5-HALOGEN-SUBSTITUTED OXINDOLE DERIVATIVES AND USE THEREOF FOR TREATING VASOPRESSINE-DEPENDENT DISEASES

The present invention relates to novel substituted oxindole derivatives, pharmaceutical compositions comprising them, and their use for the treatment of vasopressin-dependent disorders.

Vasopressin is an endogenous hormone which exerts various effects on organs and tissues. It is suspected that the vasopressin system is involved in various pathological states such as, for example, heart failure and high blood pressure. At present, three receptors (V1a, V1b or V3 and V2) via which vasopressin mediates its numerous effects are known. Antagonists of these receptors are therefore being investigated as possible new therapeutic approaches for the treatment of diseases (M. Thibonnier, Exp.Opin. Invest. Drugs 1998, 7(5), 729-740).

Novel substituted oxindoles having a phenylsulfonyl group in position 1 are described herein. 1-Phenylsulfonyl-1,3-dihydro-2*H*-indol-2-ones have previously been described as ligands of vasopressin receptors. WO 93/15051, WO 95/18105, WO 98/25901, WO 01/55130, WO 01/55134, WO 01/164668 and WO 01/98295 also describe derivatives having arylsulfonyl groups in position 1 of the oxindole structure. These compounds differ from the compounds of the invention essentially through the substituents in position 3.

Thus, WO 93/15051 and WO 98/25901 describe 1-phenylsulfonyl-1,3-dihydro-2*H*-indol-2-ones, in which the oxindole structure is substituted in position 3 by two alkyl radicals which may also together form a cycloalkyl radical (spiro linkage), as ligands of vasopressin receptors. As alternative, the spiro ring may comprise heteroatoms such as oxygen and nitrogen (optionally with substituents).

WO 95/18105 describes 1-phenylsulfonyl-1,3-dihydro-2*H*-indol-2-ones having a nitrogen atom in position 3 as ligands of vasopressin receptors. In addition, radicals selected from optionally substituted alkyl, cycloalkyl, phenyl or benzyl radicals are bonded in position 3.

WO 03/008407 describes 1-phenylsulfonyloxindoles in which pyridylpiperazines are linked via a urea, carbamate or 2-oxoethyl group to the oxindole in position 3.

WO 2005/030755 describes as example 105 5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-

3-(2-methoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate.

WO 2006/005609 describes as example 66 the dihydrochloride of 4-(1-methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxyphenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide.

Besides the binding affinity for the vasopressin V1b receptor, further properties may be advantageous for the treatment and/or prophylaxis of vasopressin-dependent disorders, such as, for example:

1.) a selectivity for the vasopressin V1b receptor compared with the vasopressin V1a receptor, i.e. the quotient of the binding affinity for the V1a receptor (Ki(V1a) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor (Ki(V1b)) (determined in the unit "nanomolar (nM)"). A larger quotient Ki(V1a)/Ki(V1b) means a greater V1b selectivity;

2.) a selectivity for the vasopressin V1b receptor compared with the vasopressin V2 receptor, i.e. the quotient of the binding affinity for the V2 receptor (Ki(V2) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor (Ki(V1b)) (determined in the unit "nanomolar (nM)"). A larger quotient Ki(V2)/Ki(V1b) means a greater V1b selectivity;

3.) a selectivity for the vasopressin V1b receptor compared with the oxytocin OT receptor, i.e. the quotient of the binding affinity for the OT receptor (Ki(OT) (determined in the unit "nanomolar (nM)") and the binding affinity for the V1b receptor (Ki(V1b)) (determined in the unit "nanomolar (nM)"). A larger quotient Ki(OT)/Ki(V1b) means a greater V1b selectivity.

4.) the metabolic stability, for example determined from the half-lives, measured in vitro, in liver microsomes from various species (e.g. rat or human);

5.) no or only low inhibition of cytochrome P450 (CYP) enzymes: cytochrome P450 (CYP) is the name for a superfamily of heme proteins having enzymatic activity (oxidase). They are also particularly important for the degradation (metabolism) of foreign substances

such as drugs or xenobiotics in mammalian organisms. The principal representatives of the types and subtypes of CYP in the human body are: CYP 1A2, CYP 2C9, CYP 2D6 and CYP 3A4. If CYP 3A4 inhibitors (e.g. grapefruit juice, cimetidine, erythromycin) are used at the same time as medicinal substances which are degraded by this enzyme system and thus compete for the same binding site on the enzyme, the degradation thereof may be slowed down and thus effects and side effects of the administered medicinal substance may be undesirably enhanced;

6.) a suitable solubility in water (in mg/ml);

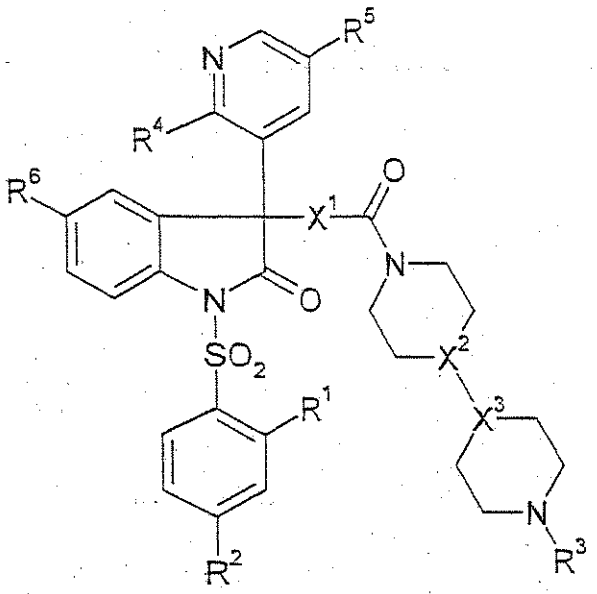
7.) suitable pharmacokinetics (time course of the concentration of the compound of the invention in plasma or in tissue, for example brain). The pharmacokinetics can be described by the following parameters: half-life (in h), volume of distribution (in $l \cdot kg^{-1}$), plasma clearance (in $l \cdot h^{-1} \cdot kg^{-1}$), AUC (area under the curve, area under the concentration-time curve, in $ng \cdot h \cdot l^{-1}$), oral bioavailability (the dose-normalized ratio of AUC after oral administration and AUC after intravenous administration), the so-called brain-plasma ratio (the ratio of AUC in brain tissue and AUC in plasma);

8.) no or only low blockade of the hERG channel: compounds which block the hERG channel may cause a prolongation of the QT interval and thus lead to serious disturbances of cardiac rhythm (for example so-called "torsade de pointes"). The potential of compounds to block the hERG channel can be determined by means of the displacement assay with radiolabelled dofetilide which is described in the literature (G. J. Diaz et al., Journal of Pharmacological and Toxicological Methods, 50 (2004), 187-199). A smaller IC50 in this dofetilide assay means a greater probability of potent hERG blockade. In addition, the blockade of the hERG channel can be measured by electrophysiological experiments on cells which have been transfected with the hERG channel, by so-called whole-cell patch clamping (G. J. Diaz et al., Journal of Pharmacological and Toxicological Methods, 50 (2004), 187-199).

It was therefore an object of the present invention to provide compounds for the treatment or prophylaxis of various vasopressin-dependent diseases. The compounds were intended to have a high activity and selectivity, especially a high affinity and selectivity vis-à-vis the vasopressin V1b receptor. In addition, the substance of the invention was intended to have one or more of the aforementioned advantages 1.) to 8.).

SUMMARY

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



(I)

in which

R^1 is hydrogen, methoxy or ethoxy;

R^2 is hydrogen or methoxy;

R^3 is hydrogen, methyl, ethyl, n-propyl or isopropyl;

R^4 is ethoxy or isopropoxy;

R^5 is H or methyl;

R^6 is Cl or F;

X^1 is O, NH or CH_2; and

X^2 and X^3 are N or CH, with the proviso that X^2 and X^3 are not simultaneously N;

and their pharmaceutically acceptable salts thereof.

In a second aspect, there is provided a pharmaceutical composition comprising at least one compound of the formula I as defined above and/or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

In a third aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasopressin-dependent diseases.

In a fourth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from diabetes, insulin resistance, nocturnal enuresis, incontinence and diseases in which impairments of blood clotting occur, and/or for delaying micturition.

In a fifth aspect, there is provided the use of compounds of formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from hypertension, pulmonary hypertension, heart failure, myocardial infarction, coronary spasm, unstable angina, PTCA (percutaneous transluminal coronary angioplasty), ischemias of the heart, impairments of the renal system, edemas, renal vasospasm, necrosis of the renal cortex, hyponatremia, hypokalemia, Schwartz-Bartter syndrome, impairments of the gastrointestinal tract, gastritic vasospasm, hepatocirrhosis, gastric and intestinal ulcers, emesis, emesis occurring during chemotherapy, and travel sickness.

In a sixth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from affective disorders.

In a seventh aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from anxiety disorders and stress-dependent anxiety disorders.

In an eighth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from memory impairments and Alzheimer's disease.

In a ninth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from psychoses and psychotic disorders.

In a tenth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from Cushing's syndrome and other stress-dependent diseases.

In an eleventh aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from sleep disorders.

In a twelfth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from depressive disorders.

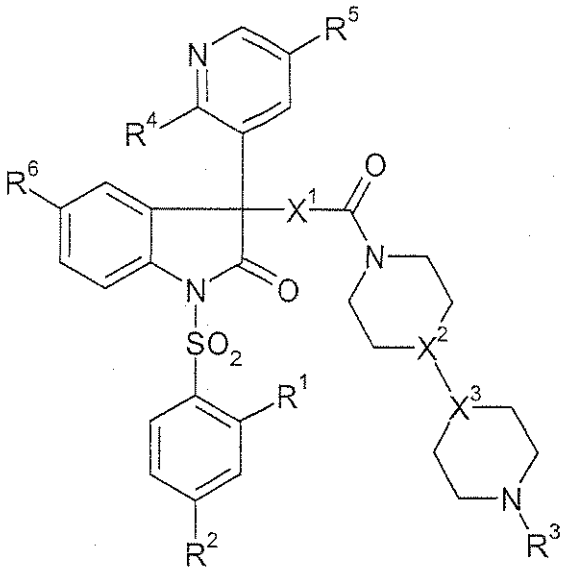
In a thirteenth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasomotor symptoms and/or thermoregulatory dysfunctions.

In a fourteenth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of drug or pharmaceutical dependencies and/or dependencies mediated by other factors; of stress caused by withdrawal of one or more factors mediating the dependence; and/or of stress-induced relapses into drug or pharmaceutical dependencies and/or dependencies mediated by other factors.

In a fifteenth aspect, there is provided the use of compounds of the formula I as defined above or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from schizophrenia and psychosis.

DETAILED DESCRIPTION

The object is achieved by compounds of the formula I



(I)

in which

R^1 is hydrogen, methoxy or ethoxy;

R^2 is hydrogen or methoxy;

R^3 is hydrogen, methyl, ethyl, n-propyl or isopropyl;

R^4 is ethoxy or isopropoxy;

R^5 is H or methyl;

R^6 is Cl or F;

X^1 is O, NH or CH_2; and

X^2 and X^3 are N or CH, with the proviso that X^2 and X^3 are not simultaneously N;

and their pharmaceutically acceptable salts and prodrugs thereof.

Accordingly, the present invention relates to compounds of the formula I (also "compounds I" hereinafter) and the pharmaceutically acceptable salts of the compounds I and the prodrugs of the compounds I.

The pharmaceutically acceptable salts of compounds of the formula I, which are also referred to as physiologically tolerated salts, are ordinarily obtainable by reacting the free

base of the compounds I of the invention (i.e. of the compounds I according to structural formula I) with suitable acids. Examples of suitable acids are listed in "Fortschritte der Arzneimittelforschung", 1966, Birkhäuser Verlag, vol.10, pp. 224-285. These include for example hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulfonic acid, acetic acid, formic acid, maleic acid and fumaric acid.

The term "prodrugs" means compounds which are metabolized in vivo to the compounds I of the invention. Typical examples of prodrugs are described in C.G. Wermeth (editor): The Practice of Medicinal Chemistry, Academic Press, San Diego, 1996, pages 671-715. These include for example phosphates, carbamates, amino acids, esters, amides, peptides, ureas and the like. Suitable prodrugs in the present case may be for example compounds I in which the outer nitrogen atom of the outer piperidine/piperazine ring forms an amide/peptide linkage by this nitrogen atom being substituted by a C_1-C_4-alkylcarbonyl group, e.g. by acetyl, propionyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl or tert-butylcarbonyl (pivaloyl), by benzoyl, or by an amino acid residue linked via CO, e.g. glycine, alanine, serine, phenylalanine and the like linked via CO, in the position of the radical R^3. Further suitable prodrugs are alkylcarbonyloxyalkyl carbamates in which the outer nitrogen atom of the outer piperidine/piperazine ring has in the position of the radical R^3 a group of the formula $-C(=O)-O-CHR^a-O-C(=O)-R^b$ in which R^a and R^b are independently of one another C_1-C_4-alkyl. Such carbamates are described for example in J. Alexander, R. Cargill, S. R. Michelson, H. Schwam, J. Medicinal Chem. 1988, 31(2), 318-322. These groups can then be eliminated under metabolic conditions and result in compounds I in which R^3 is H.

C_1-C_4-Alkyl is in the context of the present invention a linear or branched alkyl radical having 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl or tert-butyl.

C_1-C_3-Alkoxy is in the context of the present invention a linear or branched alkyl radical linked via an oxygen atom and having 1 to 3 carbon atoms. Examples are methoxy, ethoxy, n-propoxy and isopropoxy.

The compounds of the invention of the formula I, their pharmacologically acceptable salts and their prodrugs may also be present in the form of solvates or hydrates. Solvates mean in the context of the present invention crystalline forms of the compounds I or of their

pharmaceutically acceptable salts or prodrugs thereof which comprise solvent molecules incorporated in the crystal lattice. The solvent molecules are preferably incorporated in stoichiometric ratios. Hydrates are a specific form of solvates; the solvent in this case is water.

The statements made hereinafter concerning suitable and preferred features of the invention, especially concerning the radicals R^1, R^2, R^3, R^4, R^5, R^6, X^1, X^2 and X^3 in the compound I, but also concerning the features of the process of the invention and of the use according to the invention apply both taken on their own and preferably in any possible combination with one another.

The compounds I are preferably provided in the form of the free base (i.e. according to structural formula I) or in the form of their acid addition salts.

In a preferred embodiment, R^1 is hydrogen or methoxy.

In a particularly preferred embodiment, R^1 and R^2 are methoxy.

In a preferred embodiment, R^3 is hydrogen, methyl or ethyl, in particular hydrogen or methyl and is specifically methyl.

