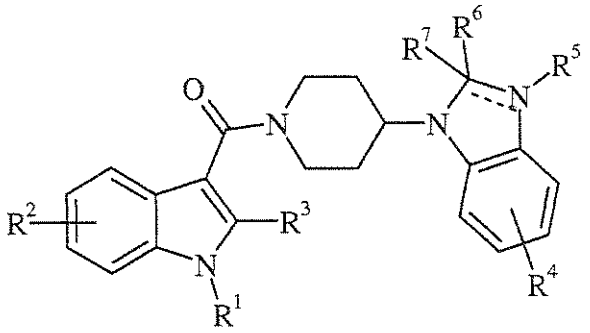
Case 23236

# INDOL-3-YL-CARBONYL-PIPERIDIN-BENZOIMIDAZOL DERIVATIVES AS V1A RECEPTOR ANTAGONISTS

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



(I)

wherein the dotted line is either nil or a double bond;

$R^1$ is H,

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

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

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

CN,

$OR^i$,

$NR^iR^{ii}$,

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

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

$C_{1-6}$-alkyl,

$C_{1-6}$-alkoxy,

$C_{3-6}$-cycloalkyl,

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

$NR^iR^{ii}$,

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

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

$R^2$ is one or more of H, OH, halo, CN, nitro, $C_{1-6}$-alkyl optionally substituted by –$NR^{iii}R^{iv}$, $C_{1-6}$-alkoxy, -O-$CH_2$-$C_{2-6}$-alkenyl, benzyloxy,
or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H,
or is halo,
or is -(CO)-$R^c$, wherein $R^c$ is:
$C_{1-6}$-alkyl,
-$(CH_2)_n$-$NR^iR^{ii}$,
-$(CH_2)_n$-$NR^{iii}R^{iv}$,
5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl,
or is $C_{1-6}$-alkyl or aryl, which are optionally substituted by
halo,
-O(CO)-$C_{1-6}$-alkyl,
or by –NH(CO)$R^d$, wherein $R^d$ is $C_{1-6}$-alkyl optionally substituted by halo or nitro, or $R^d$ is aryl or a 5 or 6 membered heteroaryl, which are optionally substituted by halo, nitro, $C_{1-6}$-alkyl or $C_{1-6}$-haloalkyl;

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

$R^5$ is H, $C_{1-6}$-alkyl, -$(CH_2)_m$-$NR^iR^{ii}$, aryl, or -$(CH_2)_n$-(CO)-$R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl, when the dotted line is nil,
or is nil when the dotted line is a double bond;

$R^6$ is nil when the dotted line is a double bond;

$R^7$ is H,
Cl or,
$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,
or $R^6$ and $R^7$ together form a C=O group when the dotted line is nil;

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

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

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

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

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

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

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

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

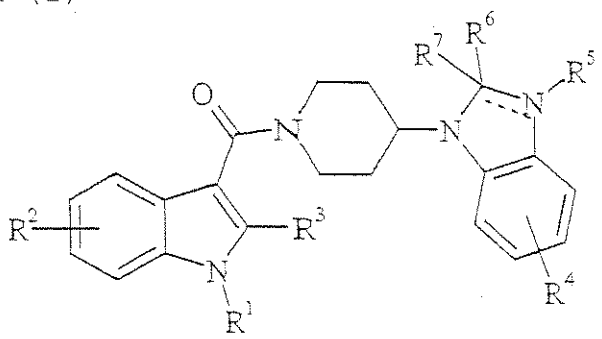
downregulation of the V1a receptor using antisense oligonucleotide injection in the septum also causes a reduction in anxious behavior ( Landgraf, R., R. Gerstberger, et al. (1995). "V1 vasopressin receptor antisense oligodeoxynucleotide into septum reduces vasopressin binding, social discrimination abilities, and anxiety-related behavior in rats." Regul Pept 59(2): 229-39).

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

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

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

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



(I)

wherein the dotted line is either nil or a double bond;

$R^1$ is H,

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

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

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

CN,

$OR^i$,

$NR^iR^{ii}$,

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

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

$C_{1-6}$-alkyl,

$C_{1-6}$-alkoxy,

$C_{3-6}$-cycloalkyl,

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

$NR^iR^{ii}$,

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

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

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

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

$R^3$ is H,

or is halo,

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

$C_{1-6}$-alkyl,

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

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

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

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

halo,

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl, when the dotted line is nil,

or is nil when the dotted line is a double bond;

$R^6$ is nil when the dotted line is a double bond;

$R^7$ is H,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

or $R^6$ and $R^7$ together form a C=O group when the dotted line is nil;

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

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

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

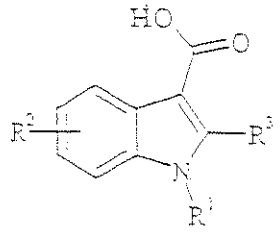
$R^{iii}$ and $R^{iv}$ are H or $C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

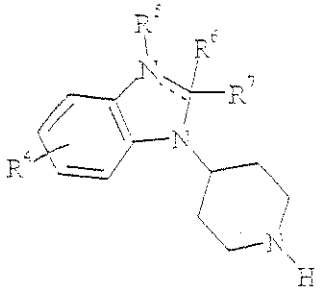
as well as pharmaceutically acceptable salts thereof.

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



II

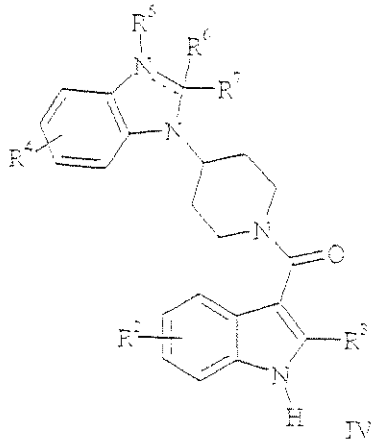
with a compound of formula (III):



III

in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as disclosed.

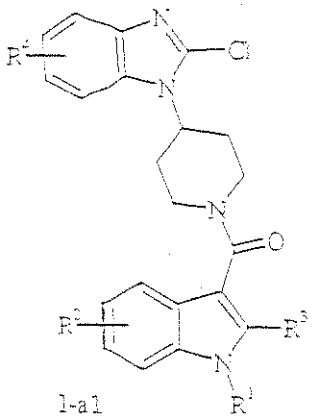
In a third aspect, there is provided a process for the preparation of the compounds of formula (I) as disclosed above, comprising the step of reacting a compound of formula (IV):



IV

with a compound of formula $R^1 - X$, in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as disclosed.

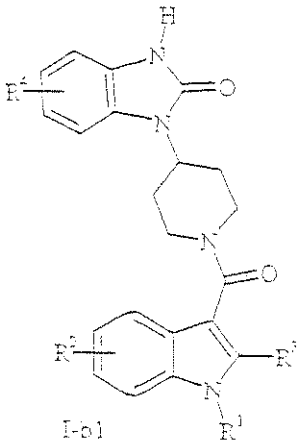
In a fourth aspect, there is provided a process for the preparation of the compounds of formula (I-a) as disclosed, comprising the step of reacting a compound of formula (I-a1):



I-a1

with an amine of formula $HNR^eR^f$, in order to obtain a compound of formula (I-a), wherein $R^7$ is $NR^eR^f$ and $R^1$ to $R^4$ are as disclosed.

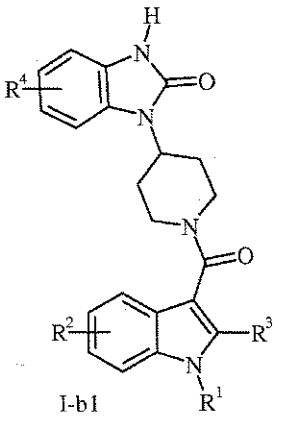
In a fifth aspect, there is provided a process for the preparation of the compounds of formula (I-a) as disclosed comprising the step of reacting a compound of formula (I-b1):



I-b1

with $POCl_3$ in order to obtain a compound of formula (I-a), wherein $R^1$ to $R^4$ are as disclosed and $R^7$ is CI.

In a sixth aspect, there is provided a process for the preparation of the compounds of formula (I-b) as disclosed comprising the step of reacting a compound of formula (I-b1):



I-b1

with a compound of formula $R^5$-X, in order to obtain a compound of formula (I-b), wherein $R^1$ and $R^5$ are different from H and wherein $R^2$ to $R^4$ are as disclosed.

In a seventh aspect, there is provided a compound formula (I-a) or (I-b) obtainable by a process as disclosed above.

In an eighth aspect, there is provided a compound of formula (I), (I-a) or (I-b) as disclosed for a use in the prevention or treatment of dysmenorrheal, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephritic syndrome, obsessive compulsive disorder, anxious and depressive disorders.

In a ninth aspect, there is provided a pharmaceutical composition comprising a compound of formula (I), (I-a) or (I-b) as disclosed.

In a tenth aspect, there is provided a use of a compound of formula (I), (I-a) or (I-b) as disclosed for the preparation of a medicament.

As used herein, the term "aryl" means a monovalent cyclic aromatic hydrocarbon moiety consisting of a mono-, bi- or tricyclic aromatic ring. Examples of aryl moieties include, but are not limited to, optionally substituted phenyl, naphthyl, phenanthryl, fluorenyl, indenyl, pentalenyl, azulenyl, oxydiphenyl, biphenyl, methylenediphenyl, aminodiphenyl, diphenylsulfidyl, diphenylsulfonyl, diphenyiisopropylidenyl, benzodioxanyl, benzofuranyl, benzodioxylyl, benzopyranyl, benzoxazinyl, benzoxazinonyl, benzopiperadinyl, benzopiperazinyl, benzopyrrolidinyl, benzomorpholinyl, methylenedioxyphenyl, ethylenedioxyphenyl, as well as those specifically illustrated by the examples herein below. Substituents for aryl include but are not limited to halogen, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy. Preferred aryl are phenyl and naphthyl and still preferably phenyl.

The term "$C_{1-6}$-alkyl" denotes a saturated straight- or branched-chain group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-

butyl, i-butyl, 2-butyl, t-butyl as well as those specifically illustrated by the examples herein below. Preferred $C_{1-6}$-alkyl groups are $C_{1-4}$-groups, i.e. with 1 - 4 carbon atoms.

The term "$C_{1-6}$-alkoxy" denotes a group wherein the alkyl residues are as defined above, and which is attached via an oxygen atom. Preferred $C_{1-6}$-alkoxy groups are methoxy and ethoxy as well as those specifically illustrated by the examples herein below.

