(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 January 2007 (25.01.2007)

PCT

(10) International Publication Number
WO 2007/009662 A1

(51) International Patent Classification:
A61K 31/496 (2006.01) *C07D 413/12* (2006.01)
C07D 407/06 (2006.01) *C07D 413/14* (2006.01)
C07D 407/14 (2006.01) *C07D 417/14* (2006.01)
C07D 409/06 (2006.01) *C07D 471/04* (2006.01)
C07D 413/06 (2006.01) *A61P 25/00* (2006.01)

(21) International Application Number:
PCT/EP2006/006867

(22) International Filing Date: 13 July 2006 (13.07.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0514615.4 15 July 2005 (15.07.2005) GB

(71) Applicant *(for all designated States except AT, US)*: **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant *(for AT only)*: **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **HOYER, Daniel** [FR/FR]; rue Pasteur 10, F-68300 Saint-Louis (FR). **HURTH, Konstanze** [DE/FR]; 4 rue de l'ancien golf, F-68300 Saint-Louis (FR). **TROXLER, Thomas, J.** [CH/CH]; Sennweg 27, CH-4246 Wahlen b. Laufen (CH).

(74) Agent: **ROTH, Peter, R.**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

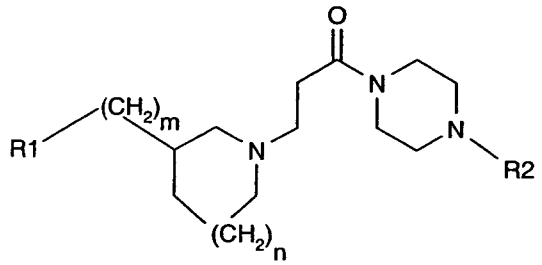
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** SUBSTITUTED PIPERIDINE DERIVATIVES AS SOMATOSTATIN SST1 RECEPTOR ANTAGONISTS



(I)

(57) **Abstract:** Compound of the formula (I) wherein R^1, R^2, n and m are as defined in the specification. The compounds of formula (I) are somatostatin sst1 receptor antagonists.

WO 2007/009662 A1

SUBSTITUTED PIPERIDINE DERIVATIVES AS SOMATOSTATIN SST1 RECEPTOR ANTAGONISTS

Summary of the Invention

The present invention relates to 3-substituted piperidine derivatives, their preparation, their use as or in pharmaceuticals and pharmaceutical compositions comprising them.

Background of the Invention

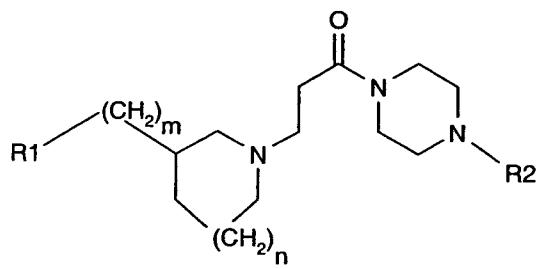
A number of compounds having sst1 antagonistic activity are known, e.g. from International Application WO 03/40125.

A problem to be solved by the present invention is to provide further compounds with this activity and/or other useful pharmaceutical activities and properties.

A novel class of compounds has been found that solves this problem and shows pharmaceutical usefulness as described in more detail below.

Detailed Description of the Invention

The present invention relates especially to a compound of formula I



(I)

wherein

R1 is unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl;

R2 is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

and each of n and m, independently of the other, is 0, 1 or 2;

or a salt thereof.

In addition, the present invention relates to methods for the manufacture or a compound of the formula I or a salt thereof, the use of a compound of the formula I, or a salt thereof, in the therapeutic and/or diagnostic treatment of the animal or human body or for the manufacture of pharmaceuticals, a method of treatment comprising administering a compound of the formula I, or a salt thereof, to an animal or a human, and pharmaceutical compositions comprising them, as well as to other embodiments of the invention given below in more detail.

Unless otherwise indicated, the general terms and names used in the description of the present invention preferably have the following meanings (where more specific definitions, in each case separately, or in combination, may be used to replace more general terms in order to define more preferred embodiments of the invention):

The term "lower" or "C_1-C_7-" defines a moiety with up to and including maximally 7, especially up to and including maximally 4, carbon atoms, said moiety being branched or straight-chained. Lower or C_1-C_7-alkyl, for example, is n-pentyl, n-hexyl or n-heptyl or preferably C_1-C_4-alkyl, especially as methyl, ethyl, n-propyl, sec-propyl, n-butyl, isobutyl, sec-butyl, tert-butyl.

In unsubstituted or substituted aryl, aryl is preferably a mono-, bi- or tricyclic aromatic hydrocarbon group with 6 to 14 ring carbon atoms, especially phenyl, naphthyl or fluorenyl, each of which is unsubstituted or substituted by one or more, especially 1 to 3, substituents independently selected preferably from alkyl, preferably C_1-C_7-alkyl, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl or hexyl (especially n-hexyl); cycloalkyl, especially C_3-C_8-cycloalkyl; phenyl or (1- or 2-) napthyl, each of which is unsubstituted or substituted with one or more, especially up to three, substituents selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, such as trifluoromethyl, C_1-C_7-alkoxy, such as methoxy, halo-C_1-C_7-alkoxy, such as trifluoromethoxy, nitro, cyano, and halo; unsubstituted, C_1-C_7-alkoxy-substituted or halosubstituted phenyl- C_1-C_7- alkyl; hydroxy; hydroxy-C_1-C_7-alkyl; alkoxy, preferably C_1-C_7-alkoxy, especially methoxy; phenoxy; alkanoyloxy, especially C_1-C_7-alkanoyloxy; C_1-C_7-alkanoylthio; halo; amino; N-mono- or N,N-di-(C_1-C_7-alkyl)amino; C_1-C_7-alkanoylamino; C_1-C_7-alkanoyl; carboxy; C_1-C_7-alkoxycarbonyl; cyano; carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl; C_1-C_7-alkylsulfonyl; sulfamoyl; and nitro. Very preferred as unsubstituted or substituted aryl is phenyl that is unsubstituted or substituted by one or more, especially up to

three, substituents as described above for aryl, especially cyano, C_1-C_7-alkoxy, nitro and/or especially halo. Examples of preferred unsubstituted or substituted aryl moieties are 3-fluoro-4-nitrophenyl, 4-cyanophenyl, 3,4-difluorophenyl, 4-cyano-2,6-difluorophenyl, 4-nitrophenyl, 4-fluorophenyl or (especially 9-) fluorenyl.

In unsubstituted or substituted heterocyclyl, heterocyclyl is preferably a ring with 3 to 20, preferably 5 to 14 ring atoms which is unsaturated, partially saturated or saturated, has one to four, preferably one to three heteroatoms independently selected from O, N (or NH) and S, is mono-, bi- or tricylic, e.g. a monocyclic heterocycle with 3 to 8, preferably 5 to 7, ring members annealed to one or two rings indeependently selected from benzo, pyridino, pyrazino, pyrimidino or pyridazino, and is unsubstituted or substituted by one or more, specially up to three moieties independently selected from those mentioned above as substituents for substituted aryl and oxo; unsubstituted or substituted heterocyclyl is, preferably, a moiety selected from (i) pyridinyl, especially 2-pyridinyl; (ii) substituted pyridinyl wherein the substituents are independently selected from one or more, especially one or two of hydroxy, halo, nitro, cyano, trifluoromethyl, C_1-C_4-alkyl and C_1-C_4-alkoxy, especially alkoxy-pyridinyl, especially C_1-C_7-alkoxy-pyridin-2-, -3- or –4-yl, or dialkoxy-pyridinyl, especially di-(C_1-C_7-alkoxy)-pyridin-2-, -3- or –4-yl; (iii) 1-alkyl-oxo-dihydropyridinyl, especially 1-(C_1-C_7-alkyl)-6-oxo-1,6-dihydropyridin-2-yl; (iv) benzo[1,2,5]oxadiazolyl, especially benzo[1,2,5]oxadiazol-5- or –6-yl; (v) benzo[1,2,5]thiadiazolyl, especially benzo[1,2,5]thiadiazol-5- or –6-yl; (vi) imidazo[1,2-b]pyridazin-8-, -7- or preferably –6-yl; (vii) 4-[1,2,5]-thiadiazolo- [3,4-b]pyridin-7-, -6- or -5-yl, (viii) xanthenyl, especially xanthen-9-yl; (ix) thioxanthenyl, especially thioxanthen-9-yl; (x) benzo[1,3]dioxol-4- or preferably -5-yl; and (xi) 2,3-dihydro-benzo[1,4]dioxin-5- or preferably -6-yl; whereby as R_1 the moieties mentioned under (ii), (viii), (ix), (x) and (xi) are especially preferred, while those under (i) and (iii) to (vii) are especially preferred as R_2. Where in any heterocyclyl moieties "unsaturated" is mentioned, this is intended to mean that the maximum number of non-cumulated double bonds is present in the ring system.