In a preferred embodiment, R^4 is ethoxy and R^5 is H.

In an alternatively preferred embodiment, R^4 is ethoxy and R^5 is methyl.

In an alternatively preferred embodiment, R^4 is isopropoxy and R^5 is H.

R^4 is particularly preferably ethoxy and R^5 is H.

In a preferred embodiment, R^6 is Cl.

In an alternatively preferred embodiment, R^6 is F.

R^6 is particularly preferably Cl.

In a preferred embodiment, X^1 is NH.

In an alternatively preferred embodiment, X^1 is O.

In an alternatively preferred embodiment, X^1 is CH_2.

X^1 is particularly preferably NH or CH_2 and especially NH.

In a preferred embodiment, one of the variables X^2, X^3 is N and the other is CH.

In a particularly preferred embodiment in this connection, X^2 is N and X^3 is CH.

In an alternatively particularly preferred embodiment, X^2 is CH and X^3 is N.

In an alternatively preferred embodiment, both variables X^2, X^3 are CH.

The invention preferably relates to compounds of the formula I in which

R^1 is hydrogen or methoxy;
R^2 is hydrogen or methoxy;
R^3 is hydrogen, methyl, ethyl, n-propyl or isopropyl, preferably hydrogen, methyl or ethyl;
R^4 is ethoxy;
R^5 is hydrogen;
R^6 is Cl;
X^1 is NH, O or CH_2;
X^2 is N or CH;
X^3 is N or CH;

where X^2 and X^3 are not simultaneously N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention particularly preferably relates to compounds of the formula I in which

R^1 is hydrogen or methoxy;
R^2 is hydrogen or methoxy;
R^3 is methyl or ethyl;
R^4 is ethoxy;

R^5 is hydrogen;
R^6 is Cl;
X^1 is NH, O or CH_2;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention more preferably relates to compounds of the formula I in which
R^1 is methoxy;
R^2 is methoxy;
R^3 is methyl or ethyl;
R^4 is ethoxy;
R^5 is hydrogen;
R^6 is Cl;
X^1 is NH, O or CH_2;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention even more preferably relates to compounds of the formula I in which
R^1 is methoxy;
R^2 is methoxy;
R^3 is methyl or ethyl;
R^4 is ethoxy;
R^5 is hydrogen;
R^6 is Cl;
X^1 is NH;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention even more preferably relates alternatively to compounds of the formula I in

which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is hydrogen;

R^6 is Cl;

X^1 is CH_2;

X^2 is N or CH;

X^3 is N or CH;

where X^2 and X^3 are not simultaneously N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is hydrogen;

R^6 is Cl;

X^1 is NH;

X^2 is N;

X^3 is CH;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention also particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is hydrogen;

R^6 is Cl;

X^1 is NH;

X^2 is CH;

X^3 is N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention also particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is hydrogen;

R^6 is Cl;

X^1 is NH;

X^2 is CH;

X^3 is CH;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention preferably relates alternatively to compounds of the formula I in which

R^1 is hydrogen or methoxy;

R^2 is hydrogen or methoxy;

R^3 is hydrogen, methyl, ethyl, n-propyl or isopropyl, preferably hydrogen, methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;

X^1 is NH, O or CH_2;

X^2 is N or CH;

X^3 is N or CH;

where X^2 and X^3 are not simultaneously N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention particularly preferably relates alternatively to compounds of the formula I in which

R^1 is hydrogen or methoxy;

R^2 is hydrogen or methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;
X^1 is NH, O or CH_2;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention more preferably relates alternatively to compounds of the formula I in which
R^1 is methoxy;
R^2 is methoxy;
R^3 is methyl or ethyl;
R^4 is ethoxy;
R^5 is methyl;
R^6 is Cl;
X^1 is NH, O or CH_2;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention more preferably still relates alternatively to compounds of the formula I in which
R^1 is methoxy;
R^2 is methoxy;
R^3 is methyl or ethyl;
R^4 is ethoxy;
R^5 is methyl;
R^6 is Cl;
X^1 is NH;
X^2 is N or CH;
X^3 is N or CH;
where X^2 and X^3 are not simultaneously N;
and the pharmaceutically acceptable salts and prodrugs thereof.

The invention even more preferably relates alternatively to compounds of the formula I in

which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;

X^1 is CH_2;

X^2 is N or CH;

X^3 is N or CH;

where X^2 and X^3 are not simultaneously N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;

X^1 is NH;

X^2 is N;

X^3 is CH;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention also particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;

X^1 is NH;

X^2 is CH;

X^3 is N;

and the pharmaceutically acceptable salts and prodrugs thereof.

The invention also particularly relates to compounds of the formula I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl or ethyl;

R^4 is ethoxy;

R^5 is methyl;

R^6 is Cl;

X^1 is NH;

X^2 is CH;

X^3 is CH;

and the pharmaceutically acceptable salts and prodrugs thereof.

Special preference is given to compound I in which

R^1 is methoxy;

R^2 is methoxy;

R^3 is methyl;

R^4 is ethoxy;

R^5 is hydrogen;

R^6 is Cl;

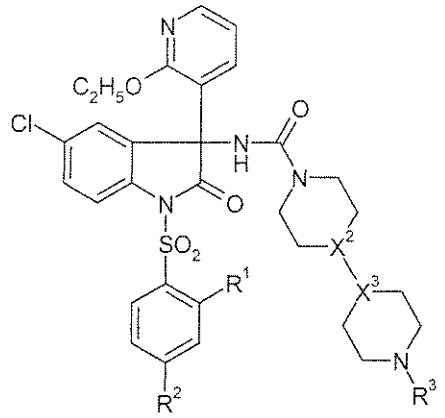
X^1 is NH;

X^2 is N;

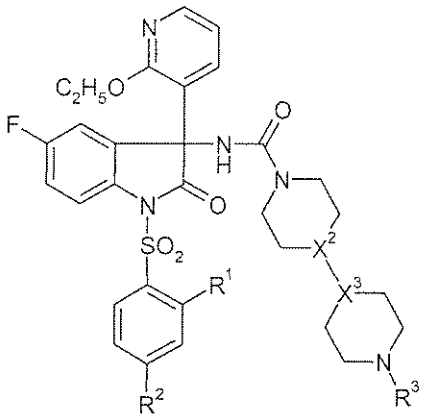
X^3 is CH;

and the pharmaceutically acceptable salts and prodrugs thereof.

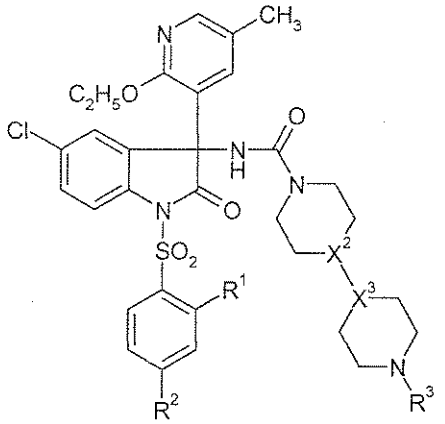
Examples of preferred embodiment of the present invention are compounds of the formula I.1 to I.18 and the pharmaceutically acceptable salts and prodrugs thereof, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in each line in the following table 1.



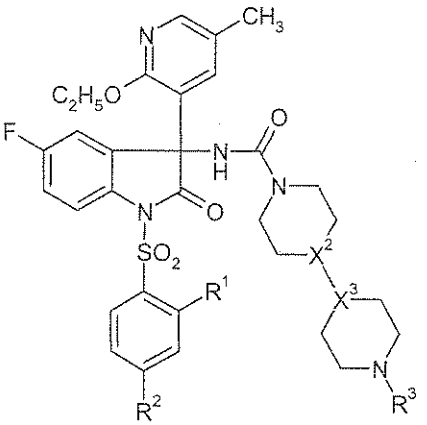
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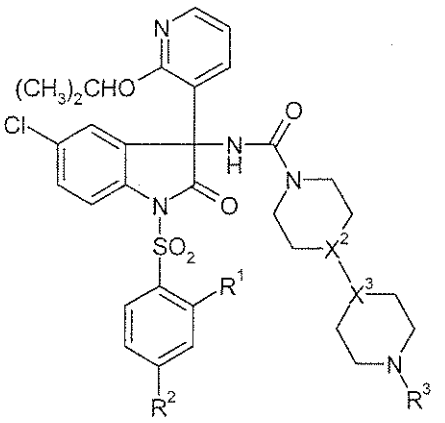
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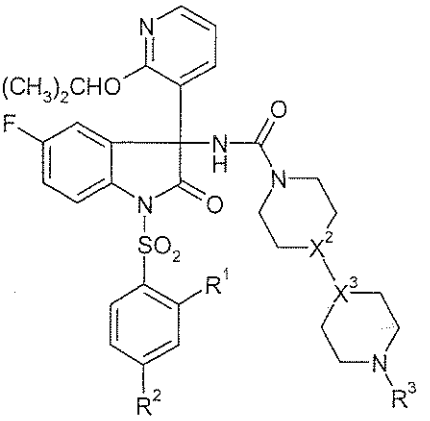
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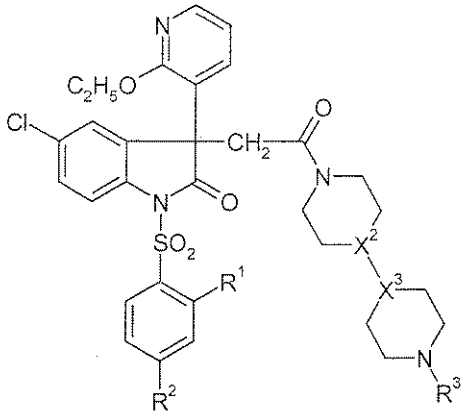


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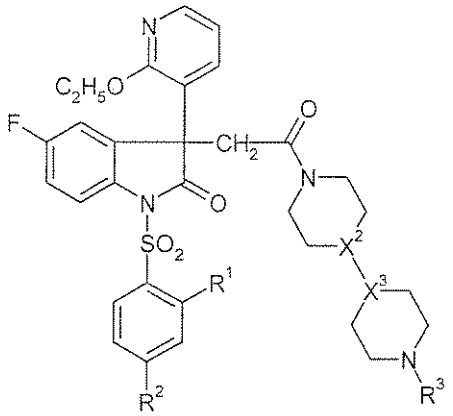


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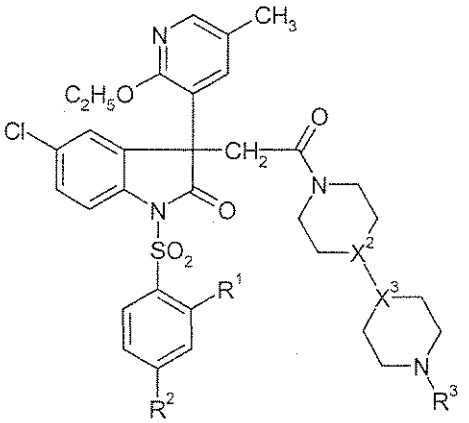
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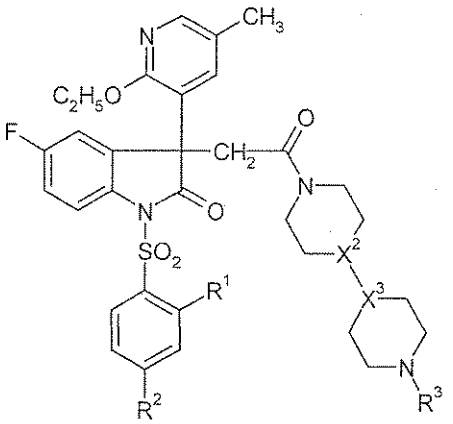
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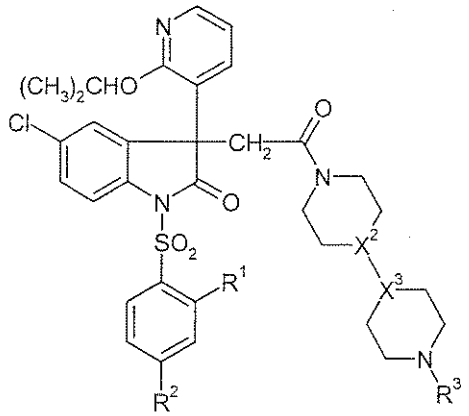
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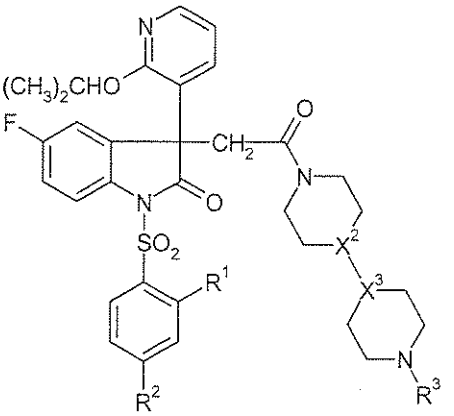
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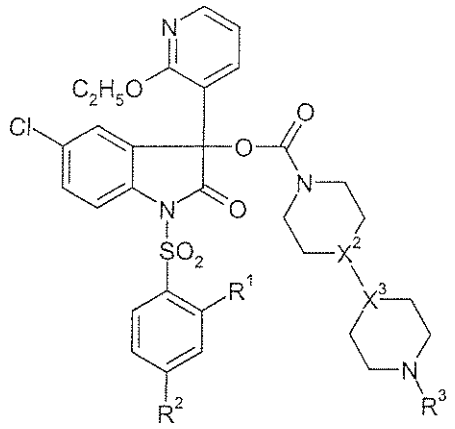


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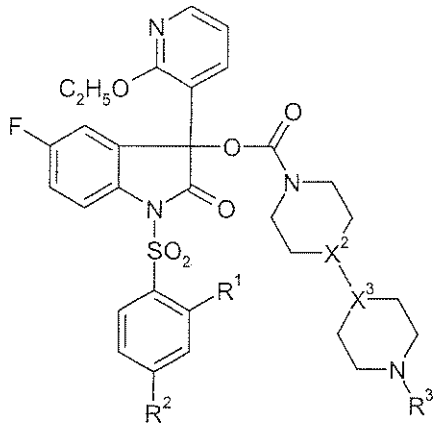