The term "$C_{2-6}$-alkenyl" denotes a carbon chain of 2 to 6 carbon atoms comprising a double bond in its chain. $C_{2-6}$-alkenyl groups include ethenyl, propen-1-yl, propen-2-yl, buten-1-yl, buten-3-yl, penten-1-yl, penten-2-yl, penten-3-yl, penten-4-yl, hexen-1-yl, hexen-2-yl, hexen-3-yl, hexen-4-yl and hexen-5-yl, as well as those specifically illustrated by the examples herein below.

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

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

The term "$C_{1-6}$-haloalkyl" denotes a $C_{1-6}$-alkyl group as defined above which is substituted by one or more halogen. Examples of $C_{1-6}$-haloalkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred $C_{1-6}$-haloalkyl are difluoro- or trifluoro-methyl or ethyl.

"$C_{1-6}$-haloalkoxy" denotes a $C_{1-6}$-alkoxy group as defined above which is substituted by one or more halogen. Examples of $C_{1-6}$-haloalkoxy include but are not limited to methoxy or ethoxy, substituted by one or more Cl, F, Br or I atom(s) as well as those groups specifically illustrated by the examples herein below. Preferred $C_{1-6}$-haloalkoxy are difluoro- or trifluoro-methoxy or ethoxy.

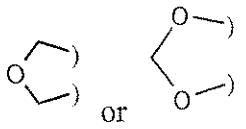
The term "$C_{3-6}$-cycloalkyl" denotes a monovalent or divalent saturated carbocyclic moiety consisting of a monocyclic ring. Cycloalkyl can optionally be substituted with one, two, three or four substituents, wherein each substituent is independently hydroxy, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, halogen, amino, unless otherwise specifically indicated. Examples of cycloalkyl moieties include optionally substituted cyclopropyl, optionally substituted cyclobutyl, optionally substituted cyclopentyl and optionally substituted cyclohexyl as well as those specifically illustrated by the examples herein below.

The term "4 to 7 membered heterocycloalkyl" means a monovalent saturated moiety, consisting of one ring of 4 to 7 atoms as ring members, including one, two, or three heteroatoms chosen from nitrogen, oxygen or sulfur, the rest being carbon atoms. 4 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, $C_{1-6}$-haloalkyl, $C_{1-6}$-hydroxyalkyl, alkoxycarbonyl, amino, $C_{1-6}$-alkylamino, di($C_{1-6}$)alkylamino, aminocarbonyl, or carbonylamino, unless otherwise specifically indicated. Examples of heterocyclic moieties include, but are not limited to, optionally substituted oxetane, optionally substituted tetrahydro-furanyl, optionally substituted piperidinyl, optionally substituted pyrrolidinyl, optionally substituted morpholinyl, optionally substituted piperazinyl, and the like or those which are specifically exemplified herein. Substituents can be selected from $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkyl, halo, CN, OH, $NH_2$, as well as those substituents which are are specifically illustrated in the examples hereinafter. Preferred 4 to 7 membered heterocycloalkyl are 5 to 6 membered heterocycloalkyl.

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

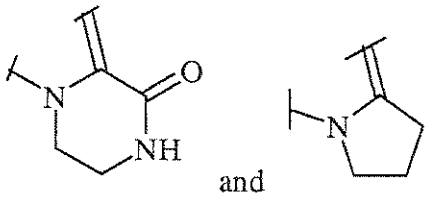
The term "sulfonylaryl" denotes an aryl group as defined hereinabove which is attached via a sulfonyl group.

The expression "two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached" or "two $R^4$ may form an oxo or dioxo bridge together with the phenyl ring to which they are attached" denotes an oxo or dioxo bridge of the following formulae:




which bind two adjacent carbon atoms of the phenyl or indole ring of the compound of formula (I) to which either $R^2$ or $R^4$ is binding.

Examples of group illustrating the expression "$R^1$ and $R^3$ together with the indole ring to which they are attached form a 5 or 6 membered heterocycloalkyl which can be substituted by =O" are:




The expression "$R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl" denotes a 5 or 6 membered heterocycloalkyl group as defined hereinabove which may be substituted by one or more $C_{1-6}$-alkyl as defined hereinabove.

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

In a certain embodiment, the compounds according to the invention are those of formula (I) wherein:

the dotted line is either nil or a double bond;

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$ or aryl when the dotted line is nil or is nil when the dotted line is a double bond;

and $R^1$, $R^2$, $R^3$, $R^4$, $R^6$ and $R^7$ are as defined above , as well as pharmaceutically acceptable salts thereof.

In a further embodiment, the compounds according to the invention are those of formula (I) wherein:

$R^1$ is H or,

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

aryl or,

5 or 6 membered heteroaryl or,

sulfonylaryl or,

$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

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

$-(CH_2)_n-(CO)-R^b$, wherein $R^b$ is aryl or 5 or 6 membered-heterocycloalkyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $-O-CH_2-C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,

halo or,

$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,

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

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$ or aryl, when the dotted line is nil, or is nil when the dotted line is a double bond;

$R^6$ is nil when the dotted line is a double bond;

$R^7$ is H,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl,

or $R^6$ and $R^7$ together form a C=O group when the dotted line is nil;

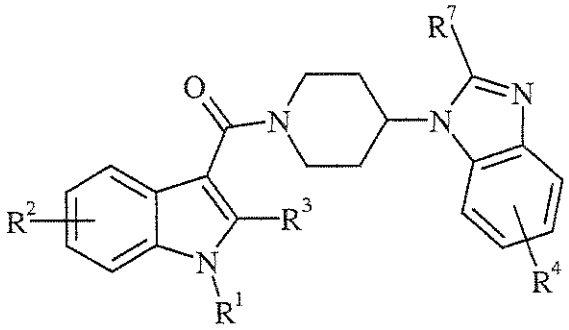
$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

Also encompassed by the compounds of formula (I) are the following compounds of formula (I-a) according to the invention:



(I-a)

wherein $R^1$ to $R^4$ and $R^7$ are as defined hereinabove for formula (I).

Further encompassed by the invention are the compounds of formula (I-a) wherein:

$R^1$ is H or,
$C_{1-6}$-alkyl optionally substituted by CN or by $C_{1-6}$-alkoxy or,
aryl or,
5 or 6 membered heteroaryl or,
sulfonylaryl or,
$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:
halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,
$-(CH_2)_m-NR^iR^{ii}$ or,
$-(CH_2)_n-(CO)-R^b$, wherein $R^b$ is aryl or 5 or 6 membered-heterocycloalkyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $-O-CH_2-C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,
halo or,
$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,
$C_{1-6}$-alkyl or aryl, which are optionally substituted by
$-O(CO)-C_{1-6}$-alkyl,

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

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

$R^7$ is H,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I-a) are those compounds of formula (I-a), wherein:

$R^1$ is H or,

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

$-(CH_2)_m-R^a$ wherein $R^a$ is aryl, which is optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

$R^2$ is one or more of H, halo or $C_{1-6}$-alkoxy;

$R^3$ is H or,

$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl or 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl or,

$C_{1-6}$-alkyl;

$R^4$ is H;

$R^7$ is Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

m is 1 to 6;

as well as pharmaceutically acceptable salts thereof, for example the following compounds:

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

(1-Benzyl-2-methyl-1H-indol-3-yl)-{4-[2-(4-methyl-piperazin-1-yl)-benzoimidazol-1-yl]-piperidin-1-yl}-methanone;

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-morpholin-4-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

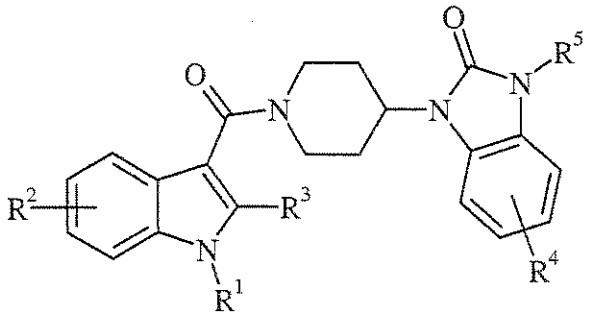
(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-piperidin-1-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

[4-(2-Chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone;

[4-(2-Dimethylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone; and

[4-(2-Methylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone.

Also encompassed by the compounds of formula (I) are the following compounds of formula (I-b) according to the invention:



(I-b)

wherein $R^1$ to $R^5$ are as defined hereinabove for formula (I).

Further encompassed by the invention are the compounds of formula (I-b) wherein:

$R^1$ is H or,

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

aryl or,

5 or 6 membered heteroaryl or,

sulfonylaryl or,

$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, -C(O)O-$C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

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

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

$NR^iR^{ii}$,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more halo, $C_{1-6}$-alkyl optionally substituted by CN, halo or $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy or $(CR^{iii}R^{iv})_n$-phenyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, -O-$CH_2$-$C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,

halo or,

-(CO)-$R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,

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

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl;

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or -(CO)O-$C_{1-6}$-alkyl;

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

Preferred compounds of formula (I-b) are those compounds of formula (I-b), wherein:

$R^1$ is H or,

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

$-(CH_2)_m-R^a$ wherein $R^a$ is aryl, which is optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy, or

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

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

$NR^iR^{ii}$,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more halo, $C_{1-6}$-alkyl optionally substituted by CN, halo or $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy or $(CR^{iii}R^{iv})_n$-phenyl;

$R^2$ is one or more of H, halo or $C_{1-6}$-alkoxy;

$R^3$ is H or,

$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl or 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl or,

$C_{1-6}$-alkyl;

$R^4$ is H;

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl;

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

In further embodiments of the invention, the compounds of formula (I-b) wherein:

$R^1$ is H or,

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

aryl or,

5 or 6 membered heteroaryl or,

sulfonylaryl or,

$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, -C(O)O-$C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

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

$-(CH_2)_n-(CO)-R^b$, wherein $R^b$ is aryl or 5 or 6 membered-heterocycloalkyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, -O-$CH_2$-$C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,

halo or,

-(CO)-$R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,

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

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$ or aryl;

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or -(CO)O-$C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

A further embodiment of the invention encompasses compounds of formula (I-b), wherein:

$R^1$ is H or,

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

$-(CH_2)_m-R^a$ wherein $R^a$ is aryl, which is optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, -C(O)O-$C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

$R^2$ is one or more of H, halo or $C_{1-6}$-alkoxy;

$R^3$ is H or,

-(CO)-$R^c$, wherein $R^c$ is $C_{1-6}$-alkyl or 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl or,

$C_{1-6}$-alkyl;

$R^4$ is H;

$R^5$ is H or $C_{1-6}$-alkyl;

m is 1 to 6;

as well as pharmaceutically acceptable salts thereof.

The following examples are according to the invention:

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

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

1-{1-[2-(Pyrrolidine-1-carbonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one; and

1-{1-[6-Chloro-1-(3,5-difluoro-benzenesulfonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one.