Halo (=halogeno) is preferably fluoro, chloro or bromo, if not indicated otherwise.

The symbols m and n each preferably stand for 1.

Due to the asymmetrical carbon atom(s) present in the compounds of formula I and their salts, the compounds may exist in optically active form as isolated enantiomers or in the

form of mixtures of optical isomers, e.g. in form of racemic mixtures. All single optical isomers as well as their mixtures including the racemic mixtures are part of the present invention. Preferably, the compounds of the formula I are in the form of pure optical isomers.

Salts of compounds of formula I are especially acid addition salts (as basic groups, such as the nitrogen atoms in the piperazine and piperidine rings are present, or, where several salt-forming groups are present, can also be mixed salts, also with bases, or internal salts. Salts are especially pharmaceutically acceptable salts of compounds of formula I. Acid addition salts are formed, for example, from compounds of formula I with inorganic acids, for example hydrohalic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with organic carboxylic, sulfonic, sulfo or phospho acids or N-substituted sulfamic acids, for example fumaric acid or acetic acid, methanesulfonic acid, N-cyclohexylsulfamic acid (forming cyclamates) or with other acidic organic compounds, such as ascorbic acid. Acid groups in a compound of the formula I, such as carboxy, are, for example, salts thereof with suitable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb of the Periodic Table of the Elements, for example sodium or potassium salts, or alkaline earth metal salts, for example magnesium or calcium salts, also zinc salts or ammonium salts, as well as salts formed with ammonia or organic amines or with quaternary ammonium compounds. Compounds of formula I having both acidic and basic groups can also form internal salts. For manufacturing, isolation and/or purification purposes, it is also possible to use pharmaceutically inacceptable salts, for example a perchlorate or picolinate salt.

Where compounds or a compound (especially of formula I) is mentioned herein, this is (if not explicitely mentioned otherwise) always intended to mean the free compound and/or a salt thereof, where salt-forming groups are present, and is also intended to comprise solvates of such a compound or salt, e.g. hydrates.

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to as agents of the invention, exhibit valuable pharmacological properties when tested in vitro using SRIF receptor expressing cell cultures and in animals, and are therefore useful as pharmaceuticals or for the preparation of pharmaceuticals.

In particular the agents of the invention bind to somatostatin receptors. More particularly they are orally active, non-peptide somatostatin sst1 receptor (previously called SSTR-1 receptor) antagonists. Among the preferred indications are: bipolar disorders, social phobias and memory impairment in various neurological disorders such as Alzheimer's disease, age associated memory impairment and other dementias. In addition, the compounds aim to treat attention deficit and hyperactivity disorders (ADHD). Further, the compounds are indicated for the treatment of aggressive states in a variety of conditions, including schizophrenia. Still further, the compounds are indicated for the treatment of negative symptoms of schizophrenia.

In addition, the agents of the invention may be useful for the treatment of tumors, for the treatment of vascular disorders and/or for the treatment of immunological diseases.

The basis for the indications can be confirmed by the range of standard tests as indicated below:

The agents of the invention can be shown to have high affinity and selectivity for somatostatin sst1 receptors (see, for example, Hoyer D, Bell GI, Berelowitz M, Epelbaum J, Feniuk W, Humphrey PPA, O'Carroll AM, Patel YC, Schonbrunn A, Taylor JE, Reisine T (1995); classification and nomenclature of somatostatin receptors. TiPS, 16: 86-88) in cerebral cortex of rat and with recombinant human and mouse versions (showing a pKd in the range from about 6 to 9, preferably in the range from 7.8 to 9.0) as described (see, for example, Siehler S., K. Seuwen & D. Hoyer. Characterisation of human recombinant somatostatin receptors: 1) radioligand binding studies (1999) Naunyn Schmiedeberg's Arch Pharmacol, 360: 488-499).

The agents of the invention further can be shown to antagonise SRIF-14-induced inhibition of forskolin-stimulated adenylate cyclase activity (pKb = 7.5-8.5) (see, for example, Siehler S. & D. Hoyer. Characterisation of human recombinant somatostatin receptors: 3) modulation adenylate cyclase activity. (1999) Naunyn Schmiedeberg's Arch Pharmacol, 360: 510-521) and/or SRIF-28 induced stimulation of luciferase activity and to be devoid of intrinsic activity at sst1 receptors (see D. Hoyer, C. Nunn, J. Hannon, P. Schoeffter, D. Feuerbach, E. Schuepbach, D. Langenegger, R. Bouhelal, K. Hurth, P. Neumann, T. Troxler, P. Pfaeffli

(2004) SRA880, a non peptide somatostatin sst1 receptor antagonist, Neuroscience letters, 361(1-3):132-5).

They can be shown to have significantly lower affinity for a range of neurotransmitter receptors and ligand-gated channels as determined in various radioligand bing tests (see, for example, Kalkman HO, N Subramanian, D Hoyer (2001) Comprehensive radioligand binding profile of iloperidone: a broad spectrum dopamine / serotonin / norepinephrine receptor antagonist for the management of psychotic disorders. Neuropsychopharmacology, 25: 9104-914).

The agents of the invention can be shown to lower aggressive behaviour in two mice models for aggression, the matched aggressive male pair and aggressive resident encounters (1-10 mg/kg s.c. and 3-30 mg/kg/p.o.) (see Dixon A.K, Huber C, Lowe DA (1994): Clozapine Promotes Approach-Oriented behaviour in male Mice. J.Clin.Psychiatry. 55: (9) Suppl.B. 4-7). They also can be shown to reverse the social withdrawal characteristic of "intruder" mice exposed to attacks from aggressive residents. Following treatment with the compounds (1-10 mg/kg, s.c. or 3-30 mg/kg/p.o.), intruder mice can be shown to increase approach behaviour towards the aggressive opponent and decreased avoidance behaviour (see Dixon A.K, Huber C, Lowe DA (1994): Clozapine Promotes Approach-Oriented behaviour in male Mice. J.Clin.Psychiatry. 55: (9) Suppl.B. 4-7). The agents of the invention, preferably when administered in a dose range from 0.03 to 3 mg/kg p.o., can be shown to enhance social exploration of "intruder" rats confronted with a "resident" rat similar to benzodiazepines (see Vassout A, Veenstra S, Hauser K, Ofner S, Brugger F, Schilling W, Gentsch C. (2000) NKP608: a selective NK-1 receptor antagonist with anxiolytic-like effects in the social interaction and social exploration test in rats. Regulatory Peptides 96, 7-16.). The marked anti-aggressive and sociotropic effects of the agents of the invention are mimicked by the anti-manic agents lithium and carbamazepine or valproate (see Dixon AK (1990) Ethopharmacology: A biological approach to the study of drug-induced changes in behaviour: Adv.study. Behaviour 19: 171-204. Dixon AK, Fisch HU, Huber C, Walser A (1989) Ethological studies in animals and man, their use in psychiatry. Pharmacopsychiatry 22 (suppl): 44-50).

The agents of the invention, preferably in a dosing range from 0.01 to 10 mg/kg, can be shown to improve the performance in step-down passive avoidance in mice (following both pre- and post-trial administration). They can be shown to enhance retrieval-performance in

step-through passive avoidance (0.1-10 mg/kg p.o.) and partially counteracted E-shock-induced amnesia (0.01-10 mg/kg p.o.). The agents of the invention can be shown to specifically enhance social recognition of familiar, but not unfamiliar juvenile rats , preferably in a dosing range from 0.03 to -3 mg/kg p.o.. Similarly, they can be shown to increase social recognition in mice, e.g. in the dosing range from 0.03 to -3 mg/kg p.o. (see Mondadori C., Jaekel J. and Preiswerk G., (1993) CGP 36742: the first orally active GABA B blocker improves the cognitive performance of mice, rats and rhesus monkeys. Behavioral and Neural Biology 60, 62-68. Thor D.H. and Holloway W.R., (1982) Social memory in the male laboratory rat. Journal of Comparative and Physiological Psychology, 96, 1000-1006). Thus, the agents of the invention can be shwon to clearly increase learning, memory and attention.

