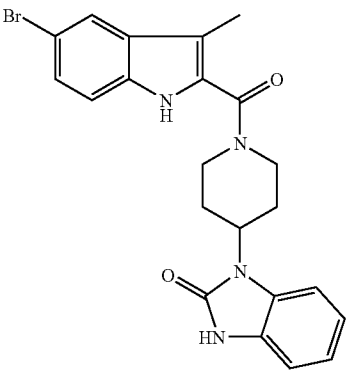


[0459] Amide coupling according to general procedure I:
[0460] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0461] Acid: 5-Methyl-3-(3-trifluoromethyl-benzoylamino)-1H-indole-2-carboxylic acid,
[0462] ES-MS m/e (%): 560.6 ($M-H^+$).

Example 13

1-[1-(5-Bromo-3-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0463]

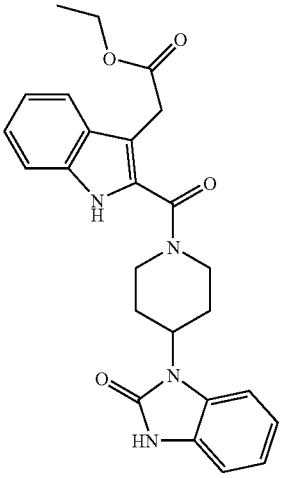


[0464] Amide coupling according to general procedure I:
[0465] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0466] Acid: 5-Bromo-3-methyl-1H-indole-2-carboxylic acid,
[0467] ES-MS m/e (%): 453.4 ($M+H^+$).

Example 14

{2-[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-3-yl}-acetic acid ethyl ester

[0468]

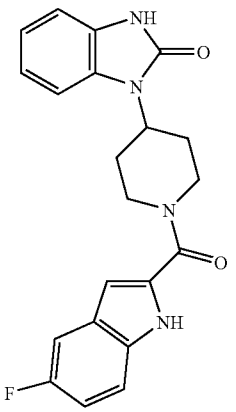


[0469] Amide coupling according to general procedure I:
[0470] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0471] Acid: 3-Ethoxycarbonylmethyl-1H-indole-2-carboxylic acid,
[0472] ES-MS m/e (%): 447.5 ($M+H^+$).

Example 15

1-[1-(5-Fluoro-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0473]

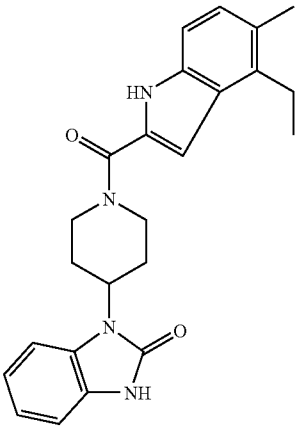


[0474] Amide coupling according to general procedure I:
[0475] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0476] Acid: 5-Fluoro-1H-indole-2-carboxylic acid,
[0477] ES-MS m/e (%): 379.4 ($M+H^+$).

Example 16

1-[1-(4-Ethyl-5-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0478]

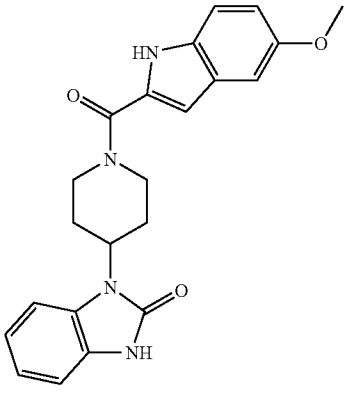


[0479] Amide coupling according to general procedure I:
[0480] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0481] Acid: 4-Ethyl-5-methyl-1H-indole-2-carboxylic acid (prepared according to DE 2203542)
[0482] ES-MS m/e (%): 403.5 ($M+H^+$).

Example 17

1-[1-(5-Methoxy-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0483]

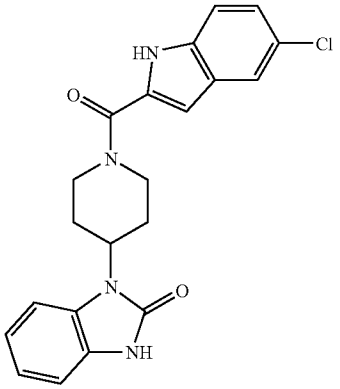


[0484] Amide coupling according to general procedure I:
[0485] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
[0486] Acid: 5-Methoxy-1H-indole-2-carboxylic acid,
[0487] ES-MS m/e (%): 391.5 ($M+H^+$).

Example 18

1-[1-[(5-Chloro-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0488]



[0489] Amide coupling according to general procedure I:

[0490] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

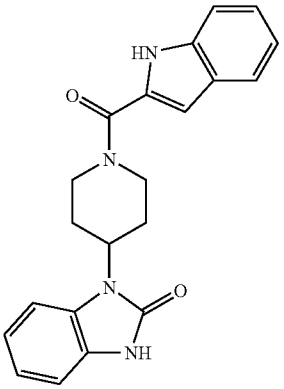
[0491] Acid: 5-Chloro-1H-indole-2-carboxylic acid,

[0492] ES-MS m/e (%): 393.5 ($M+H^+$).