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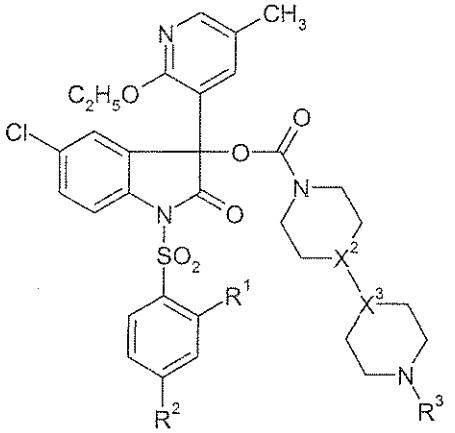
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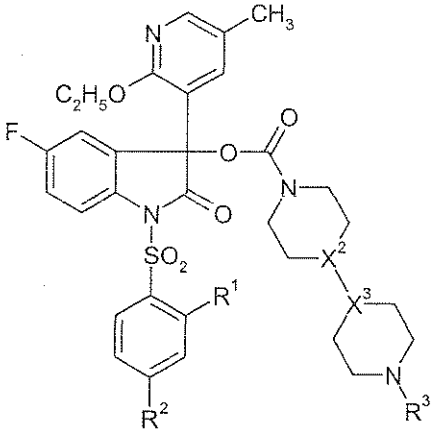
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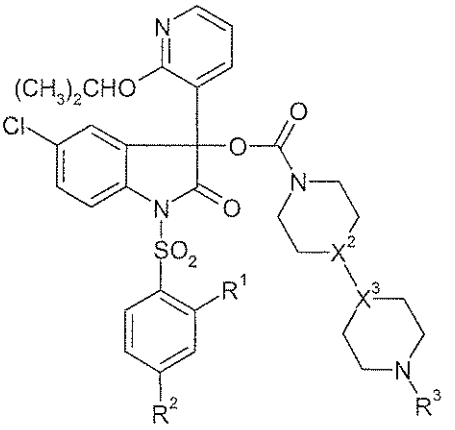
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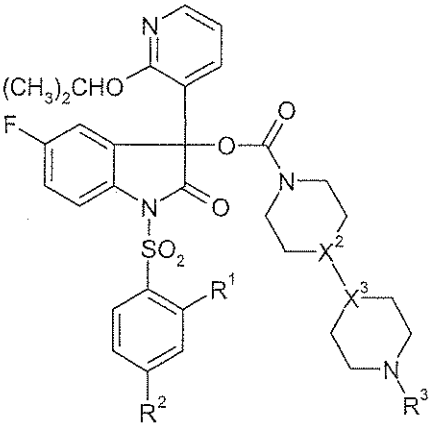
(I.15)



(I.16)



(I.17)



(I.18)

Table 1:

Example No.	X^2	X^3	R^1	R^2	R^3
A-1.	N	CH	Methoxy	Methoxy	Methyl
A-2.	N	CH	Methoxy	H	Methyl
A-3.	N	CH	Ethoxy	H	Methyl
A-4.	N	CH	H	H	Methyl
A-5.	N	CH	H	Methoxy	Methyl
A-6.	N	CH	Ethoxy	Methoxy	Methyl
A-7.	N	CH	Methoxy	Methoxy	Ethyl
A-8.	N	CH	Methoxy	H	Ethyl
A-9.	N	CH	Ethoxy	H	Ethyl
A-10.	N	CH	H	H	Ethyl
A-11.	N	CH	H	Methoxy	Ethyl
A-12.	N	CH	Ethoxy	Methoxy	Ethyl
A-13.	N	CH	Methoxy	Methoxy	n-Propyl
A-14.	N	CH	Methoxy	H	n-Propyl
A-15.	N	CH	Ethoxy	H	n-Propyl
A-16.	N	CH	H	H	n-Propyl
A-17.	N	CH	H	Methoxy	n-Propyl
A-18.	N	CH	Ethoxy	Methoxy	n-Propyl
A-19.	N	CH	Methoxy	Methoxy	Isopropyl
A-20.	N	CH	Methoxy	H	Isopropyl
A-21.	N	CH	Ethoxy	H	Isopropyl
A-22.	N	CH	H	H	Isopropyl
A-23.	N	CH	H	Methoxy	Isopropyl
A-24.	N	CH	Ethoxy	Methoxy	Isopropyl
A-25.	N	CH	Methoxy	Methoxy	H
A-26.	N	CH	Methoxy	H	H
A-27.	N	CH	Ethoxy	H	H
A-28.	N	CH	H	H	H
A-29.	N	CH	H	Methoxy	H
A-30.	N	CH	Ethoxy	Methoxy	H
A-31.	CH	N	Methoxy	Methoxy	Methyl
A-32.	CH	N	Methoxy	H	Methyl

Example No.	X^2	X^3	R^1	R^2	R^3
A-33.	CH	N	Ethoxy	H	Methyl
A-34.	CH	N	H	H	Methyl
A-35.	CH	N	H	Methoxy	Methyl
A-36.	CH	N	Ethoxy	Methoxy	Methyl
A-37.	CH	N	Methoxy	Methoxy	Ethyl
A-38.	CH	N	Methoxy	H	Ethyl
A-39.	CH	N	Ethoxy	H	Ethyl
A-40.	CH	N	H	H	Ethyl
A-41.	CH	N	H	Methoxy	Ethyl
A-42.	CH	N	Ethoxy	Methoxy	Ethyl
A-43.	CH	N	Methoxy	Methoxy	n-Propyl
A-44.	CH	N	Methoxy	H	n-Propyl
A-45.	CH	N	Ethoxy	H	n-Propyl
A-46.	CH	N	H	H	n-Propyl
A-47.	CH	N	H	Methoxy	n-Propyl
A-48.	CH	N	Ethoxy	Methoxy	n-Propyl
A-49.	CH	N	Methoxy	Methoxy	Isopropyl
A-50.	CH	N	Methoxy	H	Isopropyl
A-51.	CH	N	Ethoxy	H	Isopropyl
A-52.	CH	N	H	H	Isopropyl
A-53.	CH	N	H	Methoxy	Isopropyl
A-54.	CH	N	Ethoxy	Methoxy	Isopropyl
A-55.	CH	N	Methoxy	Methoxy	H
A-56.	CH	N	Methoxy	H	H
A-57.	CH	N	Ethoxy	H	H
A-58.	CH	N	H	H	H
A-59.	CH	N	H	Methoxy	H
A-60.	CH	N	Ethoxy	Methoxy	H
A-61.	CH	CH	Methoxy	Methoxy	Methyl
A-62.	CH	CH	Methoxy	H	Methyl
A-63.	CH	CH	Ethoxy	H	Methyl
A-64.	CH	CH	H	H	Methyl
A-65.	CH	CH	H	Methoxy	Methyl

Example No.	X^2	X^3	R^1	R^2	R^3
A-66.	CH	CH	Ethoxy	Methoxy	Methyl
A-67.	CH	CH	Methoxy	Methoxy	Ethyl
A-68.	CH	CH	Methoxy	H	Ethyl
A-69.	CH	CH	Ethoxy	H	Ethyl
A-70.	CH	CH	H	H	Ethyl
A-71.	CH	CH	H	Methoxy	Ethyl
A-72.	CH	CH	Ethoxy	Methoxy	Ethyl
A-73.	CH	CH	Methoxy	Methoxy	n-Propyl
A-74.	CH	CH	Methoxy	H	n-Propyl
A-75.	CH	CH	Ethoxy	H	n-Propyl
A-76.	CH	CH	H	H	n-Propyl
A-77.	CH	CH	H	Methoxy	n-Propyl
A-78.	CH	CH	Ethoxy	Methoxy	n-Propyl
A-79.	CH	CH	Methoxy	Methoxy	Isopropyl
A-80.	CH	CH	Methoxy	H	Isopropyl
A-81.	CH	CH	Ethoxy	H	Isopropyl
A-82.	CH	CH	H	H	Isopropyl
A-83.	CH	CH	H	Methoxy	Isopropyl
A-84.	CH	CH	Ethoxy	Methoxy	Isopropyl
A-85.	CH	CH	Methoxy	Methoxy	H
A-86.	CH	CH	Methoxy	H	H
A-87.	CH	CH	Ethoxy	H	H
A-88.	CH	CH	H	H	H
A-89.	CH	CH	H	Methoxy	H
A-90.	CH	CH	Ethoxy	Methoxy	H

The preferred compounds among the compounds I.1 to I.18 mentioned above are those of the formulae I.1, I.3, I.5, I.7, I.9, I.11, I.13, I.15 and I.17, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in each line in table 1. Compounds among these which are in turn preferred are those of the formulae I.1, I.3, I.5, I.7 and I.13, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in each line in table 1.

Compounds particularly preferred are those of the formula I.1, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in table 1 in lines A-1, A-2, A-4, A-7, A-31, A-32, A-34, A-37, A-38, A-40, A-61, A-67 and A-85, preferably those in lines A-1, A-2, A-4, A-7, A-31, A-37, A-38, A-61 and A-67, and in particular those in lines A-1, A-4, A-7, A-31, A-37, A-61 and A-67.

Compounds particularly preferred are also those of the formula I.3, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in table 1 in lines A-1, A-7, A-31 and A-37, and preferably those in lines A-1 and A-7.

Particularly preferred compounds are also those of the formula I.5, in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in table 1 in lines A-1, A-7, A-31 and A-37, and preferably those in lines A-1 and A-7.

Particularly preferred compounds are also those of the formula 1.7 in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in table 1 in lines A-1, A-4, A-31, A-34, A-37 and A-40, and preferably in line A-1.

Particularly preferred compounds are also those of the formula 1.13 in which the radicals X^2, X^3, R^1, R^2 and R^3 assume in each case the meanings mentioned in table 1 in lines A-1, A-2, A-4, A-31, A-32 and A-34, and preferably in line A-2.

Among these particularly preferred compounds in turn preferred compounds are I.1, I.3, I.5 and I.7, in which the radicals X^2, X^3, R^1, R^2 and R^3 have the meanings indicated for the respective compounds. Particularly preferred compounds among these are those of the formulae I.1, I.3 and I.5 and especially of the formulae I.1 and I.3, with compounds of the formula I.1 being even more greatly preferred.

The compounds I of the invention have a center of chirality in position 3 of the 2-oxindole ring. The compounds of the invention may therefore be in the form of a 1:1 mixture of enantiomers (racemate) or of a nonracemic mixture of enantiomers in which one of the two enantiomers, either the enantiomer which rotates the plane of vibration of linearly polarized light to the left (i.e. minus rotation) (hereinafter (-) enantiomer) or the enantiomer which rotates the plane of vibration of linearly polarized light to the right (i.e. plus rotation) (hereinafter (+) enantiomer), is enriched, or of substantially enantiopure compounds, that

is to say of substantially enantiopure (-) enantiomer or (+) enantiomer. Since the compounds of the invention have a single center of asymmetry and no axis/plane of chirality, a nonracemic mixture can also be defined as a mixture of enantiomers in which either the R or the S enantiomer predominates. Substantially enantiopure compounds can accordingly also be defined as substantially enantiopure R enantiomer or substantially enantiopure S enantiomer.

"Substantially enantiopure compounds" means in the context of the present invention those compounds having an enantiomeric excess (ee; % ee = (R-S)/(R+S) x 100 or (S-R)/(S+R) x 100) of at least 80% ee, preferably at least 85% ee, more preferably at least 90% ee, even more preferably at least 95% ee and in particular at least 98% ee.

In one embodiment of the invention, the compounds of the invention are in the form of substantially enantiopure compounds. Particularly preferred compounds have an enantiomeric excess of at least 85% ee, more preferably of at least 90% ee, even more preferably of at least 95% ee and in particular of at least 98% ee.

The invention thus relates both to the pure enantiomers and to mixtures thereof, e.g. mixtures in which one enantiomer is present in enriched form, but also to the racemates. The invention also relates to the pharmaceutically acceptable salts and the prodrugs of the pure enantiomers of compounds I, and the mixtures of enantiomers in the form of the pharmaceutically acceptable salts and prodrugs of compounds I.

Preferred embodiments of the invention are compounds of the formula I as detailed above which are characterized in that they are in optically active form, and the enantiomer of the relevant compound of the formula I is the one which rotates the plane of vibration of polarized light to the right (i.e. plus rotation), in the form of a free base, or a pharmaceutically acceptable salt or a prodrug thereof. The enantiomers with dextrorotation or plus rotation of the compounds I are also referred to hereinafter as (+) enantiomers.

Particularly preference is given to compounds of the general formula I, pharmaceutically acceptable salts and their prodrugs as detailed above in which the corresponding (+) enantiomer is present in an optical purity (enantiomeric excess, ee) of more than 50% ee, particularly preferably of at least 80% ee, more preferably of at least 90% ee and

even more preferably of at least 95% ee and in particular of at least 98% ee.

Likewise preferred embodiments of the invention are compounds of the general formula I as detailed above which are characterized in that they are in optically inactive form, i.e. in the form of the racemate, or in the form of a pharmaceutically acceptable salt or of a prodrug of the racemate.

The statements made in the context of the present invention concerning the direction of rotation of polarized light relate preferably to the signs [(+) or (-)] as determined in chloroform as solvent or in chloroform-containing solvent mixtures, in particular in chloroform.

Examples of synthetic routes for preparing the oxindole derivatives of the invention are described below.

The compounds of the invention can be prepared by using methods described in WO 2005/030755 and WO 2006/005609 for synthesizing analogous compounds, and the preparation is outlined by way of example in synthesis schemes 1 to 3. The variables in these synthetic schemes have the same meanings as in formula I.

The 3-hydroxy-1,3-dihydroindol-2-ones IV can be obtained by addition of metallated heterocycles III onto the 3-keto group of the isatins II. The metallated heterocycles, such as, for example, the corresponding Grignard (Mg) or organyllithium compound, can be obtained in any conventional way from halogen or hydrocarbon compounds. Examples of methods are present in Houben-Weyl, Methoden der Organischen Chemie, vol. 13, 1-2, chapter on Mg and Li compounds. The isatins II are either commercially available or were prepared in analogy to methods described in the literature (Advances in Heterocyclic Chemistry, A.R. Katritzky and A.J. Boulton, Academic Press, New York, 1975, 18, 2-58; J. Brazil. Chem. Soc. 12, 273-324, 2001).