Preferred are the following examples according to the invention:

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

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

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

1-[1-(1-Isopropyl-6-methoxy-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

1-[1-(6-Fluoro-1-isopropyl-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

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

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

1-{1-[6-Chloro-1-(3-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2,3-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(3,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-phenyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(piperidine-1-carbonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2-oxo-2-piperidin-1-yl-ethyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-3-(2-oxo-2-piperidin-1-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one;

2-{3-[1-(6-Chloro-1-diethylcarbamoylmethyl-1*H*-indole-3-carbonyl)-piperidin-4-yl]-2-oxo-2,3-dihydro-benzoimidazol-1-yl}-*N*,*N*-diethyl-acetamide;

1-(1-{6-Chloro-1-[2-(3,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one; and

1-(1-{6-Chloro-1-[2-(5-methyl-2-phenyl-oxazol-4-yl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one.

Most preferred are the following compounds according to the invention:

1-{1-[6-Chloro-1-(2-dimethylamino-ethyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

2-{6-Chloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide;

1-[1-(6-Chloro-1-isopropyl-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

1-[1-(1-Benzyl-6-chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

2-{5,6-Dichloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide;

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

1-[1-(6-Chloro-5-fluoro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

2-{6-Chloro-5-methyl-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide;

1-(1-{6-Chloro-1-[2-(2,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-[1-(6-Chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-3-(2-dimethylamino-ethyl)-1,3-dihydro-benzoimidazol-2-one;

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

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

1-(1-{6-Chloro-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

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

1-{1-[6-Chloro-1-(3-fluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one; and

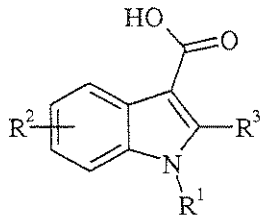
1-{1-[2-(2-Methyl-butyryl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one.

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

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

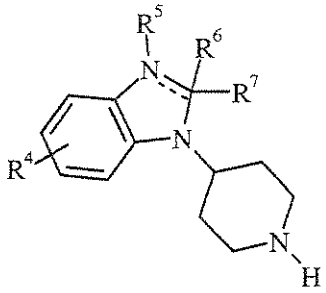
The invention further encompasses the use of a compound of formula (I), (I-a) or (I-b) for the preparation of a medicament which is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder,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

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



II

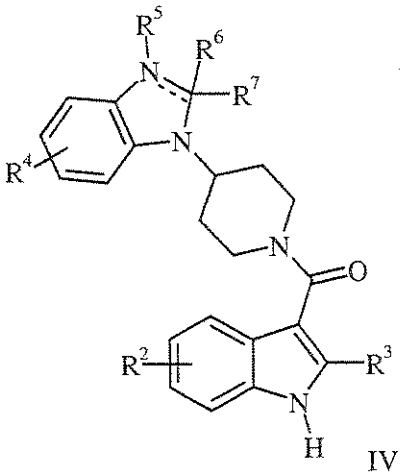
with a compound of formula (III):



III

in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as defined hereinabove. This process is described more in details with general scheme and procedure A.

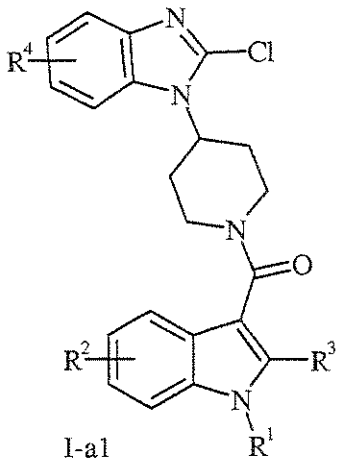
In a certain embodiment, the compounds of formula (I) may be manufactured according to a process comprising the step of reacting a compound of formula (IV):



IV

with a compound of formula $R^1$-X, in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as defined hereinabove. This process is described in details with general scheme and procedure D.

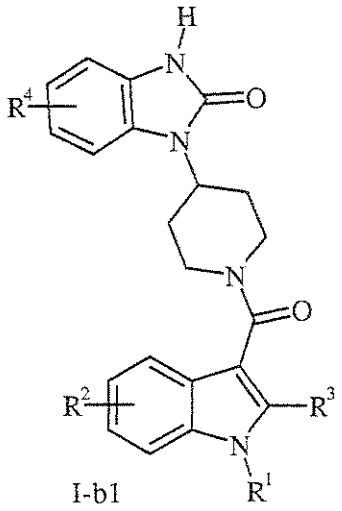
In a certain embodiment, the compounds of formula (I-a) can be manufactured according to a process comprising the step of reacting a compound of formula (I-a1):



I-a1

with an amine of formula $HNR^eR^f$, in order to obtain a compound of formula (I-a), wherein $R^7$ is $NR^eR^f$ and $R^1$ to $R^4$ are as defined hereinabove. This process is described more in details with general scheme and procedure B.

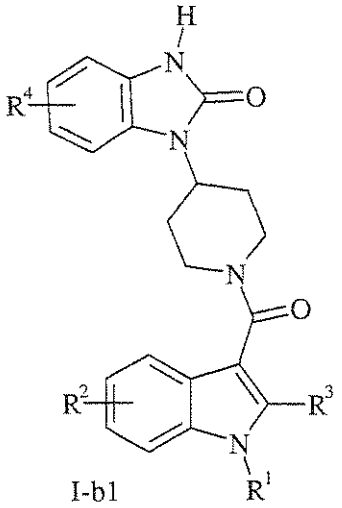
In a certain embodiment, the compounds of formula (I-a) can be manufactured according to a process comprising the step of reacting a compound of formula (I-b1):



I-b1

with $POCl_3$ in order to obtain a compound of formula (I-a), wherein $R^7$ is Cl and $R^1$ to $R^4$ are as defined hereinabove. This process is described more in details with general scheme and procedure B.

In a certain embodiment, the compounds of formula (I-b) can be manufactured according to a process comprising the step of reacting a compound of formula (I-b1):



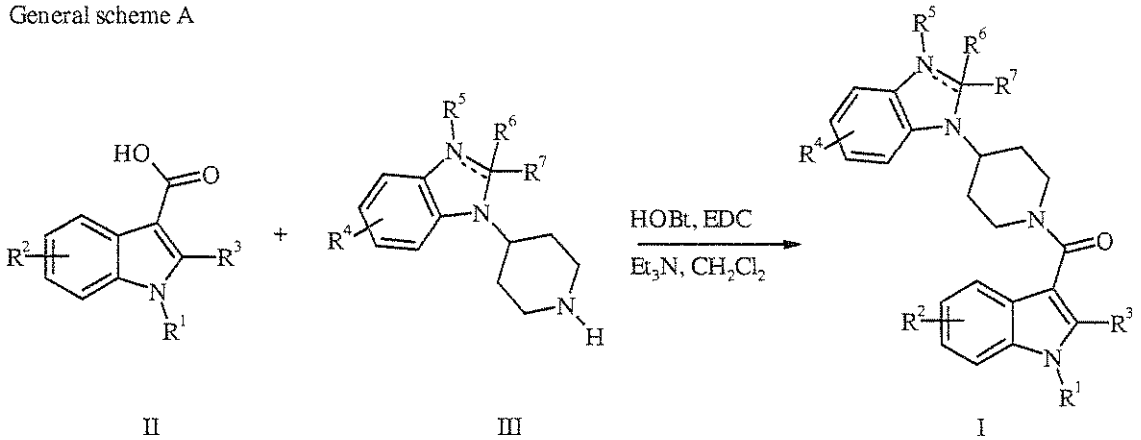
I-b1

with a compound of formula $R^5$-X, in order to obtain a compound of formula (I-b), wherein $R^1$ and $R^5$ are different from H and wherein $R^2$ to $R^4$ are as defined hereinabove. This process is described more in details with general scheme and procedure C.

The preparation of the compounds of the invention is hereafter described in more detail with general schemes A to D and corresponding general procedures.

General scheme and procedure A describe the most general route to prepare the compounds of formulae (I) and (IV), from which further compounds of formulae (I), (I-a) and (I-b) can be prepared with general schemes and procedures B, C and D.

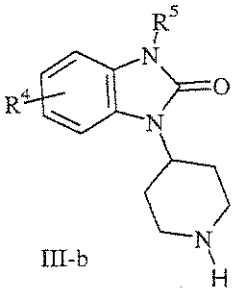
General scheme A




II III I

General scheme A

In order to obtain compounds of the formula (I-b) in a certain embodiment of the invention, a starting material of formula III-b may be used in analogy to general scheme A, namely by reacting a compound of formula II with a compound of formula (III-b):

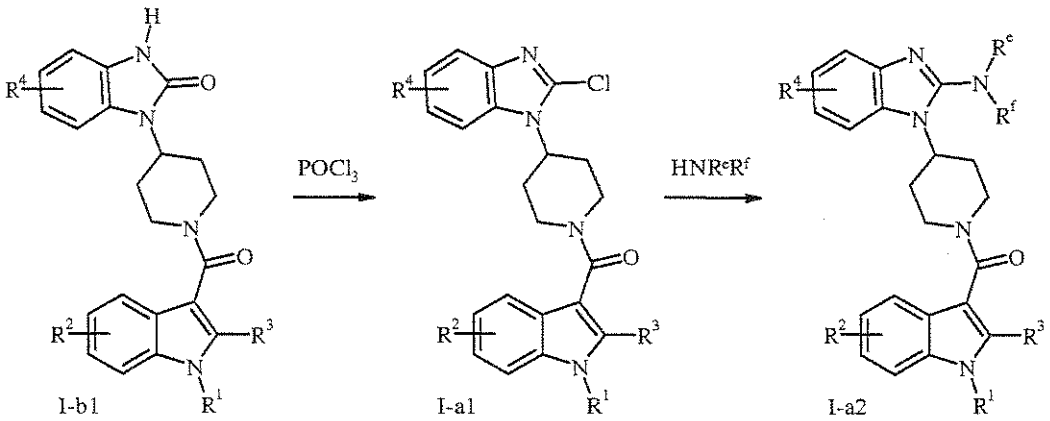


III-b

wherein $R^1$ to $R^5$ are as defined hereinabove.

Compounds of formula (I-b) can be prepared via an amide coupling between an indole 3-carboxylic acid of formula (II) and a piperidine derivative of formula (III). Indole 3-carboxylic acids of formula (II) are either commercially available or readily prepared using a procedure described in. *J.Med.Chem.* 1991, 34, 140, or prepared using a procedure described in the examples hereinafter. Alternatively, the compounds of formula (II) can be prepared following the general scheme D. The piperidine derivatives of formula (III) are either commercially available or prepared using conventional methods with commercially available starting material. An example of general procedure A is also given with general procedure I in the examples hereafter.