In the rat primary observation test, the agents of the invention when tested at a dose of, for example, 30 mg/kg p.o. can be shown to exhibit CNS activating effects. Consistently, in the sleep-wakefulness cycle in rats, the agents of the invention (e.g. at 30 mg/kg p.o.) can be shown to induce a marked increase of the wakefulness phase during the initial three hours while decreasing the REM and classical sleep phases.

The positive effects on memory acquisition/retention, combined with the sociotropic and anti-aggressive components displayed by the agents of the invention, suggest that these will prove useful in the treatment of ADHD (attention deficit and hyperactivity disorders).

Agents of the invention are also effective in the treatment of various kinds of tumors, particularly of sst1 receptor bearing tumors, as indicated in proliferation tests with various different cancer cell lines and in tumor growth experiments in nude mice with hormone dependent tumors [see for example: G. Weckbecker et al., Cancer Research 1994, 54: 6334-6337]. Thus the compounds are indicated in the treatment of, for example, cancers of the breast, the prostate, the colon, the pancreas, the brain and the lung (small cell lung cancer).

For all the above mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.1 to about 10 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily

dosage is in the range from about 5 to about 200 mg, preferably about 10 to about 100 mg of the compound conveniently administered in divided doses up to 4 times a day.

The agents of the invention may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds.

Accordingly in a further aspect the present invention provides the agents of the invention for use in the diagostic and therapeutic (including prophylactic) treatment of the animal or human body, especially as pharmaceuticals, more specifically for treatment in the above-mentioned conditions, e.g. bipolar disorders, social phobias, memory impairment, attention deficit and hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

The present invention furthermore provides a pharmaceutical composition comprising an agent of the invention in association with at least one pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner. Unit dosage forms contain, for example, from about 0.25 to about 50 mg of an agent according to the invention.

Agents of the invention may be administered by any conventional route, for example parenterally e.g. in form of injectable solutions or suspensions, or enterally, preferably orally, e.g. in the form of tablets or capsules.

The agents of the invention may alternatively be administered e.g. topically in the form of a cream, gel or the like, or by inhalation, e.g. in dry powder form.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of an agent of the invention. The composition may be buffered to a pH in the range of e.g. from 3.5 to 9.5, by a suitable buffer.

The agents of the invention can be administered either alone or in combination with other pharmaceutical agents effective in the treatment of conditions mentioned above.

Thus, the agents of the invention can be used for the treatment of depressive symptoms in combination with: tricyclics, MAO inhibitors, SSRI's, SNRI's, NK receptor antagonists, CRF-receptor antagonists, 5HT7 receptor-antagonists, mGlu receptor agonists/antagonist/modulators, GABA-A or GABA-A/B receptor agonist/antagonists or modulators, vasopressin receptor antagonists, electroconvulsive shock, sleep deprivation, or herbal medicine such as St.John's Wort.

The agents of the invention can also be used for the treatment of anxiety-symptoms in combination with: benzodiazepines including mitochondrial benzodiazepine-ligands, 5-HT1A receptor agonists, SSRI's, SNRI's, NK receptor-antagonists, CRF receptor-antagonists, vasopressin receptor-antagonists, mGlu receptor agonists/antagonist/modulators, GABA-A or GABA-A/B receptor agonists/antagonists or modulators.

The agents of the invention can further be used for the treatment of any forms of dementia, including Alzheimer's disease (SDAT) in combination with: acetylcholine-esterase inhibitors, such as rivastigmine and donepezil, mixed acetylcholine/butyrylcholine esterase-inhibitors and nicotinic-alpha7-receptor agonists.

Moreover the agents of the invention can be used for the treatment of psychotic symptoms, including positive and negative symptoms in schizophrenia and schizoid type syndromes in combination with: any typical or atypical antipsychotic, such as clozapine or haloperidol, and nicotinic-alpha7-receptor agonists.

Furthermore the agents of the invention can be used for the treatment of bipolar disorders in combination with: any antimanic agent (e.g. Lithium, Carbamazepine, Valproate) or any atypical or typical antipsychotic.

The pharmaceutical compositions for separate administration of the combination partners and for the administration in a fixed combination, i.e. a single galenical composition comprising at least two combination partners according to the invention, can be prepared in a manner known per se and are thus suitable for enteral, such as oral or rectal, and parenteral administration to mammals, including man, comprising a therapeutically effective amount of at least one pharmacologically active combination partner alone or in combination with one

or more pharmaceutically acceptable carriers, especially suitable for enteral or parenteral application.

In particular, a therapeutically effective amount of each of the combination partners may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as fixed combination.

Accordingly the invention also provides a combination comprising a therapeutically effective amount of an agent of the invention and a second drug substance, or a pharmaceutically acceptable salt thereof where salt-forming groups are present, said second drug substance being for example for use in any of the particular indications hereinbefore set forth.

The preferred indications are depression, anxiety and affective disorders, especially bipolar disorders, e.g. mania, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

In accordance with the foregoing, the present invention also provides the use of an agent of the invention as a pharmaceutical, e.g. the use for the treatment of any one or more of the disorders mentioned above, especially of e.g. bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

.

Moreover the present invention provides the use of an agent of the invention for the manufacture of a medicament for the treatment of any one or more of the conditions or disorders mentioned above, e.g. bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

In still a further aspect the present invention provides a method for the treatment (this term whereever used above or below also comprising prophylaxis) of any one or more of the conditions or disorders mentioned above, e.g. bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of an agent of the invention.

In yet a further aspect, the present invention relates to a method of preparing a pharmaceutical preparation for the treatment of any one or more of the condistions or disorders mentioned above, comprising admixing an agent of the invention with one or more carriers and/or diluents.

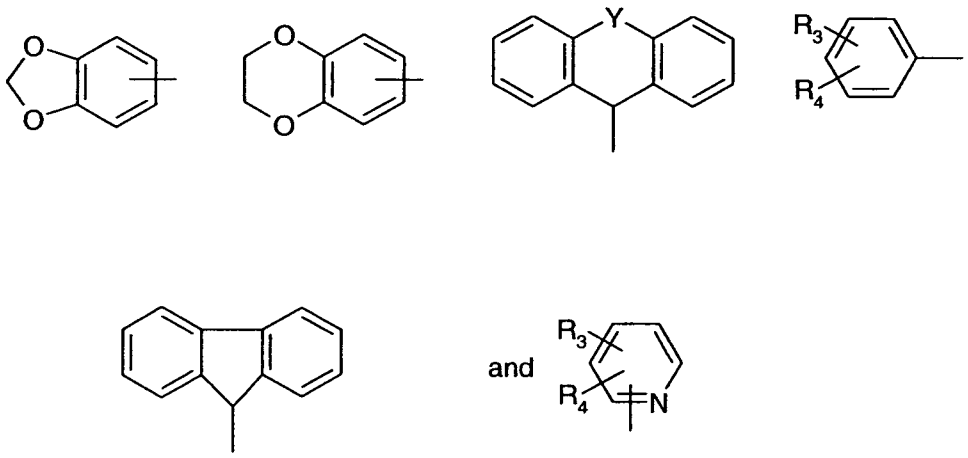
Preferred compounds of the invention have high affinity for somatostatin receptors, independently of the species, the expression system and the radioligand used, and are sst_1 selective.

They can be shown to significantly increase the duration of social contacts of the intruder rat towards the resident rat. In the social recognition test in mice, the compounds can be shown to exhibit a specific enhancing effect on the learning/memory performance.