The 3-hydroxyoxindoles IV can be converted into the compounds V which have a leaving group LG' in position 3, where the leaving group LG' is a conventional leaving group such as, for example, chlorine or bromide. The intermediate V with for example LG' = chlorine can be prepared by treating the alcohol IV with thionyl chloride in the presence of a base such as, for example, pyridine, in a suitable solvent such as, for example,

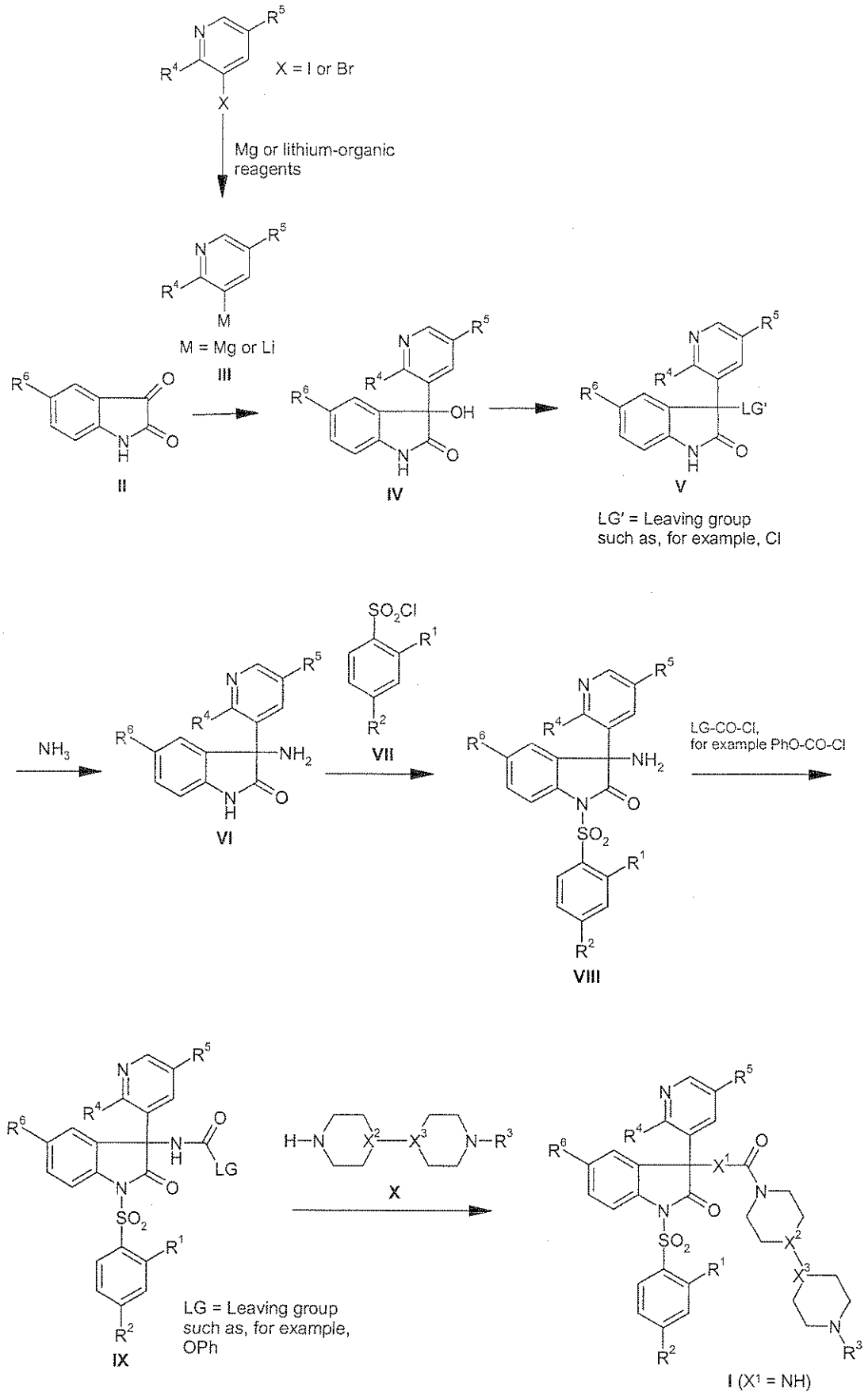
dichloromethane.

The compounds V can subsequently be reacted with amines, such as, for example, ammonia, in a substitution reaction to give the amines VI. The compounds VI can subsequently be converted by treatment with sulfonyl chlorides VII after deprotonation with a strong base such as, for example, potassium tert-butoxide or sodium hydride in DMF into the sulfonylated product VIII. The sulfonyl chlorides VII employed can either be purchased or be prepared by known processes (for example J. Med. Chem. 40, 1149 (1997)).

The compounds of the invention of the general formula I which have a urea group in position 3 can be prepared as described in WO 2005/030755 and WO 2006/005609, and shown in synthesis scheme 1, in a two-stage process: firstly, the compounds VIII are reacted with phenyl chloroformate in the presence of a base such as, for example, pyridine to give the corresponding phenyl carbamate IX.

Subsequent reaction with amines X, where appropriate at elevated temperature and with the addition of auxiliary bases such as, for example, triethylamine or diisopropylethyl-amine, leads to the compounds of the invention of the general formula (I) with a urea bridge (X^1 = NH). The amines X can be either purchased or prepared by methods known from the literature. Compounds I of the invention with R^3 = H can be prepared by using appropriate Boc-protected amines (R^3 = Boc). The Boc protective group can subsequently be removed, for example by treatment with trifluoroacetic acid in dichloromethane.

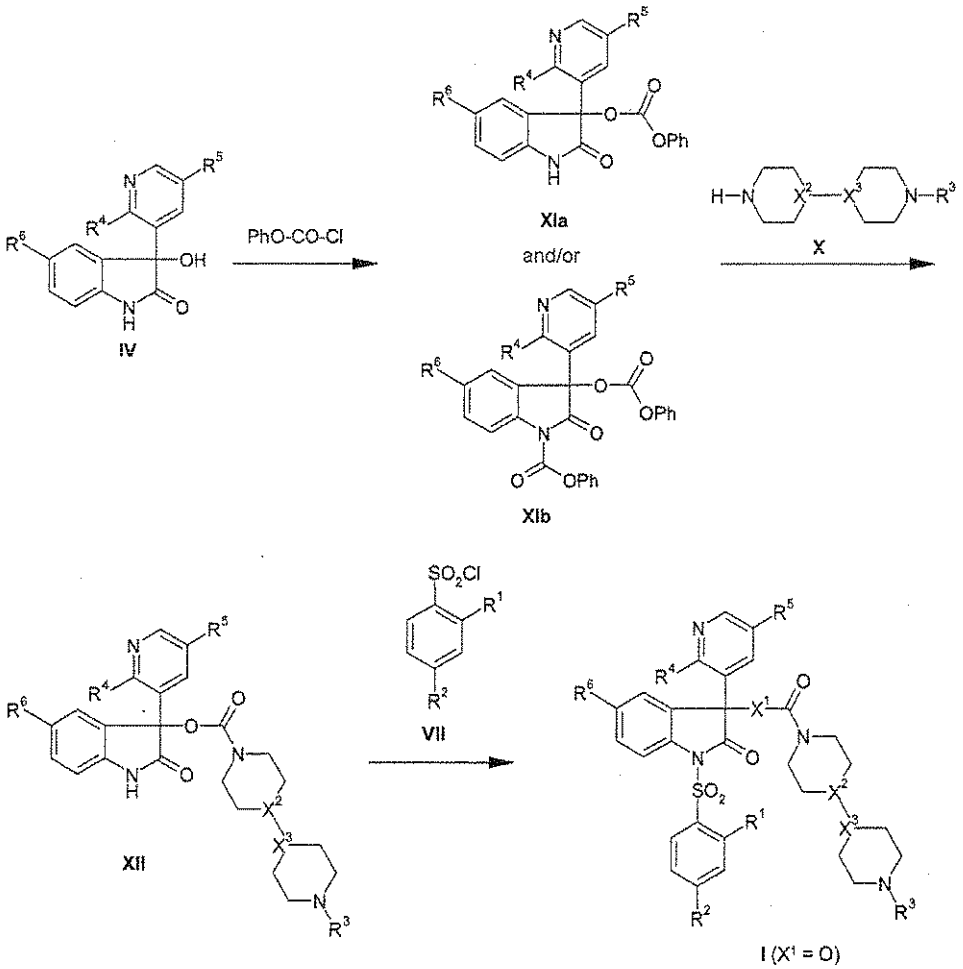
SYNTHESIS SCHEME 1


X = I or Br
Mg or lithium-organic reagents
M = Mg or Li
III
II
IV
V
LG' = Leaving group such as, for example, Cl
NH3
VI
VII
VIII
LG-CO-Cl, for example PhO-CO-Cl
X
IX
LG = Leaving group such as, for example, OPh
I (X1 = NH)

Ph = Phenyl

The compounds of the invention of the general formula I having a carbamate group in position 3 (X^1 = O) can be prepared as described in WO 2006/005609 and shown in synthesis scheme 2: firstly, the 3-hydroxy compound IV is reacted with phenyl chloroformate to give the phenyl carbonate derivatives XIa and/or XIb. The carbamate derivatives XII are obtained with an excess of amine X and can subsequently be converted under the usual conditions (deprotonation with a strong base such as, for example, sodium hydride or potassium *tert*-butoxide in a suitable solvent such as, for example, DMF, followed by treatment with sulfonyl chlorides VII) into the compounds I of the invention with a carbamate bridge.

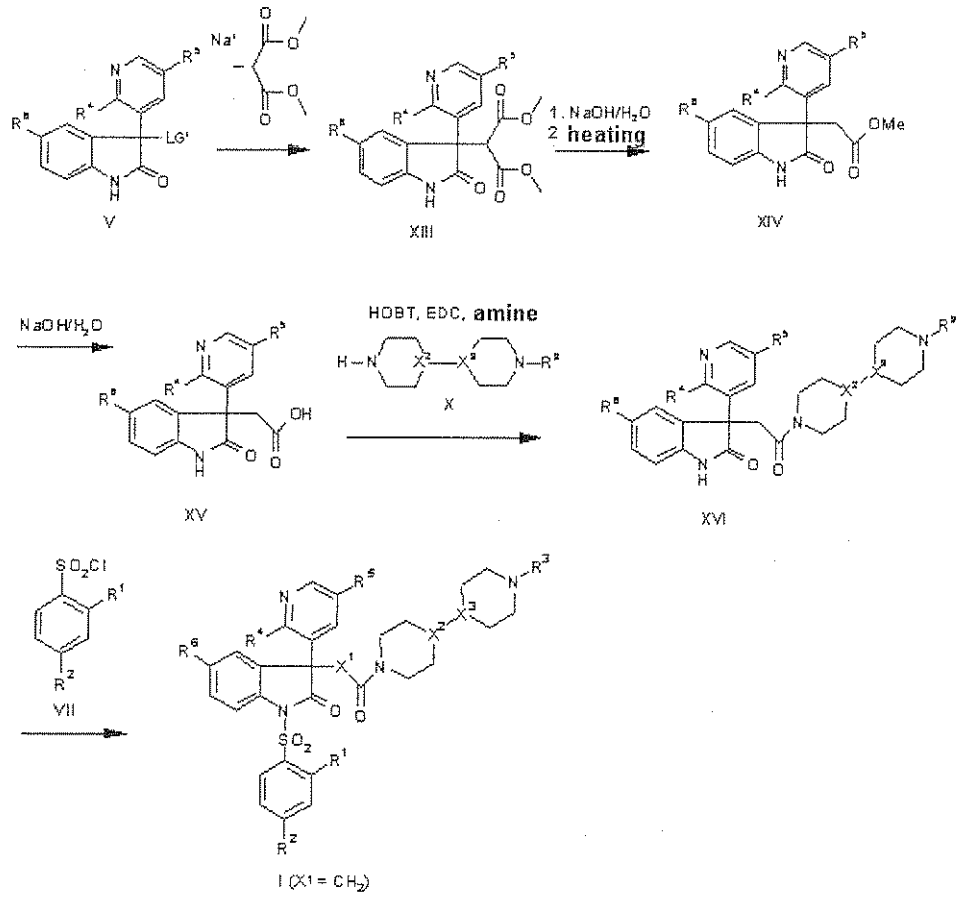
SYNTHESIS SCHEME 2



Ph = Phenyl

The compounds of the invention of the general formula I which have a 2-oxoethyl group in position 3 ($X^1 = CH_2$) can be prepared as shown in synthesis scheme 3. Introduction of the acetic acid group can take place as described in WO 2006/005609 in a 4-stage sequence (1. replacement of the leaving group LG' in V by the sodium salt of dimethyl malonate, 2. hydrolysis of the first ester group, 3. thermal decarboxylation, 4. hydrolysis of the second ester group). The amine side chain X can be coupled to the carboxylic acid XV using standard coupling reagents known in peptide chemistry, such as, for example, EDC (N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride) and HOBT (1-hydroxybenzotriazole) in a solvent such as, for example, N,N-dimethylformamide. The sulfonylation can take place by deprotonation of the coupling product XVI with a strong base such as, for example, sodium hydride or potassium *tert*-butoxide, and subsequent treatment with sulfonyl chlorides VII in a solvent such as, for example, DMF, and leads to the compounds I of the invention with an amide bridge.

SYNTHESIS SCHEME 3



Me = Methyl

A further aspect of the present invention relates to a pharmaceutical composition comprising at least one compound of the general formula I and/or a pharmaceutically acceptable salt or a prodrug thereof as detailed above, and a pharmaceutically acceptable carrier. Suitable carriers depend inter alia on the dosage form of the composition and are known in principle to the skilled worker. Some suitable carriers are described hereinafter.

A further aspect of the present invention relates to the use of compounds of the formula I and/or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasopressin-dependent diseases.

Vasopressin-dependent diseases are those in which the progress of the disease is at least partly dependent on vasopressin, i.e. diseases which show an elevated vasopressin level which may contribute directly or indirectly to the pathological condition. In other words, vasopressin-dependent diseases are those which can be influenced by modulating the vasopressin receptor, for example by administration of a vasopressin receptor ligand (agonist, antagonist, partial antagonist/agonist, inverse agonist etc.).

In a preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from diabetes, insulin resistance, nocturnal enuresis, incontinence and diseases in which impairments of blood clotting occur, and/or for delaying micturition. The term "diabetes" means all types of diabetes, especially diabetes mellitus (including type I and especially type II), diabetes renalis and in particular diabetes insipidus. The types of diabetes are preferably diabetes mellitus of type II (with insulin resistance) or diabetes insipidus.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from hypertension, pulmonary hypertension, heart failure, myocardial infarction, coronary spasm, unstable angina, PTCA (percutaneous transluminal coronary angioplasty), ischemias of the heart, impairments of the renal system, edemas, renal vasospasm, necrosis of the renal cortex, hyponatremia, hypokalemia, Schwartz-Bartter syndrome, impairments of the gastrointestinal tract, gastritic vasospasm, hepatocirrhosis, gastric and intestinal ulcers, emesis, emesis occurring during chemotherapy, and travel

sickness.

The compounds of the invention of the formula I or their pharmaceutically acceptable salts or prodrugs or the pharmaceutical composition of the invention can also be used for the treatment of various vasopressin-dependent complaints which have central nervous causes or alterations in the HPA axis (hypothalamic pituitary adrenal axis), for example for affective disorders such as depressive disorders and bipolar disorders. These include for example dysthymic disorders, phobias, post-traumatic stress disorders, general anxiety disorders, panic disorders, seasonal depression and sleep disorders.