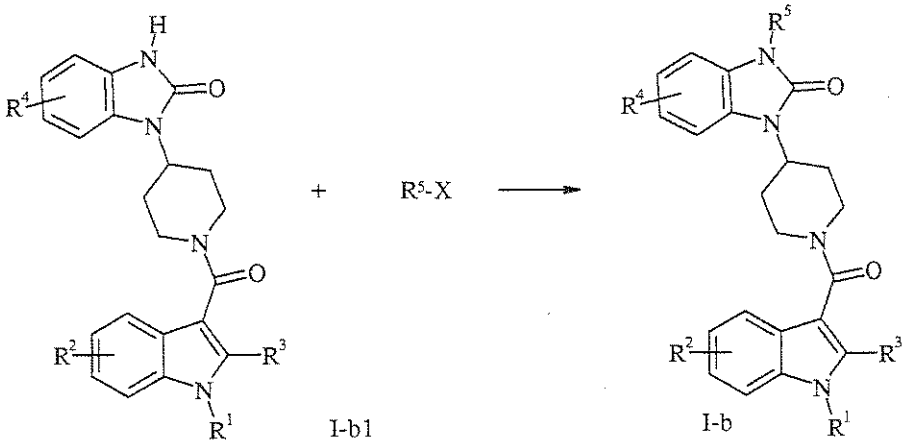
General scheme B




General procedure B

Compounds of formula (I-a2) (compounds of formula (I-a) wherein $R^7$ is $NR^eR^f$) can be prepared by reaction of a chlorobenzimidazole derivative of formula (I-a1) (compounds of formula (I-a) wherein $R^7$ is Cl) with a substituted primary of secondary commercially available amine. Derivatives of formula (I-a1) are prepared by treatment of a compound of formula (I-b1) (compounds of formula (I-b) wherein $R^5$=H) with $POCl_3$ at high temperature (e.g under reflux). General procedure B is further illustrated with the examples hereinafter.

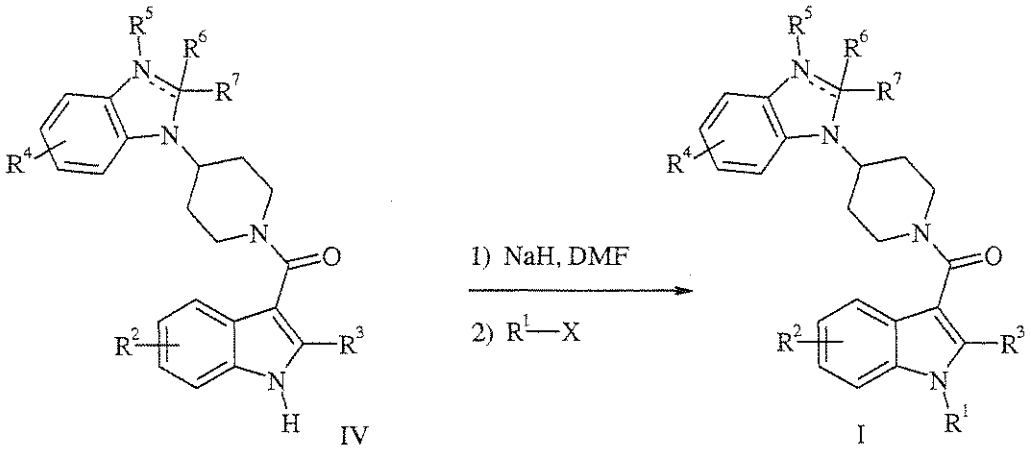
General scheme C




General procedure C

General procedure C is suitable for the preparation of compounds of formula (I-b) wherein $R^1$ and $R^5$ are different from H. Such compounds can be prepared by the alkylation or arylation of a compound of formula (I-b1), wherein $R^1$ is not H, obtained according to general procedure A, with a commercially available electrophilic reactant $R^5$-X, wherein $R^5$ is $C_{1-6}$-alkyl or aryl and X is halo. General procedure C is further illustrated with the examples hereinafter.

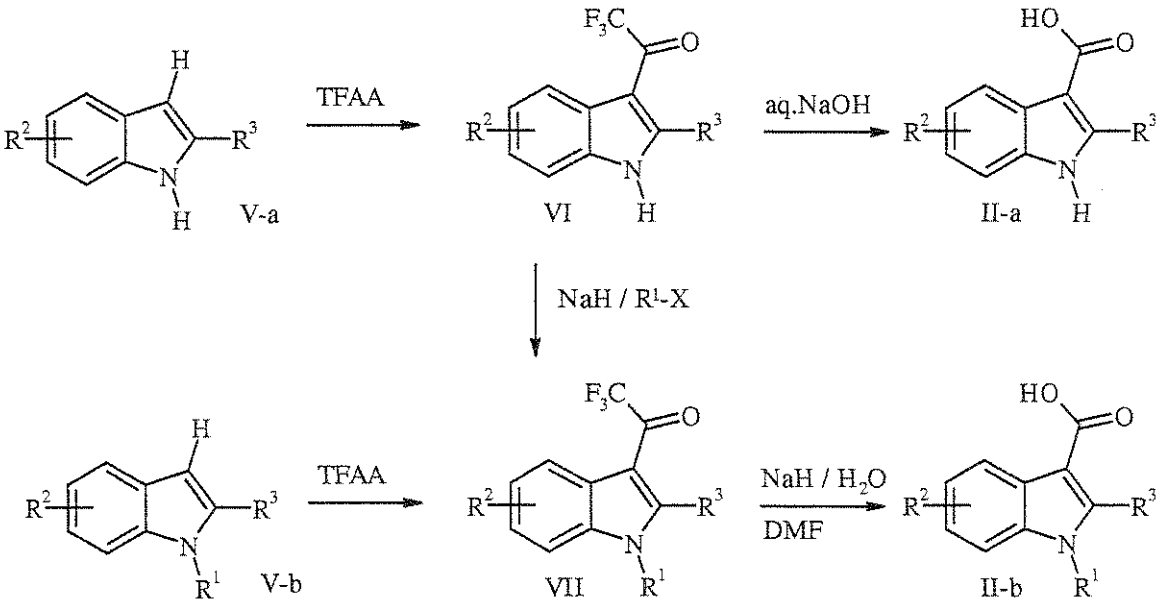
General scheme D



General scheme D

Compounds of formula (I) with $R^1$ different from H can be prepared by N-deprotonation of an indole derivative (IV) (a compound of formula (I) wherein $R^1$ is H) followed by treatment with an electrophilic reactant $R^1$-X (wherein X is a leaving group, e.g. halo) which is either commercially available or easily prepared according to methods well known in the art and commercially available starting materials. Derivatives (IV) are prepared using the method described in the general schemes and procedures A, B and C. General scheme D is hereinafter further illustrated with general procedures II, III and IV.

General scheme E




General procedure E

The treatment of an indole derivative (V-a) with the trifluoroacetic anhydride in DMF affords intermediate (VI) which can be then hydrolysed with an aqueous sodium hydroxide solution to give the 3-carboxylic acid indole derivative (II-a). Alternatively, (VI) could react with an electrophilic reactant $R^1$-X to give (VII), which is then converted to the corresponding carboxylic acid derivative (II-b) with NaH/$H_2O$ in DMF (see *J. Org Chem.*, 1993, 10, 2862). Intermediate (VII) can alternatively be obtained by treatment of an indole derivative (V-b) with trifluoroacetic anhydride in a suitable solvent, e.g. DMF, dichloromethane or 1,2-dichloroethane. Addition of a suitable base may be advantageous.

General procedure I: Amide coupling

General procedure I is a particular embodiment of general procedure A. To a stirred solution of an indole-3-carboxylic acid derivative (1 mmol) in 10 ml $CH_2Cl_2$ was added (1.3 mmol) EDC, (1.3 mmol) HOBt, (1.3 mmol) $Et_3N$ and (1 mmol) of the amine derivative. 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 procedure II: Alkylation

To a stirred solution of 1-[1-(6-chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one in DMF was added 2.1eq. NaH (60% in oil). The mixture was stirred at RT for 30 min. before adding an electrophilic reactant $R^1$-X (1.1eq.). The mixture was stirred an additional 14 hours at 60 °C and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Purification by preparative HPLC afforded the corresponding derivatives.

General procedure III: Acylation

A solution of the indole in dry DMF was treated with sodium hydride (1.05 eq) and stirred for 15min at RT, then treated with the acid chloride (1.1 eq) and stirred at RT for 2h. Purification by prep HPLC yielded the desired product.

General procedure IV: Sulphonylation

A solution of the indole in dry DMF was treated with sodium hydride (1.05 eq) and stirred for 15min at RT, then treated with the sulphonyl chloride (1.1 eq) and stirred at RT for 2h. Purification by prep HPLC yielded the desired product.

Results – V1a activity

Material & Method:

The human V1a receptor was cloned by RT-PCR from total human liver RNA. The coding sequence was subcloned in an expression vector after sequencing to confirm the identity of the amplified sequence. To demonstrate the affinity of the compounds from the present invention to the human V1a receptor binding studies were performed. Cell

membranes were prepared from HEK293 cells transiently transfected with the expression vector and grown in 20 liter fermenters with the following protocol.

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

| Compound of Example | Ki (nM) | Compound of Example | Ki (nM) |
|---|---|---|---|
| 1 | 45 | 28 | 12 |
| 3 | 18 | 29 | 22 |
| 4 | 6 | 30 | 35 |
| 8 | 13 | 31 | 25 |
| 9 | 13 | 33 | 15 |
| 10 | 39 | 34 | 9 |
| 11 | 20 | 35 | 5 |
| 12 | 13 | 36 | 6 |
| 13 | 2 | 37 | 15 |
| 14 | 32 | 38 | 2 |
| 18 | 7 | 39 | 18 |
| 19 | 5 | 40 | 13 |
| 20 | 5 | 41 | 14 |
| 21 | 6 | 42 | 18 |
| 22 | 11 | 43 | 62 |
| 23 | 6 | 44 | 17 |
| 24 | 2 | 45 | 43 |
| 25 | 20 | 46 | 2 |
| 26 | 0.7 | 47 | 5 |
| 27 | 5 | 48 | 3 |

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

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

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

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

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

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

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

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

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

Example A

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

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

Example B

Capsules of the following composition are manufactured:

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

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

Example C

Suppositories of the following composition are manufactured:

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

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

EXAMPLES

General Procedure I: amid coupling:

General procedure I is a particular embodiment of general procedure A. To a stirred solution of an indole-3-carboxylic acid derivative (1 mmol) in 10 ml $CH_2Cl_2$ was added (1.3 mmol) EDC, (1.3 mmol) HOBt, (1.3 mmol) $Et_3N$ and (1 mmol) of the amine derivative. 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.

