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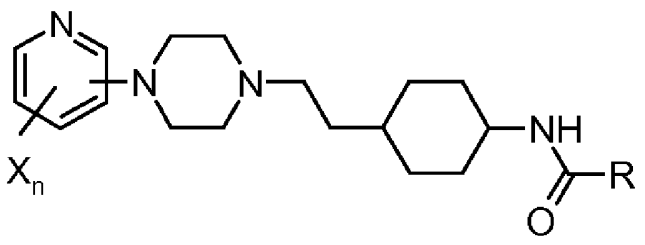
(54) Title: PYRIDINYLPIPERAZIN DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D3 RECEPTORS



(I)

(57) Abstract: The present invention relates to compounds of the general formula (I), having affinity and selectivity for the dopamine D3 receptors, their manufacture, pharmaceutical compositions containing them and their use as medicaments. The active compounds of the present invention are useful for the therapeutic and/or prophylactic treatment of cognitive disorders.

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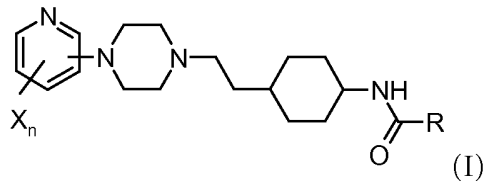
PYRIDINYLPIPERAZIN DERIVATIVES USEFUL AS MODULATORS OF DOPAMINE D3 RECEPTORS

The present invention relates to compounds of the general formula I,



(I)

wherein:

X is independently of each other halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl or C_{1-6}-alkoxy;

n is 1 or 2;

R is C_{1-6}-alkyl, wherein C_{1-6}-alkyl is optionally substituted by $-CONH_2$ or one 3 to 6 membered monocyclic cycloalkyl;

C_{1-6}-alkoxy;

as well as pharmaceutically acceptable salts thereof.

It has been surprisingly found that the compounds of formula I have affinity for dopamine D3 receptors and thus are useful in the treatment of conditions wherein modulation, especially antagonism/inhibition, of D3 receptors is beneficial, e. g. to treat drug dependency or as antipsychotic agents.

Background Information

Dopamine, a major catecholamine neurotransmitter, is involved in the regulation of a variety of functions which include emotion, cognition, motor functions, and positive reinforcement, (Purves, D. et al. (2004) Neuroscience. Sinauer, third edition, Sunderland, Massachusetts). The biological activities of dopamine are mediated through G protein-coupled receptors (GPCRs) and in human, five different dopamine receptors D_1-D_5 have been identified, where the D_2-like receptors (D_2, D_3 and D_4) couple to the G-protein $G_{\alpha I}$ (Missale, C. et al.. (1998) Dopamine receptors: from structure to function. Physiol. Rev. 78, 189-225). The D_3 dopamine receptor is most highly expressed in the nucleus accumbens (Gurevich, E. V., Joyce, J. N. (1999) Distribution of dopamine D3 receptor expressing neurons in the human forebrain: comparison with D2 receptor expressing neurons. Neuropsychopharmacology 20, 60-80), and is proposed to modulate the mesolimbic pathway consisting of neuronal projections from the ventral tegmental area, hippocampus and amygdala to the nucleus accumbens, which projects to the prefrontal and cingulate cortices as well as various thalamic nuclei. The limbic circuit is thought to be important for emotional behavior and thus D_3 receptor antagonists are proposed to modulate psychotic

symptoms such as hallucinations, delusions and thought disorder (Joyce, J. N. and Millan, M. J., (2005) Dopamine D3 receptor antagonists as therapeutic agents. Drug Discovery Today, 1 Jul, Vol. 10, No. 13, 917-25), while these antagonists spare the D_2 modulated striatal extrapyramidal system (associated with EPS induction). In addition, it has been reported that drug naive schizophrenic patients show altered levels of D_3 receptor expression (Gurevich, E. V. et al. (1997) Mesolimbic dopamine D3 receptors and use of antipsychotics in patients with schizophrenia. A postmortem study. Arch. Gen. Psychiatry 54, 225-232) and dopamine release (Laruelle, M. (2000) Imaging dopamine dysregulation in schizophrenia: implication for treatment. Presented at Workshop Schizophr.: Pathol. Bases and Mech. Antipsychotic Action, Chicago), indicating that a disturbed homeostasis of dopamine plays an important role in the etiology of schizophrenic symptoms.