Example 19

1-[1-(1H-Indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0493]



[0494] Amide coupling according to general procedure I:

[0495] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

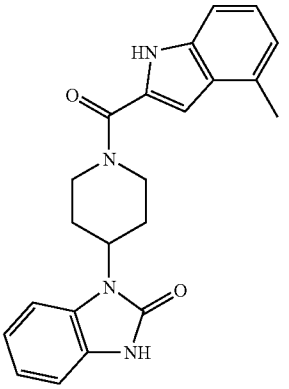
[0496] Acid: 1H-Indole-2-carboxylic acid,

[0497] ES-MS m/e (%): 359.1 ($M-H^+$).

Example 20

1-[1-(4-Methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0498]



[0499] Amide coupling according to general procedure I:

[0500] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

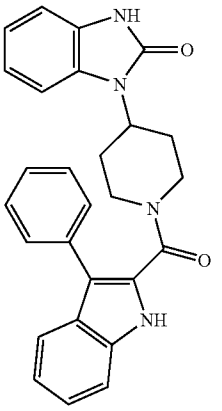
[0501] Acid: 4-Methyl-1H-indole-2-carboxylic acid,

[0502] ES-MS m/e (%): 375.5 ($M+H^+$).

Example 21

1-[1-(3-Phenyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0503]



[0504] Amide coupling according to general procedure I:

[0505] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

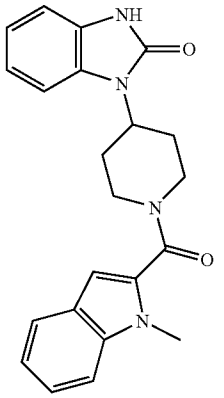
[0506] Acid: 3-Phenyl-1H-indole-2-carboxylic acid,

[0507] ES-MS m/e (%): 437.5 ($M+H^+$).

Example 22

1-[1-(1-Methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0508]



[0509] Amide coupling according to general procedure I:

[0510] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

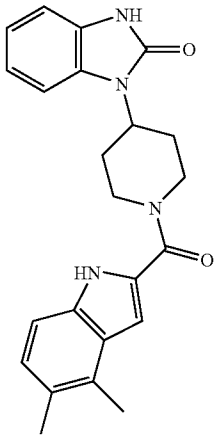
[0511] Acid: 1-Methyl-1H-indole-2-carboxylic acid,

[0512] ES-MS m/e (%): 375.5 ($M+H^+$).

Example 23

1-[1-(4,5-Dimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0513]



[0514] Amide coupling according to general procedure I:

[0515] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

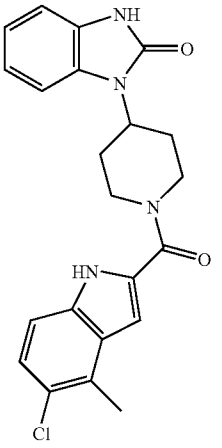
[0516] Acid: 4,5-Dimethyl-1H-indole-2-carboxylic acid (prepared according to DE 2203542)

[0517] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 24

1-[1-(5-Chloro-4-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0518]



[0519] Amide coupling according to general procedure I:

[0520] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

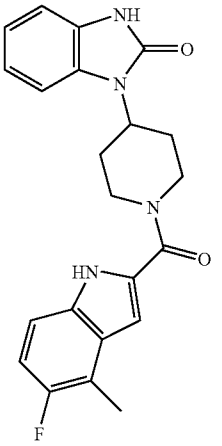
[0521] Acid: 5-Chloro-4-methyl-1H-indole-2-carboxylic acid (prepared according to DE 2203542)

[0522] ES-MS m/e (%): 407.5 ($M-H^+$).

Example 25

1-[1-(5-Fluoro-4-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0523]



[0524] Amide coupling according to general procedure I:

[0525] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

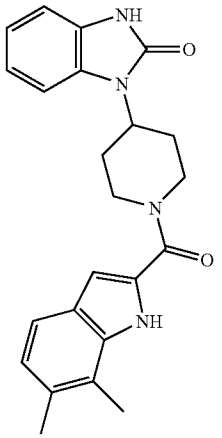
[0526] Acid: 5-Fluoro-4-methyl-1H-indole-2-carboxylic acid (prepared according to DE 2203542)

[0527] ES-MS m/e (%): 393.5 ($M+H^+$).

Example 26

1-[1-(6,7-Dimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0528]



[0529] Amide coupling according to general procedure I:

[0530] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

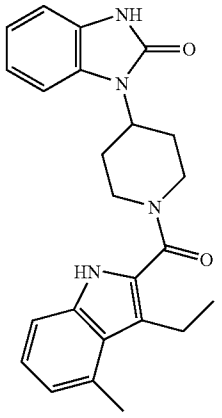
[0531] Acid: 6,7-Dimethyl-1H-indole-2-carboxylic acid,

[0532] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 27

1-[1-(3-Ethyl-4-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0533]



[0534] Amide coupling according to general procedure I:

[0535] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

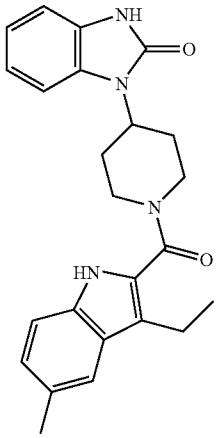
[0536] Acid: 3-Ethyl-4-methyl-1H-indole-2-carboxylic acid

[0537] ES-MS m/e (%): 403.5 ($M+H^+$).