The compounds of the invention of the formula I and their pharmaceutically acceptable salts or prodrugs or the pharmaceutical composition of the invention can likewise be employed for the treatment of anxiety disorders and stress-dependent anxiety disorders, such as, for example, generalized anxiety disorders, phobias, post-traumatic anxiety disorders, panic anxiety disorders, obsessive-compulsive anxiety disorders, acute stress-dependent anxiety disorders and social phobia.

The compounds of the invention can furthermore also be employed for the treatment of memory impairments, Alzheimer's disease, psychoses, psychotic disorders, sleep disorders and/or Cushing's syndrome, and all stress-dependent diseases.

Accordingly, a further preferred embodiment of the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of affective disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of anxiety disorders and/or stress-dependent anxiety disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of memory impairments and/or Alzheimer's disease.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of psychoses and/or psychotic disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of Cushing's syndrome or other stress-dependent diseases.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of sleep disorders.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of depressive disorders. A particular form of depressive disorders are so-called childhood onset mood disorders, i.e. depressive moods having their onset in childhood.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment of vasomotor symptoms and/or thermoregulatory dysfunctions such as, for example, the hot flush symptom.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment and/or prophylaxis of drug or pharmaceutical dependencies and/or dependencies mediated by other factors, for the treatment and/or prophylaxis of stress caused by withdrawal of one or more factors mediating the dependence and/or for the treatment and/or prophylaxis of stress-induced relapses into drug or pharmaceutical dependencies and/or dependencies mediated by other factors.

In a further preferred embodiment, the present invention relates to the use of compounds of the invention of the formula I or of pharmaceutically acceptable salts or prodrugs thereof for the manufacture of a medicament for the treatment and/or prophylaxis of schizophrenia and/or psychosis.

A further aspect of the invention relates to a method for the treatment and/or prophylaxis of vasopressin-dependent diseases, in which an effective amount of at least one compound of the invention of the formula I or of at least one pharmaceutically acceptable salt or one prodrug thereof or of a pharmaceutical composition of the invention is administered to a patient.

Concerning the definition of vasopressin-dependent diseases, reference is made to the above statements.

In a preferred embodiment of the invention, the method of the invention serves for the treatment and/or prophylaxis of disorders selected from diabetes, insulin resistance, nocturnal enuresis, incontinence and diseases in which impairments of blood clotting occur, and/or for delaying micturition. Concerning the definition of diabetes, reference is made to the above statements.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of disorders selected from hypertension, pulmonary hypertension, heart failure, myocardial infarction, coronary spasm, unstable angina, PTCA (percutaneous transluminal coronary angioplasty), ischemias of the heart, impairments of the renal system, edemas, renal vasospasm, necrosis of the renal cortex, hyponatremia, hypokalemia, Schwartz-Bartter syndrome, impairments of the gastrointestinal tract, gastritic vasospasm, hepatocirrhosis, gastric and intestinal ulcers, emesis, emesis occurring during chemotherapy, and travel sickness.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of affective disorders.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of anxiety disorders and/or stress-dependent anxiety disorders.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of memory impairments and/or Alzheimer's disease.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of psychoses and/or psychotic disorders.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of Cushing's syndrome.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of sleep disorders in a patient.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of depressive disorders. In the case of depressive disorders, specific mention is also to be made of childhood onset mood disorders, i.e. depressive moods having their onset in childhood.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of vasomotor symptoms and/or thermoregulatory dysfunctions, such as, for example, the hot flush symptom.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of drug or pharmaceutical dependencies and/or dependencies mediated by other factors, for the treatment and/or prophylaxis of stress caused by withdrawal of one or more factors mediating the dependence, and/or for the treatment and/or prophylaxis of stress-induced relapses into drug or pharmaceutical dependencies and/or dependencies mediated by other factors.

In a further preferred embodiment, the method of the invention serves for the treatment and/or prophylaxis of schizophrenia and/or psychosis.

The patient to be treated prophylactically or therapeutically with the method of the invention is preferably a mammal, for example a human or a nonhuman mammal or a nonhuman transgenic mammal. Specifically it is a human.

The compounds of the general formula I, their pharmaceutically acceptable salts and prodrugs as detailed above can be prepared by a skilled worker with knowledge of the technical teaching of the invention in implementing and/or in analogous implementation of process steps known per se.

The compounds I or their prodrugs and/or their pharmaceutically acceptable salts are distinguished by having a selectivity for the vasopressin V1b receptor subtype vis-à-vis at least one of the closely related vasopressin/oxytocin receptor subtypes (for example vasopressin V1a, vasopressin V2 and/or oxytocin).

Alternatively, or preferably in addition, the compounds I or their prodrugs and/or their pharmaceutically acceptable salts are distinguished by having an improved metabolic stability.

The metabolic stability of a compound can be measured for example by incubating a solution of this compound with liver microsomes from particular species (for example rat, dog or human) and determining the half-life of the compound under these conditions (RS Obach, Curr Opin Drug Discov Devel. 2001, 4, 36-44). It is possible in this connection to conclude from an observed longer half-life that the metabolic stability of the compound is improved. The stability in the presence of human liver microsomes is of particular interest because it makes it possible to predict the metabolic degradation of the compound in the human liver. Compounds with increased metabolic stability (measured in the liver microsome test) are therefore probably also degraded more slowly in the liver. The slower metabolic degradation in the liver may lead to higher and/or longer-lasting concentrations (active levels) of the compound in the body, so that the elimination half-life of the compounds of the invention is increased. Increased and/or longer-lasting active levels may lead to a better activity of the compound in the treatment or prophylaxis of various vasopressin-dependent diseases. In addition, an improved metabolic stability may lead to an increased bioavailability after oral administration, because the compound is subject, after absorption in the intestine, to less metabolic degradation in the liver (so-called first pass effect). An increased oral bioavailability may, owing to an increased concentration (active level) of the compound, lead to a better activity of the compound after oral administration.

The compounds of the invention are effective after administration by various routes.

Possible examples are intravenous, intramuscular, subcutaneous, topical, intratracheal, intranasal, transdermal, vaginal, rectal, sublingual, buccal or oral administration, and administration is frequently intravenous, intramuscular or, in particular, oral.

The present invention also relates to pharmaceutical compositions which comprise an effective dose of a compound I of the invention, of a pharmaceutically acceptable salt or of a prodrug thereof and suitable pharmaceutical carriers (drug carriers).

These drug carriers are chosen according to the pharmaceutical form and the desired mode of administration and are known in principle to the skilled worker.

The compounds of the invention of the formula I or optionally suitable salts of these compounds can be used to produce pharmaceutical compositions for oral, sublingual, buccal, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal, vaginal or rectal administration, and be administered to animals or humans in uniform administration forms, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases.

The suitable administration forms (dose units) include forms for oral administration such as tablets, gelatin capsules, powders, granules and solutions or suspensions for oral intake, forms for sublingual, buccal, intratracheal or intranasal administration, aerosols, implants, forms of subcutaneous, intramuscular or intravenous administration and forms of rectal administration.

The compounds of the invention can be used in creams, ointments or lotions for topical administration.

In order to achieve the desired prophylactic or therapeutic effect, the dose of the active ingredient can vary between 0.01 and 50 mg per kg of body weight and per day.

Each unit dose may comprise from 0.05 to 5000 mg, preferably 1 to 1000 mg, of the active ingredient in combination with a pharmaceutical carrier. This unit dose can be administered once to 5 times a day, so that a daily dose of from 0.5 to 25 000 mg, preferably 1 to 5000 mg, is administered.

If a solid composition is prepared in the form of tablets, the active ingredient is mixed with a solid pharmaceutical carrier such as gelatin, starch, lactose, magnesium stearate, talc, silicon dioxide or the like.

The tablets can be coated with sucrose, a cellulose derivative or another suitable substance or be treated otherwise in order to display a sustained or delayed activity and to release a predetermined amount of the active ingredient continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with an extender and including the resulting mixture in soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops may contain active ingredients together with a sweetener, which is preferably calorie-free, methylparaben or propylparaben as antiseptics, a flavoring and a suitable coloring substance.

Water-dispersible powders or granules may comprise the active ingredients mixed with dispersants, wetting agents or suspending agents, such as polyvinylpyrrolidones, and sweeteners or masking flavors.

Rectal or vaginal administration is achieved by using suppositories which are prepared with binders which melt at rectal temperature, for example cocoa butter or polyethylene glycols. Parenteral administration is effected by using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which comprise pharmacologically acceptable dispersants and/or wetting agents, for example propylene glycol or polyethylene glycol.

The active ingredient may also be formulated as microcapsules or centrosomes, if suitable with one or more carriers or additives.

The compositions of the invention may, in addition to the compounds of the invention, comprise other active ingredients which may be beneficial for the treatment of the disorders or diseases indicated above.

The present invention thus further relates to pharmaceutical compositions in which a

plurality of active ingredients are present together, where at least one of these is a compound I of the invention, salt or a prodrug thereof.

The invention is explained in more detail below by means of examples, but the examples are not to be understood to be restrictive.

The compounds of the invention can be prepared by various synthetic routes. The methods mentioned, as described accordingly in synthesis schemes 1, 2 and 3, are explained in greater detail merely by way of example using the given examples without being exclusively restricted to synthesis routes 1, 2 or 3 or analogous methods.

EXPERIMENTAL SECTION

Abbreviations used:

THF:	Tetrahydrofuran	
DMSO:	Dimethyl sulfoxide	
TFA:	Trifluoroacetic acid	
p:	pseudo (for example pt	pseudo triplet)
b:	broad (for example bs	broad singlet)
s:	singlet	
d:	doublet	
t:	triplet	
m:	multiplet	
dd:	doublet of doublets	
dt:	doublet of triplets	
tt:	triplet of triplets	

I. Preparation of the starting compounds

a) 3-Hydroxyindoles of the general formula IV

a.1 5-Chloro-3-(2-ethoxypyridin-3-yl)-3-hydroxy-1,3-dihydroindol-2-one

Formation of the sodium salt of isatin: 3.21 g (80.3 mmol) of sodium hydride (60% in mineral oil) were added in portions to 13.9 g (76.5 mmol) of 5-chloroisatin in 300 ml of THF at 0°C, and the mixture was stirred at 0°C for one hour.

Formation of the Grignard reagent: ethylmagnesium bromide (95.6 mmol, 95.6 ml of a 1M solution in THF) was added dropwise to a solution of 2-ethoxy-3-iodopyridine (20.0 g, 80.3 mmol) in 250 ml of THF keeping the temperature at between 15 and 22°C. The mixture was then stirred at room temperature for 15 min.

Grignard addition: the solution of the Grignard reagent was pumped into the ice-cooled solution of the sodium salt of isatin, and the reaction mixture was then stirred at room temperature for three hours. The mixture was poured into 10% ammonium chloride solution and extracted three times with ethyl acetate. The combined organic phases were washed with water and saturated brine, dried with magnesium sulfate and concentrated under reduced pressure. The crystalline precipitate which had formed after standing overnight at room temperature was filtered off with suction and washed with ethyl acetate. 13.3 g of the title compound were obtained as a reddish solid.

ESI-MS $[M+H^+]$ = 305 (Cl isotope pattern)

a.2 5-Chloro-3-(2-ethoxy-5-methylpyridin-3-yl)-3-hydroxy-1,3-dihydroindol-2-one

Formation of the isatin sodium salt: 1.01 g (27.5 mmol) of sodium hydride (60% in mineral oil) was added in portions to 5.0 g (27.5 mmol) of 5-chloroisatin in 100 ml of THF at 0°C, and the mixture was stirred at 0°C for one hour.

Formation of the lithium reagent: n-butyllithium (37.2 mmol, 23.2 ml of a 1.6M solution in hexane) was added dropwise to a solution, cooled to -78°C, of 3-bromo-2-ethoxy-5-methylpyridine (7.74 g, 35.8 mmol) in 100 ml of THF, keeping the temperature below -60°C, and the reaction mixture was then stirred in an acetone/dry ice bath for a further 15 min.

Addition: The solution, cooled to -78°C, of the lithiated pyridine was pumped by means of a transfer needle into the ice-cooled solution of the isatin sodium salt, and the reaction

mixture was then stirred at room temperature for 3 hours. The reaction mixture was poured into 10% ammonium chloride solution and extracted three times with ethyl acetate. The combined organic phases were washed with water and saturated brine, dried over magnesium sulfate and concentrated under reduced pressure. After treatment of the residue with dichloromethane, a beige precipitate formed and was filtered off with suction and washed with dichloromethane. 2.61 g of the title compound were obtained as a reddish solid.
ESI-MS $[M+H^+]$ = 319 (Cl isotope pattern).

a.3 5-Chloro-3-(2-isopropoxypyridin-3-yl)-3-hydroxy-1,3-dihydroindol-2-one

The title compound was prepared in analogy to the process of example a.1 using 3-iodo-2-isopropoxypyridine.

b) Amines of the general formula X

b.1 1-Ethyl-4-piperidin-4-yl-piperazine

b.1.1 tert-Butyl 4-(4-ethylpiperazin-1-yl)piperidine-1-carboxylate

29.2 g (256 mmol) of *N*-ethylpiperazine were introduced with 50.0 g (256 mmol) of *tert*-butyl 4-oxopiperidine-1-carboxylate (corresponds to 1-Boc-4-piperidone) into 800 ml of ethanol while cooling in ice. 15.4 g (256 mmol) of glacial acetic acid were added. Then 16.1 g (256 mmol) of sodium acetoxyborohydride were added in portions to the cooled reaction mixture. Initially slight gas formation was observed and, after addition of 2/3 of the reducing agent, foam formation was observed. The reaction mixture was stirred at room temperature overnight. The reaction solution was worked up by adding 200 ml of 2*N* of sodium hydroxide solution while cooling, distilling out the solvent ethanol and diluting the remaining reaction mixture with water. It was extracted with diethyl ether (2×) and was washed with saturated sodium chloride solution (1×), and the combined organic phases were dried over magnesium sulfate and filtered, and the solvent was removed in vacuo. The crude title compound was obtained as a yellow oil which was then chromatographed on a 4 l suction funnel filled with silica gel using dichloromethane and 10% methanol as eluent. In total, 40 g (135 mmol, 53%) of *tert*-butyl 4-(4-ethylpiperazin-1-yl)piperidine-1-carboxylate were obtained.

b.1.2 1-Ethyl-4-piperidin-4-ylpiperazine as chloride salt

The protective group was removed by introducing 40 g (135 mmol) of *tert*-butyl 4-(4-ethylpiperazin-1-yl)piperidine-1-carboxylate from example b.1.1 into 200 ml of methanol and 1.8 l of dichloromethane and adding 100 ml of 5-6*M* HCl solution in isopropanol. A suspension resulted, and slight gas evolution was also observable. The reaction mixture was stirred at 40°C (water bath temperature) for one hour and then stirred at room temperature for 48 hours. For complete deprotection, 50 ml of the 5-6M HCl solution in isopropanol were again added and the reaction mixture was stirred at 40°C. The dichloromethane was distilled out in a rotary evaporator. 200 ml of methanol and 30 ml of the 5-6*M* HCl solution in isopropanol were again added. The reaction mixture was stirred under reflux for one hour, during which a white suspension formed with strong evolution of gas. A mobile suspension then resulted and was cooled to room temperature. The precipitate was filtered off with suction and washed with methanol and diethyl ether. After drying, 36 g (117 mmol, 87%) of 1-ethyl-4-piperidin-4-ylpiperazine were isolated as chloride salt.