Preferred embodiments of the invention

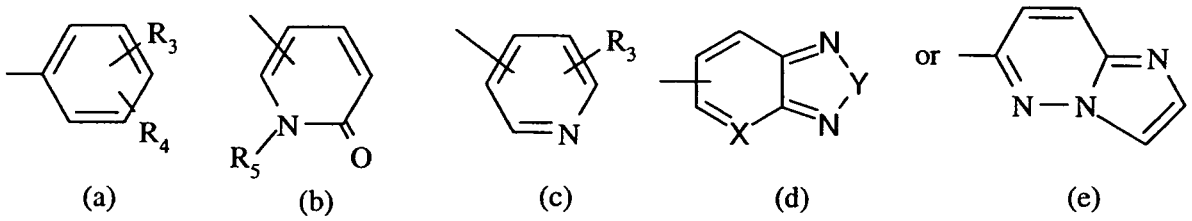
Preferred is a compound of the formula I wherein

R_1 is a moiety selected from the group consisting of



;

R2 is a moiety selected from the group consisting of moieties of the formulae



(a) (b) (c) (d) (e)

;

wherein

X is CH or N,

Y is O or S,

R_3 and R_4, independently of each other, are hydrogen, hydroxy, halogen, nitro, cyano, trifluoromethyl, C_1-C_4-alkyl or C_1-C_4-alkoxy , and

R_5 is hydrogen or C_1-C_4-alkyl,

and each of n and m is, independently of the other, 1 or 2, preferably 1;
or an (especially pharmaceutically acceptable) salt thereof, as well as any one or more of the combinations, uses and methods mentioned above with such compound or salt.

Most preferred is a compound of the formula selected from the compounds mentioned in the examples, or an (especially pharmaceutically accetptable) salt thereof, as well as any one or more of the combinations, uses and methods mentioned above with such compound or salt.

Manufacturing Processes

The compounds of the invention can be prepared in analogy to methods that, *per se*, though not for the compounds of formula I, are known in the art.

In the following description of preferred manufacturing processes for compounds of the formula I, R1, R2, m and n are as defined for compounds of the formula I or preferred versions thereof, as given above and below.

All process steps described here can be carried out under known reaction conditions, preferably under those specifically mentioned, in the absence of or usually in the presence of solvents or diluents, preferably such as are inert to the reagents used and able to dissolve these, in the absence or presence of catalysts, condensing agents or neutralising agents, for example ion exchangers, typically cation exchangers, for example in the H^+ form, depending

on the type of reaction and/or reactants at reduced, normal, or elevated temperature, for example in the range from -100°C to about 190°C, preferably from about -80°C to about 150°C, for example at -80 to -60°C, at room temperature, at - 20 to 40°C or at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, where appropriate or expedient under pressure, and/or in an inert atmosphere, for example under argon or nitrogen.

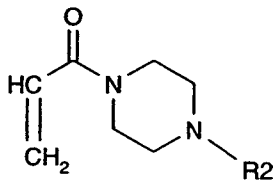
The solvents from which those solvents that are suitable for any particular reaction may be selected include, for example, water, esters, such as lower alkyl-lower alkanoates, for example ethyl acetate, ethers, such as aliphatic ethers, for example diethyl ether, or cyclic ethers, for example tetrahydrofuran, liquid aromatic hydrocarbons, such as benzene or toluene, alcohols, such as methanol, ethanol or 1- or 2-propanol, or phenols, such as phenol, nitriles, such as aceto nitrile, halogenated hydrocarbons, such as methylene chloride, acid amides, such as dimethylformamide, bases, such as heterocyclic nitrogen bases, for example pyridine, carboxylic acid anhydrides, such as lower alkanoic acid anhydrides, for example acetic anhydride, cyclic, linear or branched hydrocarbons, such as cyclohexane, hexane or iso pentane, or mixtures of those solvents, for example aqueous solutions, unless otherwise indicated in the description of the processes. Such solvent mixtures may also be used in working up, for example by chromatography or partitioning.

In the following description of some preferred methods of preparation for compounds of the formula I or salts thereof and for starting materials as well as in other processes mentioned above and below, functional groups that are not to participate in the respective reaction and which would disturb the desired reaction or lead to side reactions are present in protected form, where required. The protection of functional groups and the respective protecting groups are, for example, described in the literature, for example in standard textbooks such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973; in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999; in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London und New York 1981, in "Methoden der organischen Chemie", Houben Weyl, 4. Ausgabe, Band 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine", Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and/or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate", Georg Thieme Verlag, Stuttgart 1974. The

removal of protecting groups is possible under custommary conditions, preferably as described in the mentioned references, and at appropriate reaction stages and steps. The groups that have to be protected are known to the person having skill in the art, and therefore the introduction, presence and/or removal of protecting groups are mentioned only if very important for the process steps described below. Although not especially mentioned, it is clear that the starting materials can also be used in the form of salts where salt-forming groups are present and the formation of salts does not lead to undesired reactions.

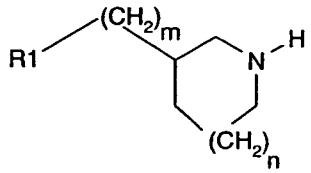
Preferably, a compound of the formula I is prepared by

a) reacting an N-acryloyl-piperazine compound of the formula II,



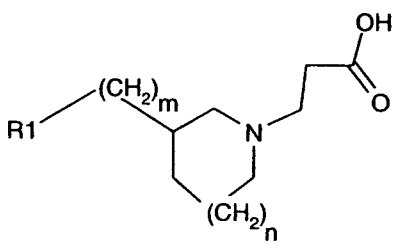
(II)

wherein R2 is as defined for a compound of the formula I, with an amino compound of the formula III,



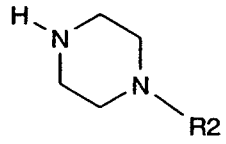
(III)

wherein R1, m and n are as defined for a compound of the formula I above or below,
or
b) reacting a carbonic acid compound of formula IV



(IV)

wherein R1, m and n are as defined for a compound of the formula I above or below, or a reactive derivative thereof, with a piperazine compound of the formula V,



(V)

wherein R2 is as defined for a compound of the formula I above or below;

and, if desired, transforming a compound of formula I into a different compound of formula I, transforming a salt of an obtainable compound of formula I into the free compound or a differrent salt, transforming an obtainable free compound of formula I into a salt, and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.

Reaction a) preferably takes place in the presence of an appropriate solvent that itself is not reactive under the reaction conditions, such as an ether, especially a cyclic ether, e.g. tetrahydrofurane, preferably at a temperature in the range from 0 to 50 °C, e.g. at room temperature, preferably in the presence of a base, especially a tertiary nitrogen base, such as a tri-lower alkylamine, e.g. triethylamine.

In reaction b), the carbonic acid of the formula IV is either converted *in situ* into a reactive derivative, e.g. by dissolving the compounds of formulae IV and V in a suitable solvent, for example *N,N*-dimethylformamide, *N,N*-dimethylacetamide, *N*-methyl-2-pyrrolidone, methylene chloride, or a mixture of two or more such solvents, and by the addition of a suitable base, for example triethylamine, diisopropylethylamine (DIEA) or *N*-methylmorpholine and a suitable coupling agent that forms a preferred reactive derivative of the carbonic acid of formula III *in situ*, for example dicyclohexylcarbodiimide/1-hydroxybenzotriazole (DCC/ HOBT); *O*-(1,2-dihydro-2-oxo-1-pyridyl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TPTU); O-benzotriazol-1-yl)-N,N,N', N'-tetramethyluronium tetrafluoroborate (TBTU); or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC). For review of other possible coupling agents, see e.g. Klauser; Bodansky, *Synthesis* **1972**, 453-463. The reaction mixture is preferably stirred at a temperature of between approximately -20 and 50 °C, especially between 0 °C and room temperature, to yield a compound of formula I. Alternatively, the carbonic acid of the formula IV is used in the form of a reactive derivative, e.g. as the carbonic acid halide,

such as chloride, as an anhydride with a carbonic acid, e.g. with a C_1-C_7-alkanoic acid, as an active ester, or in the form of an alkali metal salt, e.g. a sodium, lithum or potassium salt. In both cases, the reaction can preferably be carried out under an inert gas, e.g. nitrogen or argon.

Working up the reaction mixtures according to the above processes and purification of the compounds thus obtained may be carried out in accordance to known procedures.

Optional Reactions/Conversions:
Compounds of the formula I may be converted into different compounds of the formula I. For example, lower alkoxycarbonyl substituents may be converted into carboxyl by saponification, nitro substituents may be hydrogenated to amino.