Example 28

1-[1-(3-Ethyl-5-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0538]



[0539] Amide coupling according to general procedure I:

[0540] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

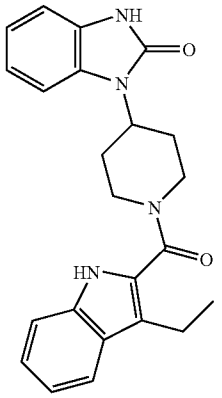
[0541] Acid: 3-Ethyl-5-methyl-1H-indole-2-carboxylic acid

[0542] ES-MS m/e (%): 403.5 ($M+H^+$).

Example 29

1-[1-(3-Ethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0543]



[0544] Amide coupling according to general procedure I:

[0545] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

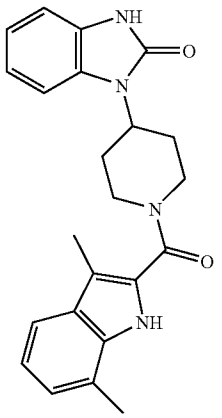
[0546] Acid: 3-Ethyl-1H-indole-2-carboxylic acid,

[0547] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 30

1-[1-(3,7-Dimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0548]



[0549] Amide coupling according to general procedure I:

[0550] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

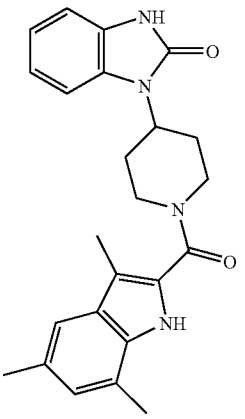
[0551] Acid: 3,7-Dimethyl-1H-indole-2-carboxylic acid

[0552] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 31

1-[1-(3,5,7-Trimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3dihydrobenzoimidazol-2-on

[0553]



[0554] Amide coupling according to general procedure I:

[0555] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

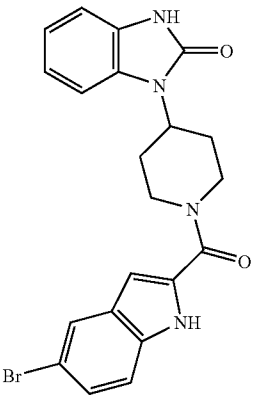
[0556] Acid: 3,5,7-Trimethyl-1H-indole-2-carboxylic acid,

[0557] ES-MS m/e (%): 403.5 ($M+H^+$).

Example 32

1-[1-(5-Bromo-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0558]



[0559] Amide coupling according to general procedure I:

[0560] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

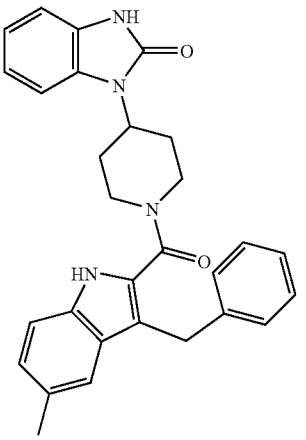
[0561] Acid: 5-Bromo-1H-indole-2-carboxylic acid,

[0562] ES-MS m/e (%): 439.0 ($M+H^+$).

Example 33

1-[1-(3-Benzyl-5-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0563]



[0564] Amide coupling according to general procedure I:

[0565] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

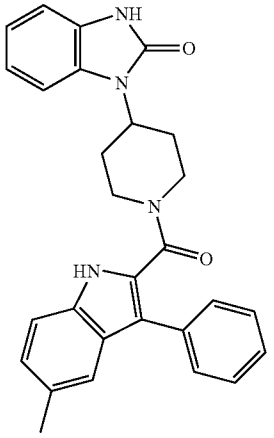
[0566] Acid: 3-Benzyl-5-methyl-1H-indole-2-carboxylic acid (prepared according to Khimiko-Farmatsevticheskii Zhurnal (1969), 3(7), 10-15)

[0567] ES-MS m/e (%): 463.6 ($M-H^+$).

Example 34

1-[1-(5-Methyl-3-phenyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0568]



[0569] Amide coupling according to general procedure I:

[0570] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

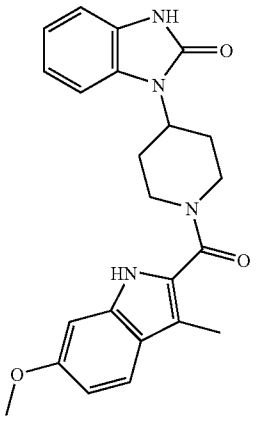
[0571] Acid: 5-Methyl-3-phenyl-1H-indole-2-carboxylic acid,

[0572] ES-MS m/e (%): 449.5 ($M-H^+$).