^{1}H-NMR (D_2O, 400 MHz) δ [ppm] = 3.74 - 3.47 (m, 11H), 3.28 (q, 2H, J = 7.3 Hz), 3.06 (dt, 2H, J = 2.2 Hz, J = 13.2 Hz), 2.38 (m, 2H, J = 13.6 Hz), 1.89 (dq, 2H, J = 4.1 Hz, J = 13.3 Hz), 1.30 (t, 3H, J = 7.3 Hz).

II. Preparation of the racemic compounds of the formula I

The compounds I of the invention were purified in some cases by preparative HPLC, for example on a Prontosil Prep 2012, C18, 125×20 mm, 5 μm column with a mobile phase gradient from 10% to 100% acetonitrile in water and 0.1% trifluoroacetic acid as modulator. The compounds I then result as trifluoroacetic acid salt.

II.1 Preparation of racemic compounds of the formula I in which X^1 is NH (examples 1 to 21)

EXAMPLE 1:

(±)-4-(1-Methylpiperidin-4-yl)piperazin-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

1.1 3,5-Dichloro-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one

4.4 ml (54.3 mmol) of pyridine were added to a suspension of 13.3 g (43.6 mmol) of 5-chloro-3-(2-ethoxypyridin-3-yl)-3-hydroxy-1,3-dihydroindol-2-one from example a.1 in 50 ml of dichloromethane. After the reaction mixture had been cooled to 0°C, 3.8 ml (52.3 mmol) of thionyl chloride was added dropwise. The mixture was stirred at room temperature for one hour and then poured into ice-water. After stirring for 15 minutes, the organic phase was separated off. The aqueous phase was extracted several times with dichloromethane. The combined organic phase was dried over magnesium sulfate and filtered, and the solvent was removed in vacuo. 15.6 g of the title compound were obtained as a yellowish solid which was employed without further purification in the next stage.

1.2 3-Amino-5-chloro-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one

104 ml (728 mmol) of a 7*N* methanolic ammonia solution were added dropwise to a cooled solution of 47 g (145 mmol) of 3,5-dichloro-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one in 250 ml of dichloromethane under a nitrogen atmosphere, and the reaction mixture was then stirred at room temperature overnight. 250 ml of water and 250 ml of dichloromethane were added to the reaction mixture. After stirring for 5 min, a white solid was precipitated and filtered off and washed with water and dichloromethane. Drying in a vacuum drying oven resulted in 26 g of the title compound as a white solid.

ESI-MS $[M+H^+]$ = 304 (Cl isotope pattern)

1.3 3-Amino-5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one

3.2 g (79 mmol) of sodium hydride (60% dispersion in mineral oil) were added in portions to a solution of 20 g (66 mmol) of 3-amino-5-chloro-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one in 50 ml of anhydrous dimethylformamide under a nitrogen atmosphere and while cooling in an ice bath. The mixture was stirred at 0°C for 10 min and then 18.7 g (79 mmol) of 2,4-dimethoxybenzenesulfonyl chloride were added, and the mixture was stirred at room temperature for 30 min. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The organic phase was

washed with saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was evaporated. The residue was purified by chromatography on silica gel (120 g Redisep cartridge, mobile phase gradient from 2 to 25% dichloromethane in ethyl acetate). 34 g of the title compound were obtained as a white solid.

ESI-MS $[M+H^+]$ = 504 (Cl isotope pattern)

1.4 Phenyl [5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carbamate

0.83 ml (6.6 mmol) of phenyl chloroformate was slowly added dropwise to a solution, cooled to 0°C, of 2.57 g (5.1 mmol) of 3-amino-5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one in 10 ml of dichloromethane and 4.1 ml of pyridine. The reaction mixture was then stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and extracted with water. The organic phase was washed with water and saturated sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was dissolved in a little dichloromethane, and six times the volume of diisopropyl ether were added. The resulting precipitate was filtered off, washed with diisopropyl ether and dried in vacuo. 3.01 g of the title compound were obtained as a white solid.

ESI-MS $[M+H^+]$ = 624 (Cl isotope pattern).

1.5 4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

A mixture of 800 mg (1.28 mmol) of phenyl [5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carbamate, 470 mg (2.56 mmol) of 1-(1-methylpiperidin-4-yl)piperazine and 5 ml of dried THF was stirred at room temperature for 24 hours. The reaction mixture was diluted with dichloromethane and washed with water and saturated sodium chloride solution, and the organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (12 g Redisep cartridge, mobile phase gradient from 2 to 12% methanol in dichloromethane). 790 mg of the title compound were obtained as a white solid.

ESI-MS $[M+H^+]$ = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.55 (2H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.75 (2H), 2.35 (4H), 2.10 (4H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.15 (3H).

The compounds of the formula I in which X^1 is NH according to examples 2 to 21 can be prepared by using the appropriate 3-hydroxyoxindoles of the formula IV, sulfonyl chlorides of the formula VII and amines of the formula X in analogy to the process for preparing example 1.

EXAMPLE 2:

(±)-4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-3-(2-ethoxypyridin-3-yl)-1-(2-methoxyphenylsulfonyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS $[M+H]^+$ = 683 (Cl isotope pattern)

EXAMPLE 3:

(±)-4-(1-Methylpiperidin-4-yl)piperazine-1-[1-phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt A-977409

ESI-MS $[M+H^+]$ = 653 (Cl isotope pattern)

EXAMPLE 4:

(±)-4-(1-Ethylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS $[M+H^+]$ = 727 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.55 (2H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.85 (2H), 2.35 (4H), 2.30 (2H), 2.10 (1H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.10 (3H), 0.95 (3H).

EXAMPLE 5:

(±)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS $[M+H^+]$ = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H), 7.55 (1H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.25 (2H), 3.85 (3H), 3.80 (2H), 3.45 (3H), 2.65 (2H), 2.40 (4H), 2.30 (4H), 2.15 (3H), 1.60 (2H), 1.15 (5H).

EXAMPLE 6:

(±)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-3-(2-ethoxypyridin-3-yl)-1-(2-methoxyphenylsulfonyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 683 (Cl isotope pattern)

EXAMPLE 7:

(±)-4-(4-Methylpiperazin-1-yl)piperidine-1-[1-phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 653 (Cl isotope pattern)

EXAMPLE 8:

(±)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H), 7.55 (1H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.80 (2H), 3.45 (3H), 2.65 (2H), 2.25-2.50 (11H), 1.65 (2H), 1.15 (5H), 0.95 (3H).

EXAMPLE 9:

(±)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[5-chloro-3-(2-ethoxypyridin-3-yl)-1-(2-methoxyphenylsulfonyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 697 (Cl isotope pattern)

EXAMPLE 10:

(±)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[1-phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 667 (Cl isotope pattern)

EXAMPLE 11:

(±)-[4,4']Bipiperidinyl-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 698 (Cl isotope pattern)

EXAMPLE 12:

(±)-1'-Ethyl-[4,4']bipiperidinyl-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 726 (Cl isotope pattern)

EXAMPLE 13:

(±)-1'-Methyl-[4,4']bipiperidinyl-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 712 (Cl isotope pattern)

^{1}H-NMR ([d$_6$]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H), 7.55 (1H), 7.40 (1H), 7.35 (1H), 7.00 (1H), 6.65 (2H), 4.20 (2H), 3.90 (2H), 3.85 (3H), 3.45 (3H), 2.90 (2H), 2.55 (2H), 2.25 (3H), 2.05 (2H), 1.55 (4H), 1.25 (3H), 1.15 (3H), 0.95 (3H).

EXAMPLE 14:

(±)-4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxy-5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

^{1}H-NMR ([d$_6$]-DMSO, 500 MHz) δ [ppm] = 9.64 (1H), 7.98 (1H), 7.93 (1H), 7.89 (1H), 7.74 (1H), 7.40 (2H), 7.32 (1H), 6.75 (1H), 6.70 (1H), 4.20 (2H), 3.88 (3H), 3.60 (2H), 3.48 (3H), 2.85-3.40 (9H), 2.80 (3H), 2.30 (2H), 2.17 (3H), 1.80 (2H), 1.15 (3H).

EXAMPLE 15:

(±)-4-(1-Ethylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxy-5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide,

trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 741 (Cl isotope pattern)

EXAMPLE 16:

(±)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxy-5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

EXAMPLE 17:

(±)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxy-5-methylpyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 741 (Cl isotope pattern)

EXAMPLE 18:

(±)-4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-isopropoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide
ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)
^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.60 (1H), 7.50 (1H), 7.40 (1H), 7.35 (1H), 6.95 (1H), 6.70 (1H), 6.65 (1H), 5.20 (1H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.75 (2H), 2.35 (4H), 2.10 (4H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.20 (3H), 1.05 (3H).

EXAMPLE 19:

(±)-4-(1-Ethylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-isopropoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide
ESI-MS [M+H$^+$] = 741 (Cl isotope pattern)

EXAMPLE 20:

(±)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-isopropoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide
ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

EXAMPLE 21:

(±)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-isopropoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 741 (Cl isotope pattern)

II.2 Preparation of racemic compounds of the formula I, in which X^1 is O (examples 22 to 27)

EXAMPLE 22:

5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate, trifluoroacetic acid salt

22.1 Phenyl 5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-3-phenoxycarbonyloxy-2,3-dihydroindole-1-carboxylate

2.6 ml (21 mmol) of phenyl chloroformate were slowly added dropwise to a solution, cooled to 0°C, of 3.00 g (9.8 mmol) of 5-chloro-3-(2-ethoxypyridin-3-yl)-3-hydroxy-1,3-dihydroindol-2-one from example a.1 in 10 ml of pyridine, and the reaction mixture was stirred at room temperature overnight. The reaction mixture was diluted with dichloromethane and extracted with water. The organic phase was washed with water and saturated sodium chloride solution, dried over magnesium sulfate and concentrated under reduced pressure. The residue was stirred with diethyl ether. 2.58 g of the title compound were obtained as a white solid.

ESI-MS [M+H$^+$] = 545 (Cl isotope pattern).

22.2 5-Chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate

A mixture of 1.29 g (2.37 mmol) of phenyl 5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-3-phenoxycarbonyloxy-2,3-dihydroindole-1-carboxylate, 1.73 g (9.46 mmol) of 1-(1-methylpiperidin-4-yl)piperazine and 10 ml of dry THF was stirred at room temperature for 72 hours. The reaction mixture was diluted with dichloromethane and extracted with water and saturated sodium chloride solution. The organic phase was dried over magnesium sulfate and concentrated under reduced pressure. The residue was stirred

with diethyl ether. 963 mg of the title compound were obtained as a white solid.
ESI-MS [M+H$^+$] = 514 (Cl isotope pattern).

22.3 5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate, trifluoroacetic acid salt

7.5 mg (0.19 mmol) of sodium hydride (60% dispersion in mineral oil) were added to a solution of 80 mg (0.16 mmol) of 5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl 4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate in 2 ml of anhydrous dimethylformamide under a nitrogen atmosphere and while cooling in an ice bath. The mixture was stirred at 0°C for 10 min and then 44 mg (0.19 mmol) of 2,4-dimethoxybenzenesulfonyl chloride were added, and the mixture was stirred at room temperature for a further 30 min. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was evaporated. The residue was purified by preparative HPLC (Prontosil Prep 2012, C18, 125×20 mm, 5 μm, gradient from 10% to 100% acetonitrile in water, 0.1% trifluoroacetic acid). 78 mg of the title compound were obtained as a white solid.
ESI-MS [M+H$^+$] = 714 (Cl isotope pattern)
^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 9.60 (1H), 8.20 (1H), 8.15 (1H), 7.85 (1H), 7.80 (1H), 7.50 (1H), 7.20 (1H), 7.10 (1H), 6.70 (2H), 4.10 (2H), 3.85 (3H), 3.55 (3H), 2.90-3.50 (11H), 2.75 (3H), 2.15 (2H), 1.75 (2H), 1.00 (3H).

The compounds of the formula I in which X^1 is O, according to examples 23 to 27, can be prepared using the appropriate 3-hydroxyoxindoles of the formula IV, sulfonyl chlorides of the formula VII and amines of the formula X in analogy to the process for preparing example 22.

EXAMPLE 23:

5-Chloro-3-(2-ethoxypyridin-3-yl)-1-(2-methoxyphenylsulfonyl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 684 (Cl isotope pattern)

EXAMPLE 24:

1-Phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(1-methylpiperidin-4-yl)piperazine-1-carboxylate, trifluoroacetic acid salt

ESI-MS $[M+H^+]$ = 654 (Cl isotope pattern)

EXAMPLE 25:

5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(4-methylpiperazin-1-yl)piperidine-1-carboxylate, trifluoroacetic acid salt

ESI-MS $[M+H^+]$ = 714 (Cl isotope pattern)

EXAMPLE 26:

5-Chloro-3-(2-ethoxypyridin-3-yl)-1-(2-methoxyphenylsulfonyl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(4-methylpiperazin-1-yl)piperidine-1-carboxylate, trifluoroacetic acid salt

ESI-MS $[M+H^+]$ = 684 (Cl isotope pattern)

EXAMPLE 27:

1-Phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl (±)-4-(4-methylpiperazin-1-yl)piperidine-1-carboxylate, trifluoroacetic acid salt

ESI-MS $[M+H^+]$ = 654 (Cl isotope pattern)

II.3 Preparation of racemic compounds of the formula I in which X^1 is CH_2 (examples 28 to 33)

EXAMPLE 28:

(±)-5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt

28.1 Dimethyl 2-[5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-malonate

11.2 ml (98 mmol) of dimethyl malonate were slowly added dropwise to a suspension,

cooled to 10°C, of 3.56 g (89 mmol) of sodium hydride (60% dispersion in mineral oil) in 150 ml of dimethylformamide, and the mixture was then stirred at room temperature for 30 minutes. Subsequently, 9.6 g (30 mmol) of 3,5-dichloro-3-(2-ethoxypyridin-3-yl)-1,3-dihydroindol-2-one from example 1.1 were added in portions, and the mixture was stirred at room temperature for 15 min. To work up the reaction it was stirred into cold 1N HCl, and dichloromethane was added. The phases were separated, and the aqueous phase was extracted with dichloromethane. The combined organic phase was washed with water and saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was removed in vacuo. The residue was recrystallized from dichloromethane/pentane. 9.01 g of the title compound were obtained as a yellowish solid.