Examples of compounds of formula I-a

Example 1

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone

A mixture of 0.45 g (0.97 mmol) of 1-[1-(1-benzyl-2-methyl-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one (the preparation of which is described hereinafter) and phosphorus oxychlorid (6 ml) was stirred at 100°C for 2 hours and then allowed to cool. The reaction mixture was poured into ice-cold water, 10N NaOH was added until the ph = 14, and the mixture was extracted with AcOEt. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Re-cristallization in $Et_2O$ afforded 0.32 g (68%) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone as white crystals. ES-MS m/e (%): 483.6 ($M+H^+$).

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available)
- Acide: 1-Benzyl-2-methyl-1H-indole-3-carboxylic acid (the preparation of which is described hereinafter),

ES-MS m/e (%): 463.2 ($M+H^+$).

1-Benzyl-2-methyl-1H-indole-3-carboxylic acid

Using the procedure described in example 8 hereinafter, from 2-methyl-1H-indole-3-carboxylic acid (described in *J.Heterocyclic Chem*. 1977, 14, 1123) was prepared 1-benzyl-2-methyl-1H-indole-3-carboxylic acid.

Example 2

(1-Benzyl-2-methyl-1H-indol-3-yl)-{4-[2-(4-methyl-piperazin-1-yl)-benzoimidazol-1-yl]-piperidin-1-yl}-methanone

A mixture of 20 mg (0.041 mmol) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone (the preparation of which is described in example 1) and *N*-methyl-piperazine was heated in a sealed tube at 90°C for 8 hours, cooled to RT and then concentrated in vacuo. Flash chromatography ($CH_2Cl_2$ / MeOH

9/1) afforded 5 mg (22%) of (1-benzyl-2-methyl-1H-indol-3-yl)-{4-[2-(4-methyl-piperazin-1-yl)-benzoimidazol-1-yl]-piperidin-1-yl}-methanone as white solid. ES-MS m/e (%): 547.5 ($M+H^+$).

Example 3

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-morpholin-4-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone

Using the same procedure described in example 2, from 30 mg (0.062 mmol) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone (the preparation of which is described in example 1) and morpholine (0.5 ml) was prepared 20 mg (60%) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-morpholin-4-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone as light yellow solid. ES-MS m/e (%): 534.2 ($M+H^+$).

Example 4

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-piperidin-1-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone

Using the same procedure described in example 2, from 30 mg (0.062 mmol) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone (the preparation of which is described in example 1) and piperidine (0.5 ml) was prepared 18 mg (54%) of (1-benzyl-2-methyl-1H-indol-3-yl)-[4-(2-piperidin-1-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone as light yellow solid. ES-MS m/e (%): 532.5 ($M+H^+$).

Example 5

[4-(2-Chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone

Using the same procedure described in example 1, from 1.700 g (4.54 mmol) of 1-[1-(2-methyl-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one (the preparation of which is described in example 10) and phosphorus oxychloride (40 ml) was prepared 0.50 g (35%) of [4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone as a light brown solid. ES-MS m/e (%): 393.2 ($M+H^+$).

Example 6

[4-(2-Dimethylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone

Using the same procedure described in example 2, from 50 mg (0.127 mmol) of [4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone (the preparation of which is described in example 5) and dimethyl amine (1.5 ml, 5.6M in EtOH) was prepared 42 mg (43%) of [4-(2-dimethylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone as light yellow solid. ES-MS m/e (%): 402.2 ($M+H^+$).

Example 7

[4-(2-Methylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone

Using the same procedure described in example 2, from 50 mg (0.127 mmol) of [4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone (the preparation of which is described in example 5) and methyl amine (1.5 ml, 8M in EtOH) was prepared 76 mg (78%) of [4-(2-methylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone as light yellow solid. ES-MS m/e (%): 388.1 ($M+H^+$).

Examples of compounds of formula I-b

Example 8

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available)
- Acide: 1-Benzyl-1H-indole-3-carboxylic acid (the preparation of which is described hereinafter),

ES-MS m/e (%): 451.3 ($M+H^+$).

1-benzyl-1H-indole-3-carboxylic acid

To a stirred solution of 0.50 g (3.10 mmol) 1H-indole-3-carboxylic acid in 5 ml DMF was added 0.27 g (6.75 mmol) of NaH (60% in oil). The mixture was stirred at RT for 30 min. and then 0.39 ml (3.28 mmol) of benzyl bromid was added. The mixture was stirred an additional hour and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Crystallization in $Et_2O$ afforded 0.61 g (78%) of 1-benzyl-1H-indole-3-carboxylic acid as a white solid. ES-MS m/e (%): 250 ($M-H^+$).

Example 9

1-{1-[(1-benzyl-2-methyl-1H-indol-3-yl)carbonyl]piperidin-4-yl}-3-methyl-1,3-dihydro-2H-benzimidazol-2-one

Amid coupling following the general procedure I:

- Amine: 1-Methyl-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (described in WO0214315),
- Acide: 1-Benzyl-2-methyl-1H-indole-3-carboxylic acid (described in example 1),

ES-MS m/e (%): 479.4 ($M+H^+$).

Example 10

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 2-Methyl-1H-indole-3-carboxylic acid (described in *J.Heterocyclic Chem.* 1977, 14, 1123),

ES-MS m/e (%): 375.2 ($M+H^+$).

Example 11

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 1-Isopropyl-6-methoxy-1H-indole-3-carboxylic acid (described in US20040067939),

ES-MS m/e (%):. 433.6 ($M+H^+$).

Example 12

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 6-Fluoro-1-isopropyl-1H-indole-3-carboxylic acid (described in US20040067939),

ES-MS m/e (%):. 421.5 ($M+H^+$).

Example 13

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 6-Chloro-1-isopropyl-1H-indole-3-carboxylic acid (described in US20040067939),

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

Example 14

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 1-Isopropyl-1H-indole-3-carboxylic acid (described in *J. Med. Chem.* 1994, 37, 2090),

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

Example 15

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 1-Methyl-1H-indole-3-carboxylic acid (commercially available),

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

Example 16

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 1H-Indole-3-carboxylic acid (commercially available),

ES-MS m/e (%):.361.2 ($M+H^+$).

Example 17

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 2-(pyrrolidine-1-carbonyl)-1H-indole-3-carboxylic acid (the preparation is described hereinafter).

ES-MS m/e (%):.456.4 ($M+H^+$).

a) (1H-indol-2-yl)-pyrrolidin-1-yl-methanone

To a stirred solution of 0.300 g (1.86 mmol) of 1H-indole-2-carboxylic acid in $CH_2Cl_2$ (10 ml) was added 0.428 g (2.23 mmol) of EDC, 0.302 g (2.23 mmol) of HOBt, 0.28 ml (2.04 mmol) of $Et_3N$ and 0.17 ml (2.04 mmol) of pyrrolidine. The reaction mixture was stirred at RT over the night 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. Re-cristallization in $Et_2O$ afforded 0.31 g (78%) of (1H-indol-2-yl)-pyrrolidin-1-yl-methanone as white crystals.

b) 2-(pyrrolidine-1-carbonyl)-1H-indole-3-carboxylic acid

Using a procedure described in *J. Med. Chem.* 1991, 34, 140, from 100 mg (0.46 mmol) of (1H-indol-2-yl)-pyrrolidin-1-yl-methanone was prepared 28 mg (23%) of 2-(pyrrolidine-1-carbonyl)-1H-indole-3-carboxylic acid as a light brown solid. ES-MS m/e (%): 257 ($M-H^+$).

Example 18

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 6-chloro-1H-indole-3-carboxylic acid (described hereinafter)

ES-MS m/e (%): 395.4 ($M+H^+$).

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

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

Example 19

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 6-chloro-5-fluoro-1H-indole-3-carboxylic acid (the preparation of which is described hereinafter),

ES-MS m/e (%):.413.2 ($M+H^+$).

a) 6-chloro-5-fluoro-1H-indole:

Following the procedure described in WO9747598, from 6-chloro-5-fluoro-1H-indole-2,3-dione was prepared 6-chloro-5-fluoro-1H-indole.

b) 6-chloro-5-fluoro-1H-indole-3-carboxylic acid:

Following a procedure described in *J. Med. Chem.* 1991, 34, 140, from 0.25 g (1.47 mmol) of 6-chloro-5-fluoro-1H-indole was prepared 0.35 g (90%) of 6-chloro-5-fluoro-1H-indole-3-carboxylic acid as a light brown solid. ES-MS m/e (%): 213 ($M-H^+$).

Example 20

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

To a stirred solution of 20 mg (0.043 mmol) of 1-[1-(1-benzyl-2-methyl-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one (the preparation of which is described hereinafter) in DMF (3 ml) at RT, was added 2.0 mg (0.051 mmol) of NaH (60% in oil). The mixture was stirred 20 min. and then 5.6 mg (0.051 mmol) of (2-chloro-ethyl)-dimethyl-amine in 1 ml of DMF was added. The mixture was stirred an additional 5 hours at 50°C and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Flash chromatography ($CH_2Cl_2$ / MeOH 8/2) afforded 12 mg (50%) of 1-[1-(1-benzyl-2-methyl-1H-indole-3-carbonyl)-piperidin-4-yl]-3-(2-dimethylamino-ethyl)-1,3-dihydro-benzoimidazol-2-one as a viscous oil. ES-MS m/e (%):.536.2 ($M+H^+$).

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 1-Benzyl-2-methyl-1H-indole-3-carboxylic acid (described in example 1),

ES-MS m/e (%): 463.2 ($M+H^+$).

Example 21

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

To a stirred solution of 40 mg (0.101 mmol) of 1-[1-(6-Chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one (the preparation of which has been described in example 18) in 5 ml DMF was added 4.2 mg (0.105 mmol) NaH (60% in oil). The mixture was stirred at RT for 30 min. and then 8.3 mg (0.11 mmol) of chloro-acetonitrile was added. The mixture was stirred an additional hour and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo. Preparative HPLC afforded 6 mg (14%) of {6-Chloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-acetonitrile as a white solid.

ES-MS m/e (%): 434 ($M+H^+$).

Example 22

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

Amid coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acide: 2-(2-Methyl-butyryl)-1H-indole-3-carboxylic acid (commercially available)

ES-MS m/e (%): 445 ($M+H^+$).

Example 23

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

Amide coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acid : 1-Benzyl-2-methyl-1H-indole-3-carboxylic acid (described herein above),

ES-MS m/e (%): 463.0 ($M-H^+$).