Example 35

1-[1-(6-Methoxy-3-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0573]



[0574] Amide coupling according to general procedure I:

[0575] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

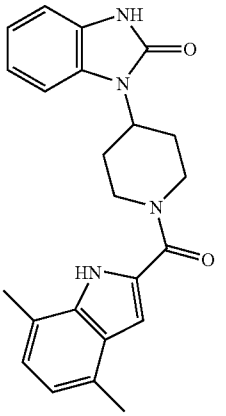
[0576] Acid: 6-Methoxy-3-methyl-1H-indole-2-carboxylic acid (prepared according to Journal of Organic Chemistry (1997), 62(26), 9298-9304)

[0577] ES-MS m/e (%): 405.5 ($M+H^+$).

Example 36

1-[1-(4,7-Dimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0578]



[0579] Amide coupling according to general procedure I:

[0580] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

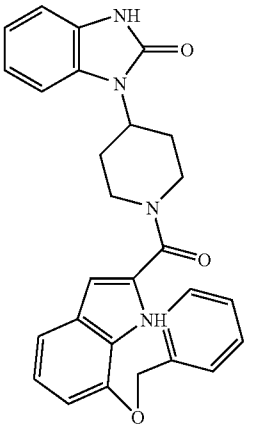
[0581] Acid: 4,7-Dimethyl-1H-indole-2-carboxylic acid,

[0582] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 37

1-[1-(7-Benzyloxy-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0583]



[0584] Amide coupling according to general procedure I:

[0585] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

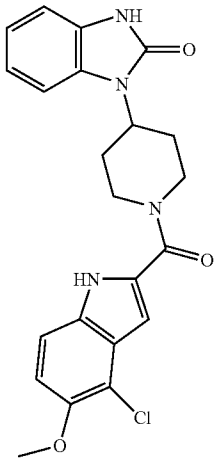
[0586] Acid: 7-Benzyloxy-1H-indole-2-carboxylic acid (preparation described in WO 2004018428)

[0587] ES-MS m/e (%): 467.6 ($M+H^+$).

Example 38

1-[1-(4-Chloro-5-methoxy-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0588]



[0589] Amide coupling according to general procedure I:

[0590] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

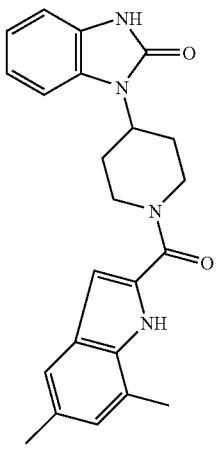
[0591] Acid: 4-Chloro-5-methoxy-1H-indole-2-carboxylic acid (preparation described in DE 2203542)

[0592] ES-MS m/e (%): 425.4 ($M+H^+$).

Example 39

1-[1-(5,7-Dimethyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0593]



[0594] Amide coupling according to general procedure I:

[0595] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

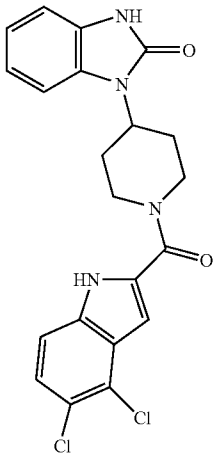
[0596] Acid: 5,7-Dimethyl-1H-indole-2-carboxylic acid,

[0597] ES-MS m/e (%): 389.5 ($M+H^+$).

Example 40

1-[1-(4,5-Dichloro-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0598]



[0599] Amide coupling according to general procedure I:

[0600] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

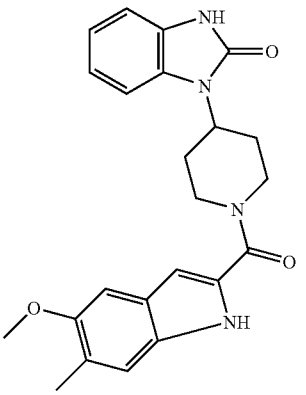
[0601] Acid: 4,5-Dichloro-1H-indole-2-carboxylic acid,

[0602] ES-MS m/e (%): 429.4 ($M+H^+$).

Example 41

1-[1-(5-Methoxy-6-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0603]



[0604] Amide coupling according to general procedure I:

[0605] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

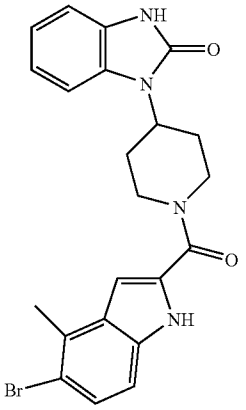
[0606] Acid: 5-Methoxy-6-methyl-1H-indole-2-carboxylic acid

[0607] ES-MS m/e (%): 405.5 ($M+H^+$).

Example 42

1-[1-(5-Bromo-4-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0608]



[0609] Amide coupling according to general procedure I:

[0610] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

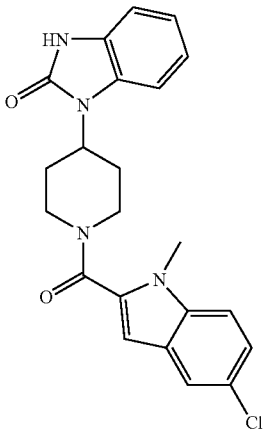
[0611] Acid: 5-Bromo-4-methyl-1H-indole-2-carboxylic acid (described in US 2004053979)

[0612] ES-MS m/e (%): 451.5 ($M-H^+$).