ESI-MS $[M+H^+]$ = 419 (Cl isotope pattern).

28.2 Methyl [5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetate

Hydrolysis: 90 ml of 2N sodium hydroxide solution were added to a solution of 9.00 g (21.5 mmol) of dimethyl 2-[5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]malonate in 9 ml of ethanol, and the mixture was stirred at room temperature for one hour. The mixture was poured into ice-cold 1N hydrochloric acid while stirring, and the mixture was extracted with dichloromethane several times. The combined organic phase was washed with water and saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was removed in vacuo. The yellowish solid resulting therefrom (8.41 g of mixture of diastereomers) was dried in a vacuum drying oven at 40°C.

Decarboxylation: The hydrolysis product (8.41 g) obtained above was heated in a one-necked flask under a blanket of nitrogen to 150°C. After evolution of CO_2 ceased, the reaction mixture was allowed to cool to room temperature and the residue was stirred with methanol. Crystals formed and were stored in a refrigerator overnight. 5.25 g of the title compound were obtained as a yellowish solid.

ESI-MS $[M+H^+]$ = 361 (Cl isotope pattern).

28.3 [5-Chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic acid

20 ml of water and 10 ml of 2N sodium hydroxide solution were added to a solution of 1.96 g (5.43 mmol) of methyl [5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-

indol-3-yl]acetate in 10 ml of ethanol. The reaction mixture was stirred at room temperature for 18 hours. The mixture was worked up by adjusting to pH 5 with 1N hydrochloric acid and then concentrating in a rotary evaporator. The residue was taken up in toluene and again evaporated to dryness, and the residue was dried in a vacuum drying oven. 3.75 g of crude product were obtained and were employed without further purification in the next stage.
ESI-MS $[M+H^+]$ = 347 (Cl isotope pattern).

28.4 5-Chloro-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one
195 mg (1.44 mmol) of 1-hydroxybenzotriazole and 276 mg (1.44 mmol) of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride were added to a solution of 1.00 g of [5-chloro-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]acetic acid in 10 ml of dimethylformamide and, after stirring for 15 minutes, 277 mg (1.51 mmol) of 1-(1-methylpiperidin-4-yl)piperazine and 1.00 ml (7.41 mmol) of triethylamine were added. The reaction mixture was stirred at room temperature overnight. The reaction mixture was mixed with water and extracted with ethyl acetate several times. The combined organic phase was extracted with water and saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was concentrated in vacuo. The residue was purified by chromatography on silica gel (12 g Redisep cartridge, mobile phase gradient from 10 to 70% methanol in dichloromethane). 311 mg of the title compound were obtained as a white foam.
ESI-MS $[M+H^+]$ = 512 (Cl isotope pattern).

28.5 5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt
6.6 mg (0.16 mmol) of sodium hydride (60% dispersion in mineral oil) were added to a solution of 70 mg (0.14 mmol) of 5-chloro-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one in 2 ml of dimethylformamide under a nitrogen atmosphere and while cooling in an ice bath. The reaction mixture was stirred at 0°C for 10 min and then 39 mg (0.16 mmol) of 2,4-dimethoxybenzenesulfonyl chloride were added, and the mixture was stirred at

room temperature for 30 min. The reaction mixture was poured into ice-water and then extracted with ethyl acetate. The organic phase was washed with saturated sodium chloride solution and dried over magnesium sulfate, and the solvent was evaporated. The residue was purified by preparative HPLC (Prontosil Prep 2012, C18, 125×20 mm, 5 μm, gradient from 10% to 100% acetonitrile in water, 0.1% trifluoroacetic acid). 45 mg of the title compound were obtained as a white solid.
ESI-MS [M+H$^+$] = 712 (Cl isotope pattern)
^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 10.25 (1H), 8.10 (1H), 7.90 (2H), 7.80 (1H), 7.35 (1H), 7.20 (1H), 7.00 (1H), 6.65 (2H), 4.10 (2H), 3.95 (2H), 3.85 (3H), 3.60 (3H), 3.55 (2H), 2.90-3.50 (11H), 2.75 (3H), 2.25 (2H), 1.90 (2H), 1.00 (3H).

The compounds of the formula I in which X^1 is CH_2, according to examples 29 to 33, can be prepared using the appropriate sulfonyl chlorides of the formula VII and amines of the formula X in analogy to the process for preparing example 28.

EXAMPLE 29:
(±)-1-Phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(1-methylpiperidin-4-yl)piperazin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 652 (Cl isotope pattern)

EXAMPLE 30:
(±)-5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 712 (Cl isotope pattern)

EXAMPLE 31:
(±)-1-Phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt
ESI-MS [M+H$^+$] = 652 (Cl isotope pattern)

EXAMPLE 32:

(±)-5-Chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(4-ethylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 726 (Cl isotope pattern)

EXAMPLE 33:

(±)-1-Phenylsulfonyl-5-chloro-3-(2-ethoxypyridin-3-yl)-3-{2-[4-(4-ethylpiperazin-1-yl)piperidin-1-yl]-2-oxoethyl}-1,3-dihydroindol-2-one, trifluoroacetic acid salt

ESI-MS [M+H$^+$] = 666 (Cl isotope pattern)

III. Preparation of the chiral compounds of the formula I

Racemic compounds of the formula I can be resolved for example by separation on a preparative chiral column.

EXAMPLE 1A and EXAMPLE 1B

Racemate resolution of (±)-4-(1-methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

100 mg of racemic 4-(1-methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide from example 1 were resolved on a chiral preparative column (Chiralcell OD, flow rate 55 ml/min) with *n*-heptane/ethanol (7:3) as eluent. Yield: 33 mg of the levorotatory enantiomer (example 1A) and 27 mg of the dextrorotatory enantiomer (example 1B).

EXAMPLE 1A:

(-)-4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.55 (2H),

7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.75 (2H), 2.35 (4H), 2.10 (4H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.15 (3H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 7.4 min

$[\alpha]^{20}_D$ = -16 (c 0.1, $CHCl_3$)

EXAMPLE 1B:

(+)-4-(1-Methylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.55 (2H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.75 (2H), 2.35 (4H), 2.10 (4H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.15 (3H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 20.0 min

$[\alpha]^{20}_D$ = +12 (c 0.1, $CHCl_3$)

The racemates of EXAMPLES 4, 5 and 8 can be resolved in an analogous manner to obtain the corresponding enantiomers.

EXAMPLE 4B:

(+)-4-(1-Ethylpiperidin-4-yl)piperazine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.85 (1H), 7.70 (1H), 7.55 (2H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.45 (3H), 3.20 (4H), 2.85 (2H), 2.35 (4H), 2.30 (2H), 2.10 (1H), 1.80 (2H), 1.65 (2H), 1.35 (2H), 1.10 (3H), 0.95 (3H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 17.9 min

$[\alpha]^{20}_D$ = +12 (c 0.1, $CHCl_3$)

EXAMPLE 5A:

(-)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H),

7.55 (1H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.25 (2H), 3.85 (3H), 3.80 (2H), 3.45 (3H), 2.65 (2H), 2.40 (4H), 2.30 (4H), 2.15 (3H), 1.60 (2H), 1.15 (5H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 7.6 min

$[\alpha]^{20}_D$ = -14 (c 0.1, $CHCl_3$)

EXAMPLE 5B:

(+)-4-(4-Methylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 713 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H), 7.55 (1H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.25 (2H), 3.85 (3H), 3.80 (2H), 3.45 (3H), 2.65 (2H), 2.40 (4H), 2.30 (4H), 2.15 (3H), 1.60 (2H), 1.15 (5H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 12.2 min

$[\alpha]^{20}_D$ = +9 (c 0.1, $CHCl_3$)

EXAMPLE 8B:

(+)-4-(4-Ethylpiperazin-1-yl)piperidine-1-[5-chloro-1-(2,4-dimethoxyphenylsulfonyl)-3-(2-ethoxypyridin-3-yl)-2-oxo-2,3-dihydro-1H-indol-3-yl]carboxamide

ESI-MS [M+H$^+$] = 727 (Cl isotope pattern)

^{1}H-NMR ([d_6]-DMSO, 500 MHz) δ [ppm] = 8.10 (1H), 7.90 (1H), 7.70 (1H), 7.60 (1H), 7.55 (1H), 7.35 (2H), 6.95 (1H), 6.65 (2H), 4.20 (2H), 3.85 (3H), 3.80 (2H), 3.45 (3H), 2.65 (2H), 2.25-2.50 (11H), 1.65 (2H), 1.15 (5H), 0.95 (3H).

HPLC (Chiralcel OD 0.46 cm × 25 cm; n-heptane/ethanol 7:3) R_f = 11.5 min

$[\alpha]^{20}_D$ = +20 (c 0.1, $CHCl_3$)

IV. DETERMINATION OF THE BIOLOGICAL ACTIVITY

1. Vasopressin V1b receptor binding assay:

Substances:

The test substances were dissolved in a concentration of 10^{-2} M in DMSO and further diluted to $5x10^{-4}$ M to $5x10^{-9}$ M. These serial DMSO predilutions were diluted 1:10 with assay buffer. The substance concentration was further diluted 1:5 in the assay mixture

(2% DMSO in the mixture).

Membrane preparation:

CHO-K1 cells with stably expressed human vasopressin V1b receptor (clone 3H2) were harvested and homogenized in 50 mM Tris-HCl and in the presence of protease inhibitors (Roche complete Mini # 1836170) using a Polytron homogenizer at intermediate setting for 2 × 10 seconds, and subsequently centrifuged at 40 000 x g for 1 h. The membrane pellet was again homogenized and centrifuged as described and subsequently taken up in 50 mM Tris-HCl, pH 7.4, homogenized and stored in aliquots frozen in liquid nitrogen at -190°C.

Binding assay:

The binding assay was carried out by the method based on that of Tahara et al. (Tahara A et al., Brit. J. Pharmacol. 125, 1463-1470 (1998)).

The incubation buffer was: 50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4.

In the assay mixture (250 µl), membranes (50 µg/ml protein in incubation buffer) from CHO-K1 cells with stably expressed human V1b receptors (cell line hV1b_3H2_CHO) were incubated with 1.5 nM ^{3}H-AVP (8-Arg-vasopressin, PerkinElmer #18479) in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4) (total binding) or additionally with increasing concentrations of test substance (displacement experiment). The nonspecific binding was determined with 1 M AVP (Bachem # H1780). All determinations were carried out as triplicate determinations. After incubation (60 minutes at room temperature), the free radioligand was filtered off by vacuum filtration (Skatron cell harvester 7000) through Wathman GF/B glass fiber filter mats, and the filters were transferred into scintillation vials. The liquid scintillation measurement took place in a model 2000 or 2200CA Tricarb instrument (Packard). Conversion of the measured cpm into dpm was carried out with the aid of a standard quench series.

Analysis:

The binding parameters were calculated by nonlinear regression in SAS. The algorithms of the program operate in analogy to the LIGAND analysis program (Munson PJ and Rodbard D, Analytical Biochem. 107, 220-239 (1980)). The Kd of ^{3}H-AVP for the recombinant human V1b receptors is 0.4 nM and was used to determine the Ki.

2. Vasopressin V1a receptor binding assay:

Substances:

The test substances were dissolved in a concentration of 10^{-2} M in DMSO. Further dilution of these DMSO solutions took place in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4).

Membrane preparation:

CHO-K1 cells with stably expressed human vasopressin V1a receptor (clone 5) were harvested and homogenized in 50 mM Tris-HCl and in the presence of protease inhibitors (Roche complete Mini # 1836170) using a Polytron homogenizer at intermediate setting for 2 × 10 seconds, and subsequently centrifuged at 40 000 x g for 1 h. The membrane pellet was again homogenized and centrifuged as described and subsequently taken up in 50 mM Tris-HCl, pH 7.4, homogenized and stored in aliquots frozen in liquid nitrogen at -190°C.

Binding assay:

The binding assay was carried out by the method based on that of Tahara et al. (Tahara A et al., Brit. J. Pharmacol. 125, 1463-1470 (1998)).

The incubation buffer was: 50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4.

In the assay mixture (250 µl), membranes (20 µg/ml protein in incubation buffer) from CHO-K1 cells with stably expressed human V1a receptors (cell line hV1a_5_CHO) were incubated with 0.04 nM ^{125}I-AVP (8-Arg-vasopressin, NEX 128) in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4) (total binding) or additionally with increasing concentrations of test substance (displacement experiment). The nonspecific binding was determined with 1 µM AVP (Bachem # H1780). Triplicate determinations were carried out. After incubation (60 minutes at room temperature), the free radioligand was filtered off by vacuum filtration (Skatron cell harvester 7000) through Wathman GF/B glass fiber filter mats, and the filters were transferred into scintillation vials.

The liquid scintillation measurement took place in a model 2000 or 2200CA Tricarb instrument (Packard). Conversion of the measured cpm into dpm was carried out with the aid of a standard quench series.

Analysis:

The binding parameters were calculated by nonlinear regression in SAS. The algorithms of the program operate in analogy to the LIGAND analysis program (Munson PJ and

Rodbard D, Analytical Biochem. 107, 220-239 (1980)). The Kd of ^{125}I-AVP for the recombinant hV1a receptors was determined in saturation experiments. A Kd of 1.33 nM was used to determine the Ki.

3. Vasopressin V2 receptor binding assay:

Substances:

The test substances were dissolved in a concentration of 10^{-2} M in DMSO. Further dilution of these DMSO solutions took place in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4).

Membrane preparation:

CHO-K1 cells with stably expressed human vasopressin V2 receptor (clone 23) were harvested and homogenized in 50 mM Tris-HCl and in the presence of protease inhibitors (Roche complete Mini # 1836170) using a Polytron homogenizer at intermediate setting for 2 × 10 seconds, and subsequently centrifuged at 40 000 x g for 1 h. The membrane pellet was again homogenized and centrifuged as described and subsequently taken up in 50 mM Tris-HCl, pH 7.4, homogenized and stored in aliquots frozen in liquid nitrogen at -190°C.