Salts of a compound of formula I with a salt-forming group may be prepared in a manner known per se from the free compound. For example, acid addition salts of compounds of formula I may be obtained by treatment of the free compound with an acid or with a suitable anion exchange reagent. Salts of a compound of the formula I can usually be converted to free compounds, e.g. by treating with suitable basic agents, for example with alkali metal carbonates, hydrogencarbonates, or hydroxides, typically potassium carbonate or sodium hydroxide. Salts of a compound of the formula I may also be converted into different salts by treatment with appropriate salts. e.g. using a molar excess thereof over the salt of a compound of the formula I.

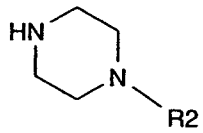
Stereoisomeric mixtures of a compound of the formula I, e.g. mixtures of enantiomers, as well as of starting materials can be separated into their corresponding isomers in a manner known per se by means of suitable separation methods. Enantiomeric mixtures for example may be separated into their individual enantiomers through the formation of diastereomeric salts, for example by salt formation with an enantiomer-pure chiral acid, or by means of chromatography, for example by HPLC, using chromatographic solid phases with chiral ligands.

Starting materials:
In view of the close relationship between the starting materials (starting materials and intermediates) in free form and in the form of their salts, any reference hereinbefore and hereinafter to a free compound or a salt thereof is to be understood as meaning also the corres-

ponding salt or free compound or salt/free compound mixture, respectively, where appropriate and expedient.

The starting materials are known in the art or can be prepared according to or in analogy to methods that are known in the art or in the examples.

A starting material of the formula II, or a salt thereof, can be prepared by reacting a piperidine compound of the formula VI,



(VI)

wherein R2 is as defined for a compound of the formula I,

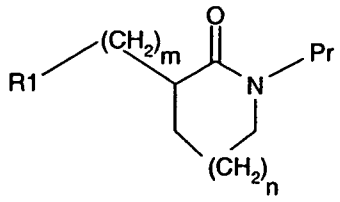
with acrylic acid or an active derivative thereof, preferably acrylic acid halide, e.g. the chloride, in an appropriate solvent, e.g. a halogenated hydrocarbon, such as methylene chloride, preferably at lowered temperatures, such as in the range from –20 to 15 °C, e.g. at about = to 5 °C, preferably in the presence of a base, such as a tertiary nitrogen base, e.g. a tri-C_1-C_7-alkylamine, for example triethylamine.

The starting materials of the formula VI can be produced by or in analogy to methods that are known in the art, for example in analogy to the method described in Example 1 by reaction of compounds of the formula VII,

R2-Hal (VII)

wherein R2 is as defined for a compound of the formula I, especially substituted aryl, and Hal is halo, especially fluoro, with piperazine, e.g. in an appropriate aprotic solvent, such as a nitrile, for example acetonitrile, in the presence of a base, e.g. an alkali metal carbonate, such as potassium carbonate, at preferred temperatures in the range from 0 to 50 °C, e.g. at about room temperature.

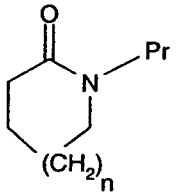
A compound of the formula III, or a salt thereof, can be prepared by reducing a lactame compound of the formula VIII,



(VIII)

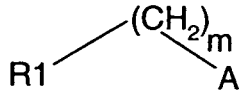
wherein R1, m and n are as defined for a compound of the formula I and Pr is an amino protecting group, e.g. benzyl, with an appropriate complex hydride, e.g. lithium aluminium hydride, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, at preferred temperatures from 10 °C to the reflux temperature, e.g. from room temperature to the reflux temperature of the mixture; and and subsequently removing the protecting group, e.g. benzyl, preferably by hydrogenation in the presence of a noble metal catalyst, e.g. palladium on charcoal (Pd/C), in an appropriate solvent, e.g. a mixture of an alcohol, such as methanol, and a carboxylic acid, e.g. acetic acid, at preferred temperatures in the range from 0 to 50 °C, e.g. at about room temperature.

A compound of the formula VIII can, for example, be obtained by reacting a compound of the formula IX,



(IX)

wherein Pr and n are as just defined, in an appropriate solvent, such as an ether, e.g. tetrahydrofurane, in the absence or presence of one or more further solvents, e.g. lower alkanes or lower cacloalkanes, such as hexane or cyclohexane, at low temperatures, e.g. in the range from –80 to –50 °C, such as about – 70 °C, preferably under an inert gas, such as argon, first in the presence of a metalating agent, e.g. litium butanide, such as sec.-butyllithium, and then with a compound of the formula



wherein R1 and m are defined as for a compound of the formula I (where m is preferably 1 or 2) and A is halo, especially bromo.

A starting material of the formula IV can, for example, be obtained by reacting a compound of the formula III, which can be obtained as described above, with a carboxyl protected form of acrylic acid in analogy to the reaction conditions mentioned above under process a) or of a 3-halo-propionic acid, such as of a 3-bromo-propionic acid, and subsequent removal of the protecting group.

Starting materials of the formula V are identical to those of the formula VI described above.

Other starting materials can be obtained according to or in analogy to known procedures or are commercially available.

The invention relates also to those forms of the process in which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. In the process of the present invention there are preferably used those starting materials which result in the compounds of formulal described at the beginning as being especially valuable. Special preference is given to reaction conditions and processes of manufacture that are analogous to those mentioned in the Examples. The invention also relates to novel starting materials described above and below that are useful in the synthesis of compounds of the formula I.

Examples

The following Examples serve to illustrate the invention without limiting the scope thereof:

Abbreviations:

abs.	absolute
AcOH	acetic acid
AcOEt	ethyl acetate
aq.	Aqueous
sec.-BuLi	sec.-butyllithium (lithium-2-butanide)
Celite®	filtering aid based on kieselguhr (Celite Corporation, Lompoc, USA)

d	day(s)
DMSO	dimethyl sulfoxide
ESI-MS	Electrospray Ionisation Mass Spectrometry
ether	diethylether
EtOH	ethanol
h	hour(s)
HPLC	high performance liquid chromatography
MeOH	methanol
min	minute(s)
MPLC	medium pressure liquid chromatography
^{1}H-NMR	Proton Nuclear Magnetic Resonance
Pd/C	Palladium on charcoal
rt	room temperature
sat.	saturated
THF	tetrahydrofurane

Solvent relations, e.g. in eluents or solvent mixtures, are given in v/v (volume by volume), temperatures in °C (uncorrected).

Example 1: (+)-4-{4-[3-(3-Benzo[1,3]dioxol-5-ylmethyl-piperidin-1-yl)-propionyl]-piperazin-1-yl}-2-fluoro-benzonitrile

A solution of 4-(4-acryloyl-piperazin-1-yl)-2-fluoro-benzonitrile (0.125 g, 0.48 mmol), (+)-3-benzo[1,3]dioxol-5-ylmethyl-piperidine (0.106 g, 0.48 mmol) and triethylamine (0.088 ml, 0.629 ml) in THF (1.6 ml) is stirred at rt for 25 h. The mixture is diluted with CH_2Cl_2 and washed with sat. aq. Na_2CO_3 solution The organic layer is separated off, dried over Na_2SO_4 and evaporated. The residue is purified by MPLC (60 g silica gel, eluent CH_2Cl_2:MeOH 9:1) to give the title compound, (+)-4-{4-[3-(3-benzo[1,3]dioxol-5-ylmethyl-piperidin-1-yl)-propionyl]-piperazin-1-yl}-2-fluoro-benzonitrile, as a colourless foam:

^{1}H-NMR (400 MHz, DMSO): δ = 7.68-7.61 (m, 1H), 6.99-6.93 (m, 1H), 6.89-6.84 (m, 1H), 6.83-6.79 (m, 1H), 6.77-6.74 (m, 1H), 6.64-6.59 (m, 1H), 5.97 (s, 2H), 3.62-3.54 (m, 4H), 3.50-3.37 (m, 4H), 2.77-2.64 (m, 2H), 2.51-2.33 (m, 6H), 1.96-1.87 (m, 1H), 1.74-1.52 (m, 4H), 1.43-1.34 (m, 1H), 0.94-0.84 (m, 1H); $[\alpha]_D^{rt}$ = +14.7° (c=0.5, EtOH), ESI-MS

$M+H^+$ = 479.3; optical purity > 99.9%, as determined by HPLC comparison with the racemate using a Chiralcel® OD-RH 150x4.6 mm column (Daicel Chiral Technologies, Inc., Exton USA; a chiral stationary phase), eluent CH_3CN + 0.1% diethylamine, flow rate 0.8 ml/min, UV detection (226 nM), retention time 4.8 min.