Example 43

1-[1-(5-Chloro-1-methyl-1H-indole-2-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

[0613]



[0614] Amide coupling according to general procedure I:

[0615] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

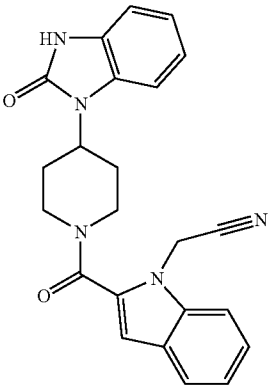
[0616] Acid: 5-Chloro-1-methyl-1H-indole-2-carboxylic acid,

[0617] ES-MS m/e (%): 409.1 ($M+H^+$).

Example 44

{2-[4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile

[0618]



[0619] Amide coupling according to general procedure I:

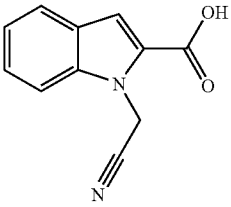
[0620] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

[0621] Acid: 1-Cyanomethyl-1H-indole-2-carboxylic acid

[0622] ES-MS m/e (%): 400.4 ($M+H^+$).

Cyanomethyl-1H-indole-2-carboxylic acid

[0623]



[0624] To a solution of 1.0 eq. of 1-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester, in a mixture of THF/H_2O ((9/1) was added LiOH.H_2O (1.0 eq.) and the reaction mixture stirred 6 h at RT, acidified to pH2 and then partially concentrated until precipitation of the crude product which was filtered off and washed with Et_2O and then dried to give the desired product as a light yellow solid (70%).

[0625] ES-MS m/e (%): 199.0 ($M-H^+$).

Example 45

{5-Chloro-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile

[0626] Amide coupling according to general procedure I:

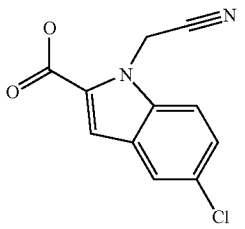
[0627] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

[0628] Acid: 5-Chloro-1-cyanomethyl-1H-indole-2-carboxylic acid

[0629] ES-MS m/e (%): 434.1 ($M+H^+$).

5-Chloro-1-cyanomethyl-1H-indole-2-carboxylic acid

[0630]



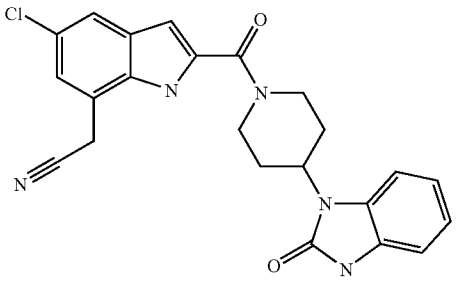
[0631] To a solution of 1.0 eq. of 5-chloro-1-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester (prepared according to Indian Journal of Chemistry, Section B: Organic Chemistry Including Medicinal Chemistry (1989), 28B(12), 1065-8) in a mixture of THF/H_2O ((9/1) was added LiOH.H_2O (1.0 eq.) and the reaction mixture stirred 6 h at R/T, acidified to pH2 and then partially concentrated until precipitation of the crude product which was filtered off and washed with Et_2O and then dried to give the desired product as a light yellow solid (84%).

[0632] ES-MS m/e (%): 232.9 ($M-H^+$).

Example 46

{5-Chloro-2-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-1H-indol-7-yl}-acetonitrile

[0633]



[0634] Amide coupling according to general procedure I:

[0635] Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,

[0636] Acid: 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid (described hereinafter),

[0637] ES-MS m/e (%): 434.3 ($M+H^+$).

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

[0638] To a stirred solution of 0.55 g (2.85 mmol) of (4-chloro-2-methyl-phenyl)-hydrazine, in acetic acid (5 ml), was added 0.34 g (2.91 mmol) of ethyl pyruvate. The mixture was stirred 2 hours at 35° C., poured onto an aqueous solution of sat. $NaHCO_3$ and then extracted with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo, to afford 0.702 g (97%) of 2-[(4-chloro-2-methyl-phenyl)-hydrazonol-propionic acid ethyl ester as a light orange solid.

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

[0639] To a solution of 0.70 g (2.75 mmol) of 2-[(4-chloro-2-methyl-phenyl)-hydrazono]-propionic acid ethyl ester in a sealed tube was added toluene (10 ml) and amberlyst 15 (1.60 g). The reaction mixture was heated at 120° C. over the night. The reaction mixture was concentrated under vacuo and purified by flash chromatography (SiO2, EtOAc/Hex 1/6) to afford 0.22 g (34%) of 5-chloro-7-methyl-1H-indole-2-carboxylic acid ethyl ester as a white solid.

[0640] ES-MS m/e (%): 238.1 ($M+H^+$).