Example 24

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

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

Using a procedure described in *J. Med. Chem.* 1991, 34, 140, from 7.0 g (0.046 mmol) of 6-chloro-1H-indole were prepared 5.80 g (64%) of 6-chloro-1H-indole-3-carboxylic acid as a light brown solid.

ES-MS m/e (%): 194 ($M-H^+$).

b) 6-Chloro-1H-indole-3-carboxylic acid methyl ester

1 g of 6-chloro-1H-indole-3-carboxylic acid were heated at reflux in MeOH with 3 drop of concentrated $H_2SO_4$ overnight. Concentration in vacuo afforded the title compound in quantitative yield.

c) 6-Chloro-1-(2-dimethylamino-ethyl)-1H-indole-3-carboxylic acid

To a stirred solution of 80 mg (0.38 mol) of 6-chloro-1H-indole-3-carboxylic acid methyl ester in 5 ml of DMF were added 50 mg of NaH (3 eq, 55 H in oil) at RT. After 20 min, 66 mg (0.45 mmol, 1.2 eq.) of (2-chloro-ethyl)-dimethyl-amine hydrochloride were added and stirring was continued overnight at 60 °C. Extraction with EtOAc/ aq. $NH_4Cl$ followed by flash chromatography yielded 45 mg of crude 6-chloro-1-(2-dimethylamino-ethyl)-1H-indole-3-carboxylic acid methyl ester.

The ester was hydrolysed in a mixture of $H_2O$/THF/MeOH (ratio 1:1:1) with $LiOH.H_2O$ (3 eq.). The reaction mixture was stirred at 40 °C overnight. The acid was extracted several times with EtOAc, and the combined organic phases were dried over $Na_2SO_4$. Recrystallisation in $Et_2O$ afforded 35 mg (34% overall yield) of the title compound as a white solid.

ES-MS m/e (%): 265.8 ($M-H^+$).

d) 1-[1-(1-Benzyl-6-chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one

Following general procedure I, the coupling of (commercially available) 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one with 1-benzyl-6-chloro-1*H*-indole-3-carboxylic acid gave the title compound.

ES-MS m/e (%): 485.5 ($M+H^+$).

## Example 25

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

Following general procedure I, the coupling of (commercially available) 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one with 1-cyclohexylmethyl-1H-indole-3-carboxylic acid (described in Bioorganic & Medicinal Chemistry Letters (2005), 15(11), 2734-2737) gave the title compound.

ES-MS m/e (%): 457.6 ($M+H^+$).

Example 26

1-{1-[6-Chloro-1-(2-dimethylamino-ethyl)-1H-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Amide coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available),
- Acid : 6-Chloro-1-(2-dimethylamino-ethyl)-1H-indole-3-carboxylic acid (described herein after),

ES-MS m/e (%): 466.0 ($M-H^+$).

Example 27

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

a) 4-(2-Oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester

To a stirred solution of 300 mg (1.4 mmol) of 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available) in 15 ml of $CH_2Cl_2$ were added 34 mg (0.28 mmol, 0.2 eq.) of DMAP, 190 µl (1.4 mmol, 1 eq.) of $Et_3N$ and 301 mg (1.4 mmol, 1 eq.) of $(BOC)_2O$. After stirring at RT overnight the reaction mixture was poured on water and extracted with $CH_2Cl_2$. Column chromatography ($SiO_2$, EtOAc/Hept. 1:1) afforded 360 mg (82%) of the title compound as a white solid.

b) 1-(2-Dimethylamino-ethyl)-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one

To a solution of 320 mg (1 mmol) of 4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carboxylic acid tert-butyl ester in 5 ml of DMF were added 218 mg (1.5 mmol, 1.5 eq.) of (2-chloro-ethyl)-dimethyl-amine hydrochloride and 418 mg (3 mmol, 3 eq.) of $K_2CO_3$. Stirring was continued at 60 °C over night. The mixture was poured on water and the product extracted with EtOAc. The organic phases were dried over $Na_2SO_4$ and concentration in vacuo afforded crude 4-[3-(2-dimethylamino-ethyl)-2-oxo-2,3-dihydro-benzoimidazol-1-yl]-piperidine-1-carboxylic acid tert-butyl ester as an off-white solid. This crude material was then dissolved in 5 ml of $CH_2Cl_2$ and 1 ml of TFA was added. After 2 hours at RT, the reaction was quenched by addition of aq. $NaHCO_3$ (pH = 9), and the product extracted with $CH_2Cl_2$. Concentration in vacuo afforded 200 mg (61%) of the title compound as a white solid.

ES-MS m/e (%): 289.3 ($M+H^+$).

c) 1-[1-(6-Chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-3-(2-dimethylamino-ethyl)-1,3-dihydro-benzoimidazol-2-one

Amide coupling following the general procedure I:

- Amine: 1-(2-Dimethylamino-ethyl)-3-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one,
- Acid : 6-Chloro-1H-indole-3-carboxylic acid.

ES-MS m/e (%): 466.0 ($M+H^+$).

Example 28

1-{1-[6-Chloro-1-(3-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure III, the acylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 3-fluoro-benzoyl chloride gave the title compound.

ES-MS m/e (%): 517.4 ($M+H^+$).

Example 29

1-(1-{6-Chloro-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-bromo-1-(3-fluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 531.3 ($M+H^+$).

Example 30

1-{1-[6-Chloro-1-(2-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure III, the acylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-fluoro-benzoyl chloride gave the title compound.

ES-MS m/e (%): 517.4 ($M+H^+$).

Example 31

1-{1-[6-Chloro-1-(2,3-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure III, the acylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2,3-difluoro-benzoyl chloride gave the title compound.

ES-MS m/e (%): 535.4 ($M+H^+$).

Example 32

1-{1-[6-Chloro-1-(3,5-difluoro-benzenesulfonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure IV, the sulphonylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 3,5-difluoro-benzenesulfonyl chloride gave the title compound.

ES-MS m/e (%): 571.4 ($M+H^+$).

Example 33

1-{1-[6-Chloro-1-(3,5-difluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 1-chloromethyl-3,5-difluoro-benzene gave the title compound.

ES-MS m/e (%): 521.4 ($M+H^+$).

Example 34

1-{1-[6-Chloro-1-(3-fluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 1-chloromethyl-3-fluoro-benzene gave the title compound.

ES-MS m/e (%): 503.4 ($M+H^+$).

Example 35

1-(1-{6-Chloro-1-[2-(2,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-chloro-1-(2,5-difluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 549.4 ($M+H^+$).

Example 36

1-(1-{6-Chloro-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-chloro-1-(2,4-difluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 549.4 ($M+H^+$).

Example 37

1-{1-[6-Chloro-1-(3,5-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure III, the acylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 3,5-difluoro-benzoyl chloride gave the title compound.

ES-MS m/e (%): 535.4 ($M+H^+$).

Example 38

1-(1-{6-Chloro-1-[2-(2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-chloro-1-(2-fluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 531.4 ($M+H^+$).

Example 39

1-(1-{6-Chloro-1-[2-(3,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one with commercially available 2-chloro-1-(3,4-difluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 549.4 ($M+H^+$).

Example 40

1-{1-[6-Chloro-1-(3,5-difluoro-phenyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

a) 1-[6-Chloro-1-(3,5-difluoro-phenyl)-1H-indol-3-yl]-2,2,2-trifluoro-ethanone

To a solution of 1-(6-chloro-1*H*-indol-3-yl)-2,2,2-trifluoro-ethanone (described in US 2004067939) in $CH_2Cl_2$ (in the presence of 0.4 nM molecular sieve) were added anhydrous $Cu(OAc)_2$ (2eq.), 3, 5-difluorophenylboronic acid (3eq.) and pyridine (4eq.). The reaction mixture was stirred at RT for 16h under an air atmosphere, filtered over

decalite, washed with $CH_2Cl_2$ and concentrated in vacuo. Chromatography (hexane/EtOAc: 9:1) gave the title compound in 71% yield.

ES-MS m/e (%): 360.0 ($M+H^+$).

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

A suspension of 1-[6-chloro-1-(3,5-difluoro-phenyl)-1H-indol-3-yl]-2,2,2-trifluoro-ethanone in 3N aqueous NaOH was stirred at 70 °C for 48 h. After washing with $CH_2Cl_2$, the aqueous phase was acidified to pH 1 and extracted with $CH_2Cl_2$. Concentrationin vacuo gave the title compound in 70% yield.

ES-MS m/e (%): 306.0 ($M-H^+$).

c) 1-{1-[6-Chloro-1-(3,5-difluoro-phenyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

Following general procedure I, the coupling of (commercially available) 1-piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one with 6-chloro-1-(3,5-difluoro-phenyl)-1*H*-indole-3-carboxylic acid gave the title compound.

ES-MS m/e (%): 507.0 ($M+H^+$).

Example 41

1-{1-[6-Chloro-1-(piperidine-1-carbonyl)-1H-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one

To a stirred solution of 30 mg of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one in 1 ml of DMF were added 1.1 eq. of NaH (55% in oil). The reaction mixture was stirred for 30 min. before the addition of 1.2 eq. of piperidine-1-carbonyl chloride. The crude reaction mixture was purified by preparative HPLC to afforded 21 mg of the title compound as a yellow powder.

ES-MS m/e (%): 506.4 ($M+H^+$).

Example 42

1-{1-[6-Chloro-1-(2-oxo-2-piperidin-1-yl-ethyl)-1H-indole-3-carbonyl]-piperidin-4-yl}-3-(2-oxo-2-piperidin-1-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one

To a stirred solution of 30 mg of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one in 1 ml of DMF were added 1.1 eq. of NaH (55% in oil). The reaction mixture was stirred for 30 min. before the addition of 1.2 eq. of 2-chloro-1-piperidin-1-yl-ethanone. The crude reaction mixture was directly purified by preparative HPLC to afforded 4 mg of the title compound as a white powder.

ES-MS m/e (%): 645.0 ($M+H^+$).

Example 43

2-{6-Chloro-3-[4-(3-diethylcarbamoylmethyl-2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-diethyl-acetamide

To a stirred solution of 30 mg of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one in 1 ml of DMF were added 1.1 eq. of NaH (55% in oil). The reaction mixture was stirred for 30 min. before the addition of 1.2 eq. of 2-chloro-N,N-diethyl-acetamide. The crude reaction mixture was purified by preparative HPLC to afforded 6 mg of the title compound as a white powder.

ES-MS m/e (%): 621.0 ($M+H^+$).

Example 44

1-(1-{6-Chloro-1-[2-(3,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one, with commercially available 2-chloro-1-(3,5-difluoro-phenyl)-ethanone gave the title compound.