Binding assay:

The binding assay was carried out by the method based on that of Tahara et al. (Tahara A et al., Brit. J. Pharmacol. 125, 1463-1470 (1998)).

The incubation buffer was: 50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4.

In the assay mixture (250 µl), membranes (50 µg/ml protein in incubation buffer) from CHO-K1 cells with stably expressed human V2 receptors (cell line hV2_23_CHO) were incubated with 1-2 nM ^{3}H-AVP (8-Arg-vasopressin, PerkinElmer #18479) in incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4) (total binding) or additionally with increasing concentrations of test substance (displacement experiment). The nonspecific binding was determined with 1 µM AVP (Bachem # H1780). Triplicate determinations were carried out.

After incubation (60 minutes at room temperature), the free radioligand was filtered off by vacuum filtration (Skatron cell harvester 7000) through Wathman GF/B glass fiber filter mats, and the filters were transferred into scintillation vials.

The liquid scintillation measurement took place in a model 2000 or 2200CA Tricarb

instrument (Packard). Conversion of the measured cpm into dpm was carried out with the aid of a standard quench series.

Analysis:

The binding parameters were calculated by nonlinear regression in SAS. The algorithms of the program operate in analogy to the LIGAND analysis program (Munson PJ and Rodbard D, Analytical Biochem. 107, 220-239 (1980)). The Kd of ^{3}H-AVP for the recombinant hV2 receptors is 2.4 nM and was used to determine the Ki.

4. Oxytocin receptor binding assay

Substances:

The substances were dissolved in a concentration of 10^{-2} M in DMSO and diluted with incubation buffer (50 mM Tris, 10 mM $MgCl_2$, 0.1% BSA, pH 7.4).

Cell preparation:

Confluent HEK-293 cells with transiently expressing recombinant human oxytocin receptors were centrifuged at 750 × g at room temperature for 5 minutes. The residue was taken up in ice-cold lysis buffer (50 mM Tris-HCl, 10% glycerol, pH 7.4 and Roche complete protease inhibitor) and subjected to an osmotic shock at 4°C for 20 minutes. The lyzed cells were then centrifuged at 750 × g at 4°C for 20 minutes, the residue was taken up in incubation buffer, and aliquots of 10^{7} cells/ml were prepared. The aliquots were frozen at -80°C until used.

Binding assay:

On the day of the experiment, the cells were thawed, diluted with incubation buffer and homogenized using a Multipette Combitip (Eppendorf, Hamburg). The reaction mixture of 0.250 ml was composed of 2 to $5x10^{4}$ recombinant cells, 3-4 nM ^{3}H-oxytocin (PerkinElmer, NET 858) in the presence of test substance (inhibition plot) or only incubation buffer (total binding). The nonspecific binding was determined with 10^{-6} M oxytocin (Bachem AG, H2510). Triplicate determinations were set up. Bound and free radioligand were separated by filtration under vacuum with Whatman GF/B glass fiber filters with the aid of a Skatron cell harvester 7000. The bound radioactivity was determined by liquid scintillation measurement in a Tricarb Beta counter, model 2000 or 2200CA (Packard).

Analysis:

The binding parameters were calculated by nonlinear regression analysis (SAS) in analogy to the LIGAND program of Munson and Rodbard (Analytical Biochem 1980; 107: 220-239). The Kd of ^{3}H-oxytocin for the recombinant hOT receptors is 7.6 nM and was used to determine the Ki.

5. Determination of the microsomal half-life:

The metabolic stability of the compounds of the invention was determined in the following assay.

The test substances were incubated in a concentration of 0.5 μM as follows:
0.5 μM test substance are preincubated together with liver microsomes from different species (from rat, human or other species) (0.25 mg of microsomal protein/ml) in 0.05 M potassium phosphate buffer of pH 7.4 in microtiter plates at 37°C for 5 min. The reaction is started by adding NADPH (1 mg/mL). After 0, 5, 10, 15, 20 and 30 min, 50 μl aliquots are removed, and the reaction is immediately stopped and cooled with the same volume of acetonitrile. The samples are frozen until analyzed. The remaining concentration of undegraded test substance is determined by MSMS. The half-life (T1/2) is determined from the gradient of the signal of test substance/unit time plot, it being possible to calculate the half-life of the test substance, assuming first order kinetics, from the decrease in the concentration of the compound with time. The microsomal clearance (mCl) is calculated from mCl = ln2/T1/2 / (content of microsomal protein in mg/ml) × 1000 [ml/min/mg] (modified from references: Di, The Society for Biomoleculur Screening, 2003, 453-462; Obach, DMD, 1999 vol 27. N 11, 1350-1359).

6. Methods for *in vitro* determination of the cytochrome P450 (CYP) inhibition

Luminescent substrates for 2C9 and 3A4:

0.4 mg/ml human liver microsomes are preincubated with the test substances to be investigated (0-20 μM), the CYP-specific substrates, in 0.05 M potassium phosphate buffer of pH 7.4 at 37°C for 10 min. The Cyp-specific substrate for CYP 2C9 is luciferin H, and for CYP 3A4 is luciferin BE. The reaction is started by adding NADPH. After incubation at RT for 30 min, the luciferin detection reagent is added, and the resulting luminescence signal is measured (modified from reference: Promega, Technical Bulletin

P450-GLO™ Assays).

Midazolam CYP 3A4 time-dependent inhibition

The assay consists of 2 parts. Firstly, the test substance is preincubated with the liver microsomes (with NADPH = preincubation, then addition of the substrate; in the second part the substrate and the test substance are added simultaneously = coincubation.

Preincubation:

0.05 mg/ml microsomal protein (human liver microsomes) are preincubated with 0-10 µM (or 50 µM) test substance in 50 mM potassium phosphate buffer for 5 min. The reaction is started with NADPH. After 30 min 4 µM midazolam (final concentration) are added, and incubation is continued for 10 min. 75 µl of the reaction solution are removed after 10 min, and stopped with 150 µl of acetonitrile solution.

Coincubation:

0.05 mg/ml microsomal protein (human liver microsomes) are preincubated with 4 µm midazolam (final concentration) and 0-10 µM (or 50 µM) test substance in 50 mM potassium phosphate buffer for 5 min. The reaction is started with NADPH. 75 µl of the reaction solution are removed after 10 min and stopped with 150 µl of acetonitrile solution. The samples are frozen until the MSMS analysis (modified from references: Obdach, Journal of Pharmacology & Experimental Therapeutics, Vol 316, 1, 336-348, 2006; Walsky, Drug Metabolism and Disposition Vol 32, 6, 647-660, 2004).

7. Method for determining the solubility in water (in mg/ml)

The solubility in water of the compounds of the invention can be determined for example by the so-called shake flask method (as specified in *ASTM International: E 1148-02, Standard test methods for measurement of aqueous solubility, Book of Standards Volume 11.05.*). This entails an excess of the solid compound being put into a buffer solution with a particular pH (for example phosphate buffer of pH 7.4), and the resulting mixture being shaken or stirred until equilibrium has been set up (typically 24 or 48 hours, sometimes even up to 7 days). The undissolved solid is then removed by filtration or centrifugation, and the concentration of the dissolved compound is determined by UV spectroscopy or high pressure liquid chromatography (HPLC) by means of an appropriate calibration plot.

8. Results

The results of the receptor binding investigations are expressed as receptor binding constants [K_i(V1b)] or selectivities [K_i(V1a)/K_i(V1b)]. The results of the investigation of the metabolic stability are indicated as microsomal clearance (mCl).

The compounds of the invention show very high affinities for the V1b receptor in these assays (maximally 100 nM, or maximally 10 nM, frequently < 1 nM). The compounds also show high selectivities vis-à-vis the V1a receptor and a good metabolic stability, measured as microsomal clearance.

The results are listed in table 2. The numbers of the compounds refer to the synthesis examples.

Table 2

Example	K_i(h-V1b)* [nM]	K_i(h-V1a)/K_i(h-V1b)*	Human microsomal clearance [μl min^{-1} mg^{-1}]
1	+++	+++	+
3	++	++	+++
13	+++	++	+
14	+++	+++	++
15	+++	++	+
16	+++	+	+
17	+++	+	+
24	++	++	++
28	+++	++	+
29	++	+	+++
32	+++	+	++
1B	+++	+++	+++
4B	+++	+++	++
5B	+++	+++	+++
8B	+++	+++	+

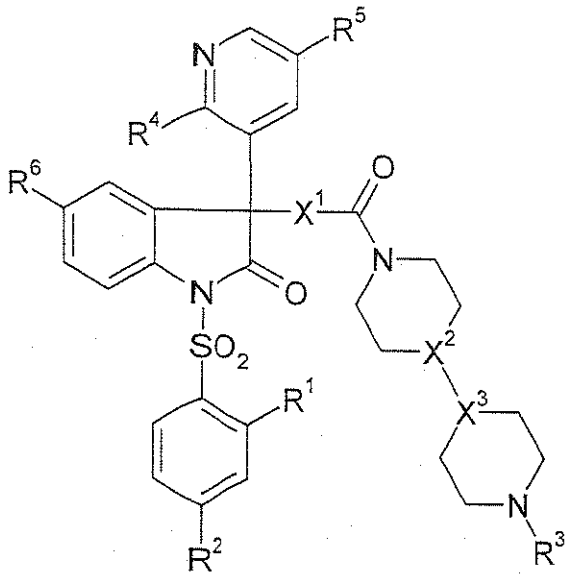
* h = human

Key:

	K_i(V1b)	K_i(h-V1a)/K_i(h-V1b)	Human microsomal clearance
+	> 10 - 100 nM	10 - < 25	> 75 - 100 μl min^{-1} mg^{-1}
++	1 - 10 nM	25 - 75	50 - 75 μl min^{-1} mg^{-1}
+++	< 1 nM	> 75	< 50 μl min^{-1} mg^{-1}

Claims

1. A compound of the formula I



(I)

in which

R^1 is hydrogen, methoxy or ethoxy;

R^2 is hydrogen or methoxy;

R^3 is hydrogen, methyl, ethyl, n-propyl or isopropyl;

R^4 is ethoxy or isopropoxy;

R^5 is H or methyl;

R^6 is Cl or F;

X^1 is O, NH or CH_2; and

X^2 and X^3 are N or CH, with the proviso that X^2 and X^3 are not simultaneously N;

and their pharmaceutically acceptable salts thereof.

2. A compound as claimed in claim 1, in which R^1 is hydrogen or methoxy.

3. A compound as claimed in claim 1, in which R^1 and R^2 are methoxy.

4. A compound as claimed in any of the preceding claims, in which R^3 is hydrogen, methyl or ethyl.

5. A compound as claimed in any of the preceding claims, in which R^4 is ethoxy and R^5 is H.

6. A compound as claimed in any of claims 1 to 4, in which R^4 is ethoxy and R^5 is methyl.

7. A compound as claimed in any of claims 1 to 4, in which R^4 is isopropoxy and R^5 is H.

8. A compound as claimed in any of the preceding claims, in which R^6 is Cl.

9. A compound as claimed in any of claims 1 to 7, in which R^6 is F.

10. A compound as claimed in any of the preceding claims, in which X^2 is N and X^3 is CH.

11. A compound as claimed in any of claims 1 to 9, in which X^2 is CH and X^3 is N.

12. A compound as claimed in any of the preceding claims, in which X^1 is O.

13. A compound as claimed in any of claims 1 to 11, in which X^1 is NH.

14. A compound as claimed in any of claims 1 to 11, in which X^1 is CH_2.

15. A compound as claimed in any of the preceding claims, in which
- R^1 is methoxy;
- R^2 is methoxy;
- R^3 is methyl;
- R^4 is ethoxy;
- R^5 is H;
- R^6 is Cl;
- X^1 is NH;
- X^2 is N; and
- X^3 is CH.

16. A compound as claimed in any of claims 1 to 14, in which
- R^1 is methoxy;
- R^2 is methoxy;
- R^3 is methyl;
- R^4 is ethoxy;
- R^5 is methyl;
- R^6 is Cl;
- X^1 is NH;
- X^2 is N; and
- X^3 is CH.

17. A compound as claimed in any of claims 1 to 14, in which

R^1 is methoxy;
R^2 is methoxy;
R^3 is ethyl;
R^4 is ethoxy;
R^5 is H;
R^6 is Cl;
X^1 is NH;
X^2 is N; and
X^3 is CH.

18. A compound as claimed in any of claims 1 to 14, in which

R^1 is methoxy;
R^2 is methoxy;
R^3 is methyl;
R^4 is ethoxy;
R^5 is H;
R^6 is Cl;
X^1 is NH;
X^2 is CH; and
X^3 is N.

19. A compound as claimed in any of the preceding claims, where the (+) enantiomer has an enantiomeric purity of at least 90% ee.

20. A compound as claimed in any of claims 1 to 18, which is the racemate.

21. A pharmaceutical composition comprising at least one compound of the formula I as defined above and/or at least one pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable carrier.

22. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasopressin-dependent diseases.

23. The use of compounds of the formula I as defined in any of claims 1 to 20 or of

pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from diabetes, insulin resistance, nocturnal enuresis, incontinence and diseases in which impairments of blood clotting occur, and/or for delaying micturition.

24. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from hypertension, pulmonary hypertension, heart failure, myocardial infarction, coronary spasm, unstable angina, PTCA (percutaneous transluminal coronary angioplasty), ischemias of the heart, impairments of the renal system, edemas, renal vasospasm, necrosis of the renal cortex, hyponatremia, hypokalemia, Schwartz-Bartter syndrome, impairments of the gastrointestinal tract, gastritic vasospasm, hepatocirrhosis, gastric and intestinal ulcers, emesis, emesis occurring during chemotherapy, and travel sickness.

25. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from affective disorders.

26. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from anxiety disorders and stress-dependent anxiety disorders.

27. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from memory impairments and Alzheimer's disease.

28. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from psychoses and psychotic disorders.

29. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from Cushing's syndrome and other stress-dependent diseases.

30. The use of compounds of the formula I as defined in any of claims 1 to 20 or

of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from sleep disorders.

31. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from depressive disorders.

32. The use as claimed in claim 31 for the treatment and/or prophylaxis of childhood onset mood disorders.

33. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of vasomotor symptoms and/or thermoregulatory dysfunctions.

34. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of drug or pharmaceutical dependencies and/or dependencies mediated by other factors; of stress caused by withdrawal of one or more factors mediating the dependence; and/or of stress-induced relapses into drug or pharmaceutical dependencies and/or dependencies mediated by other factors.

35. The use of compounds of the formula I as defined in any of claims 1 to 20 or of pharmaceutically acceptable salts thereof for the manufacture of a medicament for the treatment and/or prophylaxis of diseases selected from schizophrenia and psychosis.