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

[0641] To a solution of 0.22 g (0.9 mmol) of 5-chloro-7-methyl-1H-indole-2-carboxylic acid ethyl ester in CH_2Cl_2 (10 ml), 0.21 g of di-tert-butyl dicarbonate, 0.13 ml of Et_3N and 23 mg of DMAP were added. The reaction mixture was stirred at RT for 2 hours, poured onto an aqueous solution of HCl 1M and extracted with CH_2Cl_2. The reaction mixture was concentrated under vacuo and purified by flash chromatography (SiO2, EtOAc/Hex 1/9) to afford 0.30 g (97%) of 5-chloro-7-methyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light yellow solid.

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

[0642] To a solution of 0.30 g (0.9 mmol) of 5-chloro-7-methyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in CCl_4 (10 ml), 016 g N-bromosuccinimide (NBS) and 11 mg of benzoyl peroxide were added. The reaction mixture was heated at reflux for one hour and cooled down to RT. The succinimide was filtered off and the solvent removed under reduced pressure to afford 0.35 g (95%) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light brown solid. This product was directly used in the next step (unstable).

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

[0643] To a solution of 1.00 g (2.4 mmol) of 7-bromomethyl-5-chloro-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in DMSO (10 ml) at RT, 012 g of sodium cyanide was added. The reaction mixture was stirred at RT for one hour, poured on a saturated aqueous ammonium chloride solution and the product was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (SiO_2, EtOAc/Hex 9/1) afforded 0.31 g (36%) of 5-chloro-7-cyanomethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester as a light yellow oil.

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

[0644] To a solution of 0.30 g (0.8 mmol) of 5-chloro-7-cyanomethyl-indole-1,2-dicarboxylic acid 1-tert-butyl ester 2-ethyl ester in CH_2Cl_2 (8 ml) at RT was added 2 ml of TFA. The reaction mixture was stirred at RT for one hour and concentrated under vacuo The crude was taken up in EtOAc and neutralized with aqueous NaHCO3. The combined organic phases were dried over Na_2SO_4 and concentrated in

vacuo. Preparative HPLC (30% CH_3CN/H_2O) afforded 81 mg (35%) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester as a white solid.

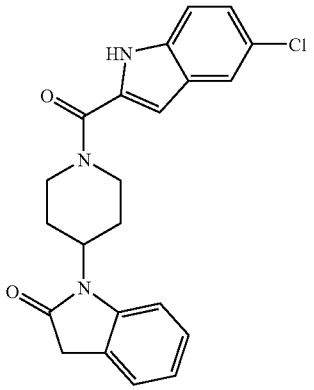
g) 5-Chloro-7-cyanomethyl-1H-indole-2-carboxylic acid

[0645] To a solution of 81 mg (0.3 mmol) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid ethyl ester in $THF/EtOH/H_2O$ (5 ml) at RT was added 39 mg of $LiOH.H_2O$. The reaction mixture was stirred at 40° C. for three hours and then acidified with aqueous HCl 1M. The product was extracted with EtOAc and concentrated under vacuo to afford 71 mg (98%) of 5-chloro-7-cyanomethyl-1H-indole-2-carboxylic acid as a white solid. ES-MS m/e (%): 232.9 ($M-H^+$).

Example 47

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

[0646]

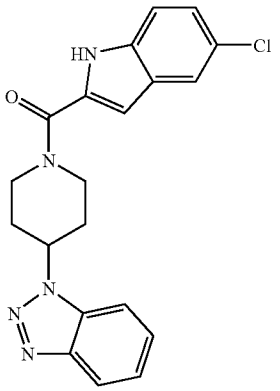


[0647] Amide coupling according to general procedure I:
[0648] Amine: 1-Piperidin-4-yl-1,3-dihydro-indol-2-one,
[0649] Acid: 5-Chloro-1H-indole-2-carboxylic acid,
[0650] ES-MS m/e (%): 394.4 ($M+H^+$).

Example 48

(4-Benzotriazol-1-yl-piperidin-1-yl)-(5-chloro-1H-indol-2-yl)-methanone

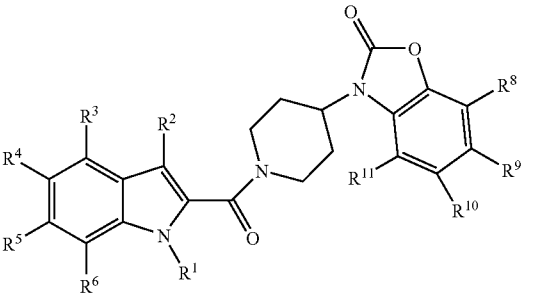
[0651]



[0652] Amide coupling according to general procedure I:
[0653] Amine: 1-Piperidin-4-yl-1H-benzotriazole,
[0654] Acid: 5-Chloro-1H-indole-2-carboxylic acid,
[0655] ES-MS m/e (%): 380.4 ($M+H^+$).