ES-MS m/e (%): 549.4 ($M+H^+$).

Example 45

1-(1-{6-Chloro-1-[2-(5-methyl-2-phenyl-oxazol-4-yl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one

Following general procedure II, the alkylation of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one, 2-bromo-1-(5-methyl-2-phenyl-oxazol-4-yl)-ethanone (described in Journal of Medicinal Chemistry (1992), 35(14), 2617-26) gave the title compound.

ES-MS m/e (%): 594.4 ($M+H^+$).

Example 46

2-{6-Chloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-dimethyl-acetamide

To a stirred solution of 30 mg of 1-[1-(6-chloro-1H-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one in 1 ml of DMF were added 1.1 eq. of NaH (55% in oil). The reaction mixture was stirred for 30 min. before the addition of 1.2 eq. of 2-chloro-N,N-dimethyl-acetamide. The crude reaction mixture was purified by preparative HPLC to afforded 10 mg of the title compound as a white powder.

ES-MS m/e (%): 480.5 ($M+H^+$).

Example 47

2-{6-Chloro-5-methyl-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-dimethyl-acetamide

a) 1-(6-Chloro-5methyl-1H-indol-3-yl)-2,2,2-trifluoro-ethanone

Using a procedure described in *J. Med. Chem.* 1991, 34, 140, from 0.250 g (0.002 mol) of 6-chloro-5-methyl-1H-indole were prepared 0.38 g (96%) of the title compound as a white solid.

b) 2-[6-Chloro-5-methyl-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N,N-dimethyl-acetamide

To a stirred solution of 1-(6-chloro-5methyl-1H-indol-3-yl)-2,2,2-trifluoro-ethanone (0.38 g) in 10 ml of DMF at 0 °C, were added 64 mg (1.1 eq.) of NaH (60% in oil). The mixture was stirred for 30 min. before 0.16 ml (1.1 eq.) of dimethylamino-acetyl chloride were added. The mixture was stirred an additional hour and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to afford 300 mg (60%) of the title compound as a white solid.

c) 6-Chloro-1-dimethylcarbamoylmethyl-5-methyl-1H-indole-3-carboxylic acid

Using a procedure similar to that described in *J. Med. Chem.* 1991, 34, 140, from 0.280 g of 2-[6-chloro-5-methyl-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N,N-dimethyl-acetamide were prepared 0.18 g (76%) of the title compound as a white solid.

d) 2-{6-Chloro-5-methyl-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-dimethyl-acetamide

Amide coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available)
- Acid : 6-Chloro-1-dimethylcarbamoylmethyl-5-methyl-1H-indole-3-carboxylic acid.

ES-MS m/e (%): 494.5 ($M+H^+$).

Example 48

2-{5,6-Dichloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-dimethyl-acetamide

a) 1-(5,6-Dichloro-1H-indol-3-yl)-2,2,2-trifluoro-ethanone

Using a procedure described in *J. Med. Chem.* 1991, 34, 140, from 0.120 g (0.64 mmol) of 5,6-dichloro-1H-indole were prepared 0.11 g (59%) of the title compound as a white solid.

b) 2-[5,6-Dichloro-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N,N-dimethyl-acetamide

To a stirred solution of 1-(5,6-dichloro-1H-indol-3-yl)-2,2,2-trifluoro-ethanone (0.11 g) in 3 ml of DMF at 0 °C, were added 18 mg (1.05 eq.) of NaH (60% in oil). The mixture was stirred for 30 min. and then 0.04 ml (1.0 eq.) of dimethylamino-acetyl chloride were added. The mixture was stirred an additional hour and then poured onto water and extracted with ethyl acetate. The combined organic phases were dried over $Na_2SO_4$ and concentrated in vacuo to afford 112 mg (78%) the title compound as a white solid.

c) 5,6-Dichloro-1-dimethylcarbamoylmethyl-1H-indole-3-carboxylic acid

Using a similar procedure described in *J. Med. Chem.* 1991, 34, 140, from 0.112 g of 2-[5,6-dichloro-3-(2,2,2-trifluoro-acetyl)-indol-1-yl]-N,N-dimethyl-acetamide were prepared 0.047 g (49%) of the title compound as a white solid

d) 2-{5,6-Dichloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-N,N-dimethyl-acetamide

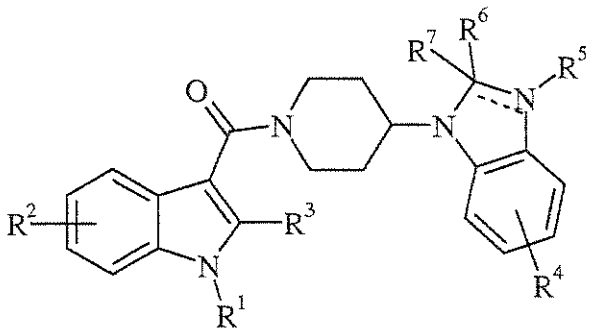
Amide coupling following the general procedure I:

- Amine: 1-Piperidin-4-yl-1,3-dihydro-benzoimidazol-2-one (commercially available)
- Acid : 5,6-dichloro-1-dimethylcarbamoylmethyl-1H-indole-3-carboxylic acid.

ES-MS m/e (%): 515.3 ($M+H^+$).

Claims

1. Compounds of the general formula (I)



(I)

wherein the dotted line is either nil or a double bond;

$R^1$ is H,

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

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

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

CN,

$OR^i$,

$NR^iR^{ii}$,

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

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

$C_{1-6}$-alkyl,

$C_{1-6}$-alkoxy,

$C_{3-6}$-cycloalkyl,

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

$NR^iR^{ii}$,

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

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

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

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

$R^3$ is H,

or is halo,

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

$C_{1-6}$-alkyl,

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

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

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

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

halo,

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl, when the dotted line is nil,

or is nil when the dotted line is a double bond;

$R^6$ is nil when the dotted line is a double bond;

$R^7$ is H,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

or $R^6$ and $R^7$ together form a C=O group when the dotted line is nil;

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

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

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

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

2. The compounds of the general formula (I) according to claim 1, wherein:
the dotted line is either nil or a double bond;
$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$ or aryl when the dotted line is nil or is nil when the dotted line is a double bond;
and $R^1$, $R^2$, $R^3$, $R^4$, $R^6$ and $R^7$ are as defined in claim 1 , as well as pharmaceutically acceptable salts thereof.

3. The compounds of formula (I) according to claim 1 or 2, wherein:
the dotted line is either nil or a double bond;
$R^1$ is H or,
$C_{1-6}$-alkyl optionally substituted by CN or by $C_{1-6}$-alkoxy or,
aryl or,
5 or 6 membered heteroaryl or,
sulfonylaryl or,
$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:
halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,
$-(CH_2)_m-NR^iR^{ii}$ or,
$-(CH_2)_n-(CO)-R^b$, wherein $R^b$ is aryl or 5 or 6 membered-heterocycloalkyl;
$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $-O-CH_2-C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;
$R^3$ is H or,
halo or,
$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,
$C_{1-6}$-alkyl or aryl, which are optionally substituted by
$-O(CO)-C_{1-6}$-alkyl,
or by $-NH(CO)R^d$, wherein $R^d$ is $C_{1-6}$-alkyl optionally substituted by halo or nitro, or $R^d$ is aryl or a 5 or 6 membered heteroaryl, which are optionally substituted by halo, nitro, $C_{1-6}$-alkyl or $C_{1-6}$-haloalkyl;
$R^4$ is one or more of H, halo, $C_{1-6}$-alkyl or $C_{1-6}$-alkoxy or two $R^4$ may form an oxo or dioxo bridge together with the phenyl ring to which they are attached;

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$ or aryl when the dotted line is nil or is nil when the dotted line is a double bond;

$R^6$ is nil when the dotted line is a double bond;

$R^7$ is H or,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl,

or $R^6$ and $R^7$ together form a C=O group when the dotted line is nil;

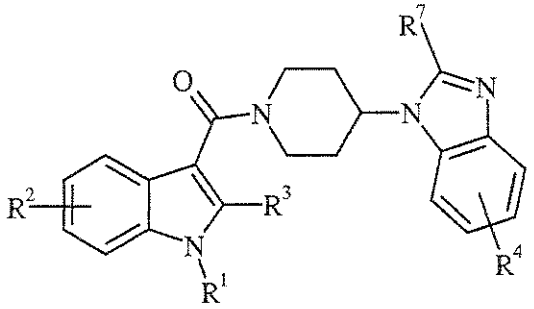
$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

4. The compounds of formula (I-a) according to any one of claims 1 to 3:



(I-a)

wherein $R^1$ to $R^4$ and $R^7$ are as defined in any one of claims 1 to 3.

5. The compounds of formula (I-a) according to claim 4, wherein:

$R^1$ is H or,

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

aryl or,

5 or 6 membered heteroaryl or,

sulfonylaryl or,

$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

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

$-(CH_2)_n-(CO)-R^b$, wherein $R^b$ is aryl or 5 or 6 membered-heterocycloalkyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, -O-$CH_2$-$C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,

halo or,

-(CO)-$R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is -$(CH_2)_n$-$NR^iR^{ii}$ or,

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

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

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

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

$R^7$ is H or,

Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or -(CO)O-$C_{1-6}$-alkyl;

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

6. The compounds of formula (I-a) according to claim 5, wherein:

$R^1$ is H or,

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

-$(CH_2)_m$-$R^a$ wherein $R^a$ is aryl, which is optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, -C(O)O-$C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

$R^2$ is one or more of H, halo or $C_{1-6}$-alkoxy;

$R^3$ is H or,

-(CO)-$R^c$, wherein $R^c$ is $C_{1-6}$-alkyl or 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl or,

$C_{1-6}$-alkyl;

$R^4$ is H;

$R^7$ is Cl or,

$NR^eR^f$, with $R^e$ and $R^f$ are H or $C_{1-6}$-alkyl or $R^e$ and $R^f$ together with the nitrogen atom to which they are attached form a 5 or 6 membered heterocycloalkyl which may be substituted by $C_{1-6}$-alkyl,

m is 1 to 6;

as well as pharmaceutically acceptable salts thereof.