The starting materials are prepared as follows:

a) (-)-3-Benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidin-2-one

1-Benzyl-piperidin-2-one (4.8 g, 25.4 mmol) in abs. THF (200 ml) is cooled to -70°C; sec.-BuLi (23.4 ml of a 1.3 M solution in cyclohexane; 30.4 mmol) is added dropwise under an Ar atmosphere and the mixture is stirred at -70°C for 30 min. A solution of 5-bromomethyl-benzo[1,3]dioxole (see Harrowven et al., Tetrahedron (2001), 57(29), 4447) (8.0 g, 37.2 mmol) in abs. THF (80 ml) is added dropwise, stirring is continued at -70°C for 3h, then at rt for 15h. sat. aq. NH_4Cl solution is added, the organic layer is separated, dried over Na_2SO_4 and evaporated. The oily residue is purified by MPLC (140 g silica gel, eluent cyclohexane, then cyclohexane:AcOEt 7:3) to give 3-benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidin-2-one as a yellow oil. Preparative resolution using a Chiralpak AD 5x50 cm/20 µm column (Daicel Chiral Technologies, Inc., Exton USA; a chiral stationary phase); eluent hexane: isopropanol 90:10; flow 80 ml/min; UV detection (210 nM) gives (-)-3-benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidin-2-one ($[\alpha]_D^{rt}$ = -61.1° (c=0.5, EtOH)).

b) (+)-3-Benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidine

To a solution of (-)-3-benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidin-2-one (1.73 g, 5.3 mmol) in THF (21 ml), $LiAlH_4$ (6.5 ml of a 1M solution in THF, 6.5 mmol) is added dropwise at rt. The mixture is refluxed for 2.5h, cooled to rt, quenched with water and filtered over Celite®. The filtrate is evaporated, the residue dissolved in AcOEt, washed with water and brine, and the aq. layers are reextracted with AcOEt, the combined organic layers are dried over Na_2SO_4 and evaporated to give (+)-3-benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidine ($[\alpha]_D^{rt}$ = 28.2° (c=0.5, EtOH)).

c) (+)-3-Benzo[1,3]dioxol-5-ylmethyl-piperidine

1.40 g (4.5 mmol) of (+)-3-benzo[1,3]dioxol-5-ylmethyl-1-benzyl-piperidine is dissolved in 35 ml MeOH and 1 ml AcOH and hydrogenated over Pd/C 10% (0.3 g) for 2d until hydrogen absorption is complete. The mixture is filtered over Celite®, and the filtrate is evaporated, di-

luted with CH_2Cl_2, washed with sat. aq. Na_2CO_3 solution and evaporated to give (+)-3-benzo[1,3]dioxol-5-ylmethyl-piperidine ($[\alpha]_D^{rt}$ = 5.9° (c=0.5, DMSO)) which is used without further purification.

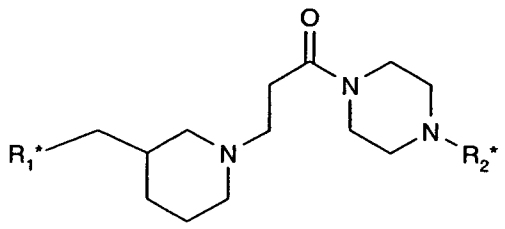
d) 2-Fluoro-4-(piperazin-1-yl)-benzonitrile

Piperazine (20.0 g, 232.3 mmol) and K_2CO_3 (16.0 g, 118.5 mmol) are dissolved in CH_3CN (85 ml). 2,4-Difluoro-benzonitrile (8.5 g, 61.1 mmol) is added and the mixture is stirred for 2h at rt, then diluted with AcOEt and washed with water. The organic layer is separated, dried over Na_2SO_4 and evaporated. Excess piperazine is removed by MPLC (100 g silica gel, eluent CH_2Cl_2:MeOH 85:15). A second chromatographic purification (300 g silica gel, eluent toluene:EtOH: AcOH 4:4:1) yields the acetate salt of 2-fluoro-4-(piperazin-1-yl)-benzonitrile that is crystallized from AcOEt, filtered off and washed with ether. The free base is isolated by extraction with sat. aq. Na_2CO_3 solution/AcOEt.

e) 4-(4-Acryloyl-piperazin-1-yl)-2-fluoro-benzonitrile

A solution of 2-fluoro-4-(piperazin-1-yl)-benzonitrile (0.53 g, 2.56 mmol) and triethylamine (0.5 ml, 3.59 mmol) in CH_2Cl_2 (13 ml) is added dropwise to a cooled solution (0-5°C) of acryloyl chloride (0.25 ml, 3.15 mmol) in CH_2Cl_2 (3 ml). After complete addition, the mixture is stirred at rt for 1h, sat. aq. Na_2CO_3 solution is added and stirring is continued for 20 min. The organic layer is separated off, dried over Na_2SO_4 and evaporated. Upon addition of AcOEt, 4-(4-acryloyl-piperazin-1-yl)-2-fluoro-benzonitrile crystallizes out, is filtered off, washed with AcOEt and air-dried.

In analogy to example 1 and/or the methods mentioned above, the following examples are prepared:



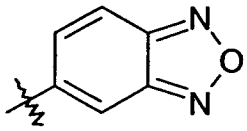
Example No.	R_1*	R_2*	α_D (c=0.5)	salt form	mp. (°C)

2	benzo[1,3]dioxol-5-yl	benzo[1,2,5]oxadiazol-5-yl*	positive (EtOH)	free base	n.d. (amorphous)
3	benzo[1,3]dioxol-5-yl	4-cyano-phenyl	(*rac.*)	phosphate	115-117
4	benzo[1,3]dioxol-5-yl	4-[1,2,5]-thiadiazolo-[3,4-b]pyridin-5-yl**	positive (DMSO)	free base	96-101
5	benzo[1,3]dioxol-5-yl	3,4-difluoro-phenyl	(*rac.*)	free base	188-192
6	benzo[1,3]dioxol-5-yl	4-cyano-2,6-difluoro-phenyl	(*rac.*)	phosphate	115-125
7	benzo[1,3]dioxol-5-yl	4-nitro-phenyl	(*rac.*)	free base	n.d. (amorphous)
8	benzo[1,3]dioxol-5-yl	2-pyridyl	(*rac.*)	phosphate	101-108
9	benzo[1,3]dioxol-5-yl	1-methyl-6-oxo-1,6-dihydro-pyridin-2-yl	(*rac.*)	phosphate	118-125
10	benzo[1,3]dioxol-5-yl	imidazo[1,2-b]py ridazin-6-yl***	(*rac.*)	free base	107-118
11	6-methoxy-pyri-din-3-yl	benzo[1,2,5]oxadiazol-5-yl	(*rac.*)	hydrochloride	n.d. (amorphous)
12	4-fluoro-phenyl	benzo[1,2,5]oxadiazol-5-yl	(*rac.*)	hydrochloride	n.d. (amorphous)
13	2,3-dihydro-ben-zo[1,4]dioxin-6-yl	benzo[1,2,5]oxadiazol-5-yl	positive (MeOH)	hydrochloride	96 (decomposition)
14	2-methoxy-pyri-din-3-yl	benzo[1,2,5]oxadiazol-5-yl	(*rac.*)	phosphate	143-150
15	2,6-dimethoxy-pyridin-3-yl	benzo[1,2,5]oxadiazol-5-yl	Positive (MeOH)	free base	n.d. (amorphous)
16	9H-thioxanthene-9-yl	4-nitro-phenyl	(*rac.*)	fumarate	215-219
17	pyridin-3-yl	benzo[1,2,5]oxadiazol-5-yl	(*rac.*)	hydrochloride	n.d. (oil)

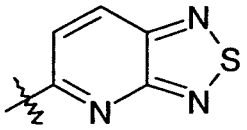
(rac): These compounds are present as racemates.

n.d. = not determined.