1. A compound of formula (Id)

(Id)



R^1 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH, or
—(C_{1-6}-alkylene)-C(O)—NR^aR^b;
R^2 is hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy,
—(C_{1-6}-alkylene)-NR^cR^d,
—(C_{1-6}-alkylene)-C(O)R^f,
benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or
phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
R^3 is hydrogen, halo, or C_{1-6}-alkyl;
R^4 is hydrogen,
halo,
C_{1-6}-alkyl,
halo-C_{1-6}-alkyl,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy, or
—O—C_{2-10}-alkenyl;
R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;
or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
—R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2;
R^6 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH,
—(C_{1-6}-alkylene)-NR^gR^h,
—(C_{1-6}-alkylene)-C(O)—NR^iR^j,
—O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
nitro,
halo,
cyano,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy,
halo-C_{1-6}-alkyl,
—(C_{1-6}-alkylene)-C(O)R^f,
phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,

—(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,
each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein
—R^5-R^6— is —O—$(CH_2)_n$—C(O)—,
—C(O)—$(CH_2)_n$—O—, or
—O—$(CH_2)_n$—O— wherein n is 1 or 2;
R^7 is hydrogen or C_{1-6}-alkyl;
R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}alkoxy;
R^a, R^b, R^i and R^j are each independently
hydrogen,
C_{1-6}-alkyl,
—(C_{1-6}-alkylene)-NR^kR^l, wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl,
or R^a and R^b, or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
R^c, R^d, R^g and R^h are each independently
hydrogen,
C_{1-6}-alkyl,
—C(O)R^e, or —$S(O)_2R^e$
wherein R^e is selected from the group of
hydrogen,
C_{1-6}-alkyl, and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;
R^f is selected from
hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy; and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or a pharmaceutically acceptable salt thereof.

2. The compound of claim **1**, wherein R^a and R^b, R^c and R^d, R^i and R^j, or R^g and R^h together with the nitrogen to which they are attached form piperazine, 4-(C_{1-6}-alkyl)-piperazine, 4-methylpiperazine, morpholine, piperidine, or pyrrolidine.

3. The compound of claim **1**, wherein R^m is a 5- or 6-membered heteroaryl selected from the group consisting of pyridine, pyrimidine, pyrazine, pyridazine, imidazole, pyrazole, oxazole, and isoxazole.

4. The compound of claim **1**, wherein R^m is a 4- or 6-membered heterocycloalkyl selected from the group consisting of pyrrolidine, oxethane, tetrahydropyrane, piperidine, morpholine, and piperazine.

5. The compound of claim **1**, wherein R^1 is hydrogen or C_{1-6}-alkyl, optionally substituted by CN or OH.

6. The compound of claim **1**, wherein
R^2 is hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy,
—(C_{1-6}-alkylene)-NR^cR^d,
wherein R^c and R^d are each independently
hydrogen,
—C(O)R^e, or —$S(O)_2R^e$
wherein R^e is selected from the group of
hydrogen,
C_{1-6}-alkyl, and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or
R^c and R^d together with the nitrogen to which they are bound form isoindole-1,3-dione,
——(C_{1-6}-alkylene)-C(O)R^f,
wherein R^f is selected from
hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy, and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl,
C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
benzyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or
phenyl, optionally subsitituted by halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano.

7. The compound of claim **1**, wherein R^3 is hydrogen or halo.

8. The compound of claim **1**, wherein
R^4 is hydrogen;
halo;
C_{1-6}-alkyl; or
C_{1-6}-alkoxy;
or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
—R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2.

9. The compound of claim **1**, wherein
R^5 is hydrogen, C_{1-6}-alkyl, or C_{1-6}-alkoxy,
or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
—R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2.

10. The compound of claim **1**, wherein
R^6 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH,
—(C_{1-6}-alkylene)-NR^gR^h
wherein R^g and R^h are each independently selected from hydrogen and C_{1-6}-alkyl;
or wherein R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
—(C_{1-6}-alkylene)-C(O)—NR^iR^j
wherein R^i and R^j are each independently
hydrogen;
C_{1-6}-alkyl;
—(C_{1-6}-alkylene)-NR^kR^l;
wherein R^k and R^l are each independently hydrogen or
C_{1-6}-alkyl;

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

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

nitro;

halo;

cyano;

C_{1-6}-alkoxy;

halo-C_{1-6}-alkoxy;

halo-C_{1-6}-alkyl;

—(C_{1-6}-alkylene)-$C(O)R^f$;

wherein R^f is selected from

hydrogen;

C_{1-6}-alkyl;

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

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

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

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

—R^5-R^6— is —O—(CH_2)$_n$—C(O)—,

—C(O)—(CH_2)$_n$—O—, or

—O—(CH_2)$_n$—O— wherein n is 1 or 2.

11. The compound of claim **1**, wherein

R^6 is hydrogen,

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

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

nitro;

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

—R^5-R^6— is —O—(CH_2)$_n$—C(O)—,

—C(O)—(CH_2)$_n$—O— wherein n is 1 or 2.