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

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-chloro-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

(1-Benzyl-2-methyl-1H-indol-3-yl)-{4-[2-(4-methyl-piperazin-1-yl)-benzoimidazol-1-yl]-piperidin-1-yl}-methanone;

(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-morpholin-4-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

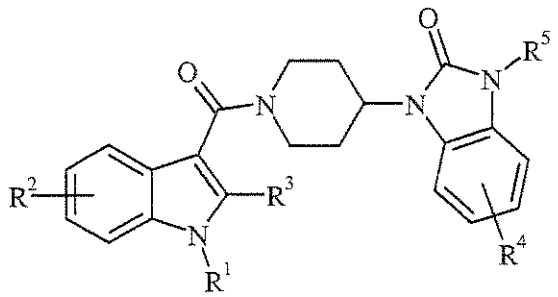
(1-Benzyl-2-methyl-1H-indol-3-yl)-[4-(2-piperidin-1-yl-benzoimidazol-1-yl)-piperidin-1-yl]-methanone;

[4-(2-Chloro-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone;

[4-(2-Dimethylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone; and

[4-(2-Methylamino-benzoimidazol-1-yl)-piperidin-1-yl]-(2-methyl-1H-indol-3-yl)-methanone.

8. The compound of formula (I-b) according to any one of claims 1 to 3:



(I-b)

wherein $R^1$ to $R^5$ are as defined in any one of claims 1 to 3.

9. The compound of formula (I-b) according to claim 8:

wherein

$R^1$ is H or,

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

aryl or,

5 or 6 membered heteroaryl or,

sulfonylaryl or,

$-(CH_2)_m-R^a$ wherein $R^a$ is $C_{3-6}$-cycloalkyl, 5 or 6 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy,

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

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

$NR^iR^{ii}$,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more halo, $C_{1-6}$-alkyl optionally substituted by CN, halo or $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy or $(CR^{iii}R^{iv})_n$-phenyl;

$R^2$ is one or more of H, halo, CN, nitro, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $-O-CH_2-C_{2-6}$-alkenyl, benzyloxy, or two $R^2$ may form an oxo or dioxo bridge together with the indole ring to which they are attached;

$R^3$ is H or,

halo or,

$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl, 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl, or $R^c$ is $-(CH_2)_n-NR^iR^{ii}$ or,

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

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

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

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

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl;

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

10. The compounds of formula (I-b) according to claim 9, wherein:

$R^1$ is H or,

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

$-(CH_2)_m-R^a$ wherein $R^a$ is aryl, which is optionally substituted by one or more substituents selected from the group consisting of:

halo, CN, $C_{1-6}$-alkyl, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy, $-C(O)O-C_{1-6}$-alkyl and phenyl optionally substituted by halo, $C_{1-6}$-alkyl, $C_{1-6}$-haloalkyl or $C_{1-6}$-alkoxy, or

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

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

$NR^iR^{ii}$,

4 to 7 membered-heterocycloalkyl, aryl, or 5 or 6 membered heteroaryl which are optionally substituted by one or more halo, $C_{1-6}$-alkyl optionally substituted by CN, halo or $C_{1-6}$-alkoxy, $C_{1-6}$-alkoxy, $C_{1-6}$-haloalkoxy or $(CR^{iii}R^{iv})_n$-phenyl;

$R^2$ is one or more of H, halo or $C_{1-6}$-alkoxy;

$R^3$ is H or,

$-(CO)-R^c$, wherein $R^c$ is $C_{1-6}$-alkyl or 5 or 6 membered heterocycloalkyl optionally substituted by $C_{1-6}$-alkyl or,

$C_{1-6}$-alkyl;

$R^4$ is H;

$R^5$ is H, $C_{1-6}$-alkyl, $-(CH_2)_m-NR^iR^{ii}$, aryl, or $-(CH_2)_n-(CO)-R^b$ wherein $R^b$ is $NR^iR^{ii}$ or 4 to 7 membered-heterocycloalkyl;

$R^i$ and $R^{ii}$ are independently selected from H, $C_{1-6}$-alkyl or $-(CO)O-C_{1-6}$-alkyl;

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

m is 1 to 6;

n is 0 to 4;

as well as pharmaceutically acceptable salts thereof.

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

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

1-{1-[(1-benzyl-2-methyl-1H-indol-3-yl)carbonyl]piperidin-4-yl}-3-methyl-1,3-dihydro-2H-benzimidazol-2-one;

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

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

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

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

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

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

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

1-{1-[2-(Pyrrolidine-1-carbonyl)-1H-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

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

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

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

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

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

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

1-[1-(1-Benzyl-6-chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-1,3-dihydro-benzoimidazol-2-one;

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

1-{1-[6-Chloro-1-(2-dimethylamino-ethyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-[1-(6-Chloro-1*H*-indole-3-carbonyl)-piperidin-4-yl]-3-(2-dimethylamino-ethyl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(3-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2-fluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2,3-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-benzenesulfonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3-fluoro-benzyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(2,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(2,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-benzoyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(2-fluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-(1-{6-Chloro-1-[2-(3,4-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(3,5-difluoro-phenyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(piperidine-1-carbonyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-1,3-dihydro-benzoimidazol-2-one;

1-{1-[6-Chloro-1-(2-oxo-2-piperidin-1-yl-ethyl)-1*H*-indole-3-carbonyl]-piperidin-4-yl}-3-(2-oxo-2-piperidin-1-yl-ethyl)-1,3-dihydro-benzoimidazol-2-one;

2-{3-[1-(6-Chloro-1-diethylcarbamoylmethyl-1*H*-indole-3-carbonyl)-piperidin-4-yl]-2-oxo-2,3-dihydro-benzoimidazol-1-yl}-*N*,*N*-diethyl-acetamide;

1-(1-{6-Chloro-1-[2-(3,5-difluoro-phenyl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

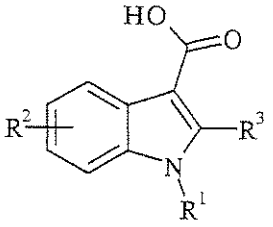
1-(1-{6-Chloro-1-[2-(5-methyl-2-phenyl-oxazol-4-yl)-2-oxo-ethyl]-1*H*-indole-3-carbonyl}-piperidin-4-yl)-1,3-dihydro-benzoimidazol-2-one;

2-{6-Chloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide;

2-{6-Chloro-5-methyl-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide;

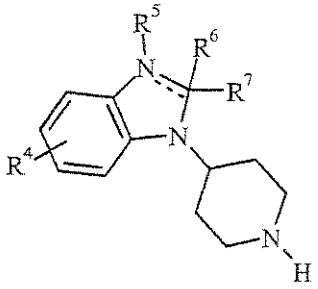
2-{5,6-Dichloro-3-[4-(2-oxo-2,3-dihydro-benzoimidazol-1-yl)-piperidine-1-carbonyl]-indol-1-yl}-*N*,*N*-dimethyl-acetamide.

12. A process for the preparation of the compounds of formula (I) according to any of claims 1 to 11, comprising the step of reacting a compound of formula (II):



II

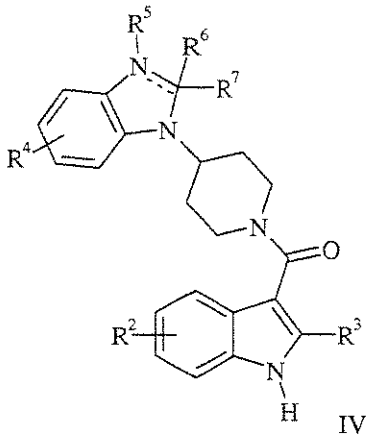
with a compound of formula (III):



III

in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as defined in any one of claims 1 to 3.

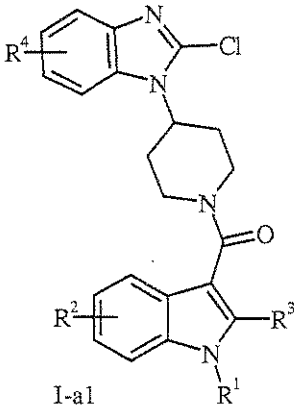
13. A process for the preparation of the compounds of formula (I) according to any one of claims 1 to 11, comprising the step of reacting a compound of formula (IV):



IV

with a compound of formula $R^1$-X, in order to obtain a compound of formula (I), wherein $R^1$ to $R^7$ are as defined in any one of claims 1 to 3.

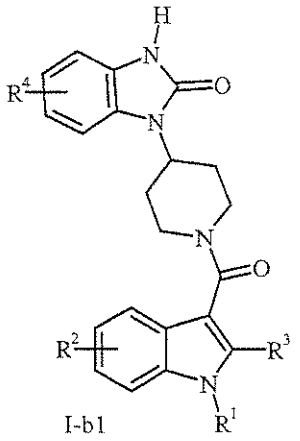
14. A process for the preparation of the compounds of formula (I-a) according to any one of claims 4 to 7, comprising the step of reacting a compound of formula (I-a1):



I-a1

with an amine of formula $HNR^eR^f$, in order to obtain a compound of formula (I-a), wherein $R^7$ is $NR^eR^f$ and $R^1$ to $R^4$ are as defined in claim 4.

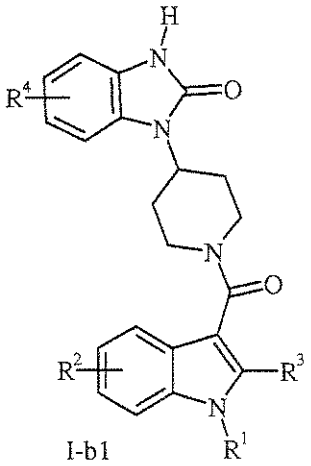
15. A process for the preparation of the compounds of formula (I-a) according to any one of claims 4 to 7 comprising the step of reacting a compound of formula (I-b1):



I-b1

with $POCl_3$ in order to obtain a compound of formula (I-a), wherein $R^1$ to $R^4$ are as defined in claim 4 and $R^7$ is Cl.

16. A process for the preparation of the compounds of formula (I-b) according to any one of claims 8 to 12 comprising the step of reacting a compound of formula (I-b1):



I-b1

with a compound of formula $R^5$-X, in order to obtain a compound of formula (I-b), wherein $R^1$ and $R^5$ are different from H and wherein $R^2$ to $R^4$ are as defined in claim 8.

17. A compound formula (I-a) or (I-b) obtainable by a process according to any one of claims 12 to 16.

18. A compound of formula (I), (I-a) or (I-b) according to any one of claims 1 to 11 for a use in the prevention or treatment of dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxious and depressive disorders.

19. A pharmaceutical composition comprising a compound of formula (I), (I-a) or (I-b) according to any one of claims 1 to 11.

20. A pharmaceutical composition according to claim 19, wherein it is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxious and depressive disorders.

21. Use of a compound of formula (I), (I-a) or (I-b) according to any one of claims 1 to 11 for the preparation of a medicament.

22. Use according to claim 21, wherein the medicament is useful against dysmenorrhea, hypertension, chronic heart failure, inappropriate secretion of vasopressin, liver cirrhosis, nephrotic syndrome, obsessive compulsive disorder, anxious and depressive disorders.

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