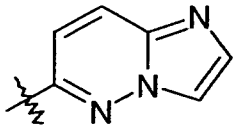
* This moiety has the formula



** This moiety has the formula



*** This moiety has the formula



Example 17: Soft Capsules

5000 soft gelatin capsules, each comprising as active ingredient 0.05 g of one of the compounds of formula I mentioned in any one of the preceding Examples, are prepared as follows:

Composition

Active ingredient	250 g
Lauroglycol	2 litres

Preparation process: The pulverized active ingredient is suspended in Lauroglykol® (propylene glycol laurate, Gattefossé S.A., Saint Priest, France) and ground in a wet pulverizer to produce a particle size of about 1 to 3 μm. 0.419 g portions of the mixture are then introduced into soft gelatin capsules using a capsule-filling machine.

Example 18: Tablets comprising compounds of the formula I

Tablets, comprising, as active ingredient, 100 mg of any one of the compounds of formula I of Examples 1 to 16 are prepared with the following composition, following standard procedures:

Composition

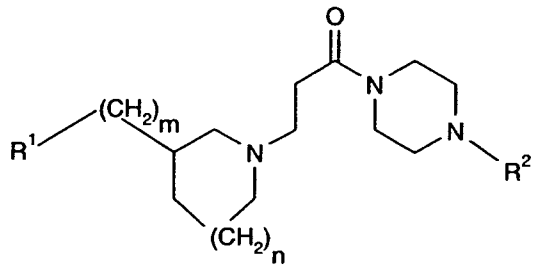
Active Ingredient	100 mg
crystalline lactose	240 mg
Avicel	80 mg
PVPPXL	20 mg
Aerosil	2 mg
magnesium stearate	5 mg
	447 mg

Manufacture: The active ingredient is mixed with the carrier materials and compressed by means of a tabletting machine (Korsch EKO, Stempeldurchmesser 10 mm).

Avicel® is microcrystalline cellulose (FMC, Philadelphia, USA).
PVPPXL is polyvinylpolypyrrolidone, cross-linked (BASF, Germany).
Aerosil® is silcium dioxide (Degussa, Germany).

What is claimed is:

1. A compound of the formula (I)



(I)

wherein

R^1 is unsubstituted or substituted aryl, unsubstituted or substituted heterocyclyl;

R^2 is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl;

and each of n and m, independently of the other, is 0, 1 or 2;

or a salt thereof;

wherein when R^1 and/or R^2 is substituted aryl, the substituents are one or more substituents independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, nitro, cyano, halo; unsubstituted-, C_1-C_7-alkoxy-substituted or halosubstituted phenyl- C_1-C_7- alkyl; hydroxy; hydroxy-C_1-C_7-alkyl; alkoxy, C_1-C_7-alkoxy, phenoxy; alkanoyloxy, C_1-C_7-alkanoyloxy; C_1-C_7-alkanoylthio; halo; amino; N-mono- or N,N-di-(C_1-C_7-alkyl)amino; C_1-C_7-alkanoylamino; C_1-C_7-alkanoyl; carboxy; C_1-C_7-alkoxycarbonyl; cyano; carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl; C_1-C_7-alkylsulfonyl; sulfamoyl; and nitro;

and wherein when R^1 and/or R^2 is substituted heterocyclyl, the substituents are one or more substituents independently selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, nitro, cyano, halo; unsubstituted-, C_1-C_7-alkoxy-substituted or halo-substituted phenyl- C_1-C_7- alkyl; hydroxy; hydroxy-C_1-C_7-alkyl; alkoxy, C_1-C_7-alkoxy, phenoxy; alkanoyloxy, C_1-C_7-alkanoyloxy; C_1-C_7-alkanoylthio; halo; amino; N-mono- or N,N-di-(C_1-C_7-alkyl)amino; C_1-C_7-alkanoylamino; C_1-C_7-alkanoyl; carboxy; C_1-C_7-alkoxycarbonyl; cyano; carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl; C_1-C_7-alkylsulfonyl; sulfamoyl; nitro and oxo.

2. A compound of the formula I according to claim 1, wherein

R^1 is unsubstituted or substituted aryl wherein aryl is phenyl, naphthyl or fluorenyl, each of which is unsubstituted or substituted by one or more substituents independently selected from alkyl; cycloalkyl; phenyl or (1- or 2-) napthyl, each of which is unsubstituted or substituted with one or more substituents selected from C_1-C_7-alkyl, halo-C_1-C_7-alkyl, C_1-C_7-alkoxy, halo-C_1-C_7-alkoxy, nitro, cyano, and halo; unsubstituted, C_1-C_7-alkoxy-substituted or halosubstituted phenyl- C_1-C_7- alkyl; hydroxy; hydroxy-C_1-C_7-alkyl; alkoxy; phenoxy; alkanoyloxy, C_1-C_7-alkanoylthio; halo; amino; N-mono- or N,N-di-(C_1-C_7-alkyl)amino; C_1-C_7-alkanoylamino; C_1-C_7-alkanoyl; carboxy; C_1-C_7-alkoxycarbonyl; cyano; carbamoyl, N-mono- or N,N-di-(C_1-C_7-alkyl)carbamoyl; C_1-C_7-alkylsulfonyl; sulfamoyl; and nitro;
or is unsubstituted or substituted heterocyclyl, where heterocyclyl is preferably a ring with 3 to 20 ring atoms which is unsaturated, partially saturated or saturated, has one to four heteroatoms independently selected from O, N (or NH) and S, is mono-, bi- or tricylic, and is unsubstituted or substituted by up to three moieties independently selected from those mentioned above as substituents for substituted aryl and oxo;

R^2, is independently selected from the moieties mentioned for R1 and is thus identical to or different from R1, is unsubstituted or substituted aryl or unsubstituted or substituted heterocyclyl as mentioned under R1 in the preceding paragraph,
n is 1 or 2, and
m is 1 or 2,
or a pharmaceutically acceptable salt thereof.

3. A compound of the formula I according to claim 1, wherein
R^1 is phenyl that is unsubstituted or substituted by one or more substituents independently selected from cyano, C_1-C_7-alkoxy, nitro and halo, fluorenyl or is unsubstituted or substituted heterocyclyl selected from the group consisting of pyridinyl, substituted pyridinyl wherein the substituents are independently selected from one or more of hydroxy, halo, nitro, cyano, trifluoromethyl, C_1-C_4-alkyl and C_1-C_4-alkoxy, 1-alkyl-oxo-dihydropyridinyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, imidazo[1,2-b]pyridazin-8-, -7- or –6-yl, 4-[1,2,5]-thiadiazolo-[3,4-b]pyridin-7-, -6- or -5-yl, xanthenyl, thioxanthenyl, benzo[1,3]dioxol-4- or -5-yl; and 2,3-dihydro-benzo[1,4]dioxin-5- or -6-yl;

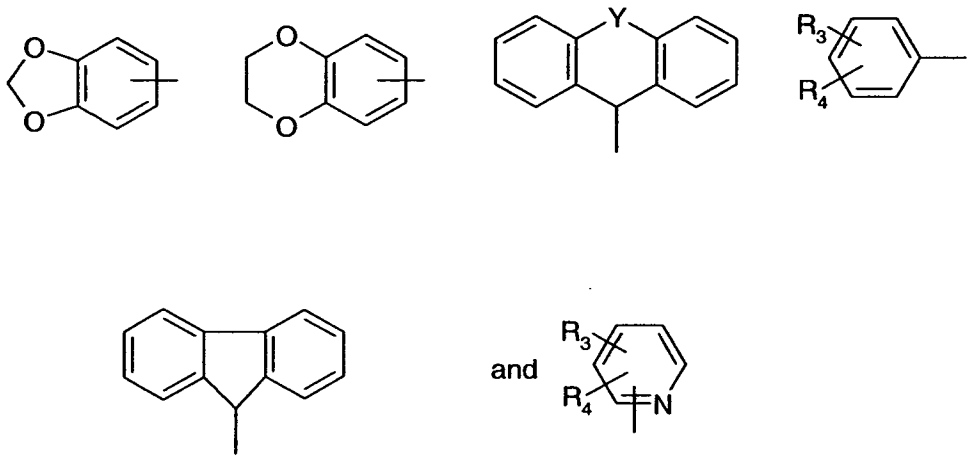
R^2, which is independently selected from the moieties mentioned for R1 and is thus identical to or different from R1, is unsubstituted or substituted phenyl or unsubstituted or substituted heterocyclyl as mentioned under R1 in the preceding paragraph;

and each of n and m is 1;

or a pharmaceutically acceptable salt thereof.