12. The compound of claim **1**, wherein R^7 is hydrogen.

13. The compound of claim **1**, wherein R^8, R^9, R^{10}, and R^{11} are hydrogen.

14. The compound of claim **1**, wherein R^8, R^9, R^{10}, and R^{11} are each independently hydrogen or halogen.

15. The compound of claim **1**, wherein R^9 is fluoro and R^8, R^{10}, and R^{11} are hydrogen.

16. The compound of claim **1**, wherein R^8, R^9, and R^{11} are hydrogen, and R^{10} is bromo.

17. The compound of claim **1**, wherein R^8, R^9, R^{10}, and R^{11} are each independently hydrogen or methyl.

18. The compound of claim **1**, wherein R^8, R^9, and R^{10} are hydrogen and R^{11} is methyl.

19. The compound of claim **1**, wherein

R^1 is hydrogen or C_{1-6}-alkyl, optionally substituted by CN or OH;

R^2 is hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy,

—(C_{1-6}-alkylene)-NR^cR^d,

wherein R^c and R^d are each independently

hydrogen,

—$C(O)R^e$, or —$S(O)_2R^e$,

wherein R^e is selected from

hydrogen,

C_{1-6}-alkyl, and

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

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

—(C_{1-6}-alkylene)-$C(O)R^f$,

wherein R^f is selected from

hydrogen,

C_{1-6}-alkyl,

C_{1-6}-alkoxy, and

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

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

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

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

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

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

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

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

R^6 is hydrogen,

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

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

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

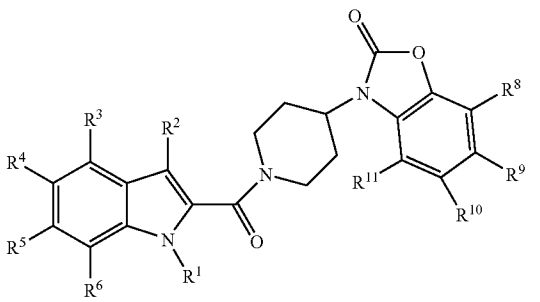
—R^5-R— is —O—(CH_2)$_n$—C(O)—; or —C(O)—(CH_2)$_n$—O— and n is 1 or 2;

R^7 is hydrogen;

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

20. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (Id)

(Id)



R^1 is hydrogen,

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

—(C_{1-6}-alkylene)-C(O)—NR^aR^b;

R^2 is hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy,
—(C_{1-6}-alkylene)-NR^cR^d,
—(C_{1-6}-alkylene)-$C(O)R^f$,
benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano, or
phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
R^3 is hydrogen, halo, or C_{1-6}-alkyl;
R^4 is hydrogen,
halo,
C_{1-6}-alkyl,
halo-C_{1-6}-alkyl,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy, or
—O—C_{2-10}-alkenyl;
R^5 is hydrogen, halo, C_{1-6}-alkyl, or C_{1-6}-alkoxy;
or R^4 and R^5 are bound together to form a ring with the benzo moiety, wherein
—R^4-R^5— is —O—$(CH_2)_n$—O— wherein n is 1 or 2;
R^6 is hydrogen,
C_{1-6}-alkyl, optionally substituted by CN or OH,
—(C_{1-6}-alkylene)-NR^gR^h,
—(C_{1-6}-alkylene)-C(O)—NR^iR^j,
—O-benzyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
nitro,
halo,
cyano,
C_{1-6}-alkoxy,
halo-C_{1-6}-alkoxy,
halo-C_{1-6}-alkyl,
—(C_{1-6}-alkylene)-$C(O)R^f$,
phenyl, optionally subsitituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano,
—(C_{1-3}-alkylene)-R^m, wherein R^m is phenyl, a 5- to 6-membered heteroaryl, 4- to 6-membered heterocycloalkyl or 3 to 6-membered cycloalkyl,
each optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or R^5 and R^6 are bound together to form a ring with the benzo moiety, wherein
—R^5-R^6— is —O—$(CH_2)_n$—C(O)—,
—C(O)—$(CH_2)_n$—O—, or
—O—$(CH_2)_n$—O— wherein n is 1 or 2;
R^7 is hydrogen or C_{1-6}-alkyl;
R^8, R^9, R^{10}, and R^{11} are each independently hydrogen, halo, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy or halo-C_{1-6}alkoxy;
R^a, R^b, R^i and R^j are each independently
hydrogen,
C_{1-6}-alkyl,
—(C_{1-6}-alkylene)-NR^kR^l,
wherein R^k and R^l are each independently hydrogen or C_{1-6}-alkyl, or R^a and R^b, or R^i and R^j together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
R^c, R^d, R^g and R^h are each independently
hydrogen,
C_{1-6}-alkyl,
—$C(O)R^e$, or —$S(O)_2R^e$
wherein R^e is selected from the group of
hydrogen,
C_{1-6}-alkyl, and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form a five or six membered heterocycle comprising one or two heteroatoms selected from the group of nitrogen, oxygen and sulfur;
or R^c and R^d, or R^g and R^h together with the nitrogen to which they are bound form isoindole-1,3-dione;
R^f is selected from
hydrogen,
C_{1-6}-alkyl,
C_{1-6}-alkoxy; and
phenyl, optionally substituted by one or more halo, halo-C_{1-6}-alkyl, C_{1-6}-alkyl, C_{1-6}-alkoxy, halo-C_{1-6}-alkoxy, nitro, or cyano;
or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

* * * * *