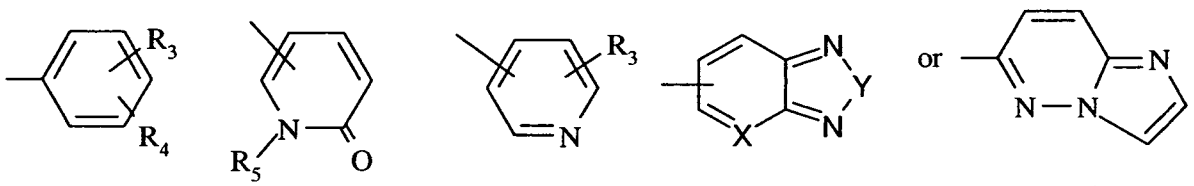
4. A compound of the formula I according to claim 1, wherein

R_1 is a moiety selected from the group consisting of



;

R2 is a moiety selected from the group consisting of moieties of the formulae



(a) (b) (c) (d) (e)

;

X is CH or N,

Y is O or S,

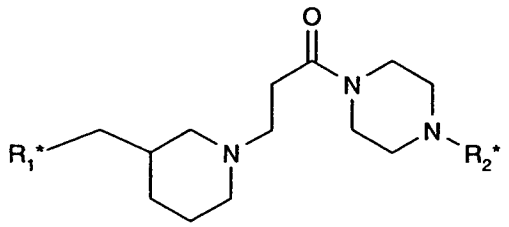
R_3 and R_4, independently of each other, are hydrogen, hydroxy, halogen, nitro, cyano, trifluoromethyl, C_1-C_4-alkyl or C_1-C_4-alkoxy , and

R_5 is hydrogen or C_1-C_4-alkyl;

and each of m and n is independently of the other 1 or 2.

5. A compound of the formula I, selected from the group consisting of the compound named (+)-4-{4-[3-(3-benzo[1,3]dioxol-5-ylmethyl-piperidin-1-yl)-propionyl]-piperazin-1-yl}-2-fluoro-benzonitrile and the compounds 2 to 16 in the following table of the formula

:



Compound No..	R_1*	R_2*	Enantiomer or racemate
2	benzo[1,3]dioxol-5-yl	benzo[1,2,5]oxadiazol-5-yl	(+)-enantiomer
3	benzo[1,3]dioxol-5-yl	4-cyano-phenyl	racemate
4	benzo[1,3]dioxol-5-yl	4-[1,2,5]-thiadiazolo-[3,4-b]pyridin-5-yl	(+)-enantiomer
5	benzo[1,3]dioxol-5-yl	3,4-difluoro-phenyl	racemate
6	benzo[1,3]dioxol-5-yl	4-cyano-2,6-difluoro-phenyl	racemate
7	benzo[1,3]dioxol-5-yl	4-nitro-phenyl	racemate
8	benzo[1,3]dioxol-5-yl	2-pyridyl	racemate
9	benzo[1,3]dioxol-5-yl	1-methyl-6-oxo-1,6-dihydro-pyridin-2-yl	racemate
10	benzo[1,3]dioxol-5-yl	imidazo[1,2-b]py ridazin-6-yl	racemate
11	6-methoxy-pyri-din-3-yl	benzo[1,2,5]oxadiazol-5-yl	racemate
12	4-fluoro-phenyl	benzo[1,2,5]oxadiazol-	racemate

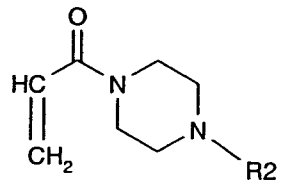
		5-yl	
13	2,3-dihydro-benzo[1,4]dioxin-6-yl	benzo[1,2,5]oxadiazol-5-yl	(+)-enantiomer
14	2-methoxy-pyridin-3-yl	benzo[1,2,5]oxadiazol-5-yl	racemate
15	2,6-dimethoxy-pyridin-3-yl	benzo[1,2,5]oxadiazol-5-yl	(+)-enantiomer
16	9H-thioxanthene-9-yl	4-nitro-phenyl	racemate
17	pyridin-3-yl	benzo[1,2,5]oxadiazol-5-yl	racemate

or a – preferably pharmaceutically acceptable - salt thereof.

6. A compound of formula (I) according to any one of claims 1 to 5 in the form of a pure enantiomer.

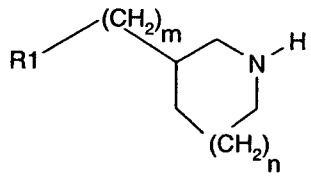
7. A process for the preparation of a compound of the formula I according to any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, comprising

a) reacting an N-acryloyl-piperazine compound of the formula II,



(II)

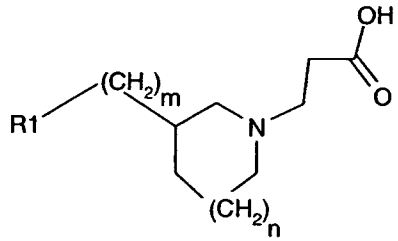
wherein R2 is as defined for a compound of formula I, with compound of formula III,



(III)

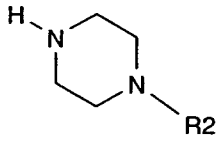
wherein R1, m and n are as defined for a compound of the formula I above or below, or

b) reacting a carbonic acid compound of formula IV



(IV)

wherein R1, m and n are as defined for a compound of the formula I above or below, or a reactive derivative thereof, with a piperazine compound of the formula V,



(V)

wherein R2 is as defined for a compound of the formula I above or below;

and, if desired, transforming a compound of formula I into a different compound of formula I, transforming a salt of an obtainable compound of formula I into the free compound or a differrent salt, transforming an obtainable free compound of formula I into a salt, and/or separating obtainable mixtures of isomers of compounds of formula I into the individual isomers.

8. A pharmaceutical composition comprising a compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 and a pharmaceutically acceptable carrier.

9. A compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 for use in the diagnostic and/or therapeutic treatment of the animal, especially mammalian, or human body.

10. The use of a compound of the formula I, or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 for the preparation of a pharmaceutical composition for the treatment of one or more disorders selected from the group consisting of mental disorders, disorders of the nervous system, tumors, vascular disorders and immunological diseases; especially for the treatment of bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

11. A method for the prevention, treatment or delay of progression of one of more disorders selected from the group consisting of mental disorders, disorders of the nervous system, tumors, vascular disorders and/or for immunological diseases; especially for the treatment of bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia, in a subject in need of such treatment, which comprises administering to such subject a therapeutically effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6.

12. A combination comprising a therapeutically effective amount of a compound of the formula (I), or a pharmaceutically acceptable salt thereof, according to any one of claims 1 to 6 and a second drug substance, or a pharmaceutically acceptable salt thereof, said second drug substance being for use in the treatment of mental disorders, disorders of the nervous system, tumors, vascular disorders and/or for immunological diseases; especially of bipolar disorders, social phobias, memory impairment, attention deficit, hyperactive disorders, aggressive states and/or negative symptoms of schizophrenia.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/006867

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/496 C07D407/06 C07D407/14 C07D409/06 C07D413/06
C07D413/12 C07D413/14 C07D417/14 C07D471/04 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98/18786 A (NOVO NORDISK A/S) 7 May 1998 (1998-05-07) the whole document	1-12
A	EP 1 086 947 A (PFIZER PRODUCTS INC) 28 March 2001 (2001-03-28) the whole document	1-12

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 September 2006	06/10/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bérillon, Laurent

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/006867

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/006867

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9818786 A	07-05-1998	AU 4772497 A	22-05-1998
		EP 0937065 A1	25-08-1999
		JP 2001502712 T	27-02-2001
		US 6020349 A	01-02-2000
		ZA 9709701 A	21-05-1998
EP 1086947 A	28-03-2001	BR 0003880 A	02-10-2001
		CA 2316767 A1	01-03-2001
		JP 3338022 B2	28-10-2002
		JP 2001114761 A	24-04-2001