Detailed description of the invention

Compounds of formula I and its pharmaceutically acceptable salts have been found to be useful in the treatment of all aspects of drug dependency, including drug intake, relapse to drug-seeking behaviour following abstinence and withdrawal symptoms from drugs of abuse such as alcohol, cocaine, opiates, nicotine, benzodiazepines and inhibition of tolerance induced by opioids, as well as for the treatment of drug craving. It is also useful as an antipsychotic agent for example in the treatment of schizophrenia, schizo-affective disorders, schizophreniform diseases, psychotic depression (which term includes bipolar depression, unipolar depression, single or recurrent major depressive episodes with or without psychotic features, catatonic features, melancholic features, atypical features or postpartum onset, seasonal affective disorder and dysthymia, depressive disorders resulting from a general medical condition including, but not limited to, myocardial infarction, diabetes, miscarriage or abortion), anxiety disorders (which includes generalised anxiety and social anxiety disorder), mania, acute mania, paranoid and delusional disorders. The compounds are also useful for the treatment of a family of related disorders referred to as somatoform disorders, as well as for the treatment of premature ejaculation. The compounds are further useful for the treatment of attention-deficit hyperactivity disorder (ADHD), addiction (smoking cessation, cocaine and others) and obsessive compulsive disorder (OCD).

Compounds of formula I may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, salicylate, sulphate, pyruvate, citrate, lactate, mandelate, tartarate, and methanesulphonate. Preferred are the hydrochloride salts. Also solvates and hydrates of compounds of formula I and their salts form part of the present invention.

Compounds of formula I can have one or more asymmetric carbon atoms and can exist in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers,

diastereoisomeric racemates or mixtures of diastereoisomeric racemates. The optically active forms can be obtained for example by resolution of the racemates, by asymmetric synthesis or asymmetric chromatography (chromatography with a chiral adsorbens or eluant). The invention embraces all of these forms.

It will be appreciated, that the compounds of general formula I in this invention may be derivatized at functional groups to provide derivatives which are capable of conversion back to the parent compound in vivo. Physiologically acceptable and metabolically labile derivatives, which are capable of producing the parent compounds of general formula I in vivo are also within the scope of this invention.

As used herein, the term "C_{1-6}-alkyl" denotes monovalent linear or branched saturated hydrocarbon moiety, consisting solely of carbon and hydrogen atoms, having from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl and the like. Preferred alkyl groups are groups with 1, 2, 3 or 4 carbon atoms. Most preferred alkyl groups are methyl and ethyl.

The term "halogen" denotes chlorine (chloro, Cl), iodine (iodo, I), fluorine (fluoro, F) and bromine (bromo, Br). Preferred halogen are fluoro, chloro and bromo, more preferred are fluoro and chloro, most preferred is fluoro.

The term "C_{1-6}-alkoxy" denotes a group –O-R' wherein R' is C_{1-6}-alkyl as defined above. Preferred C_{1-6}-alkoxy is ethyl-OCH_3.

The term "C_{1-6}-haloalkyl" denotes an alkyl group as defined above wherein at least one of the hydrogen atoms of the alkyl group is replaced by a halogen atom, preferably fluoro or chloro, most preferably fluoro. Examples of haloalkyl include but are not limited to methyl, ethyl, propyl, isopropyl, isobutyl, sec-butyl, tert-butyl, pentyl or n-hexyl wherein one or more hydrogen atoms are replaced by Cl, F, Br or I atom(s), as well as those haloalkyl groups specifically illustrated by the examples herein below. Among the preferred haloalkyl groups are monofluoro-, difluoro- or trifluoro-methyl, –ethyl or -propyl, for example 3,3,3-trifluoropropyl, 2-fluoroethyl, 2,2,2-trifluoroethyl, fluoromethyl, trifluoromethyl.

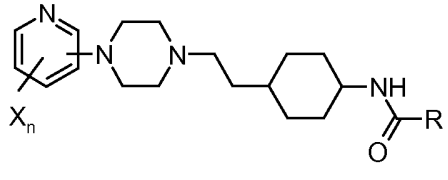
The phrase "3 to 6 membered monocyclic cycloalkyl" refers to a monovalent saturated monocyclic hydrocarbon radical of 3 to 6 ring carbon atoms. Examples are cyclopropyl, cyclobutanyl, cyclopentyl or cyclohexyl. Preferred examples are cyclopropyl, cyclopentyl and cyclohexyl.

The terms "pharmaceutically acceptable salt" or “pharmaceutically acceptable acid addition salt” embrace salts with inorganic and organic acids, such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid, citric acid, formic acid, fumaric acid, maleic acid, acetic acid, succinic acid, tartaric acid, methane-sulfonic acid, p-toluenesulfonic acid

and the like.

When indicating the number of subsituents, the term “one or more” means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents. Thereby, one, two or three substituents are preferred.

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



(I)

wherein:

X is independently of each other halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl or C_{1-6}-alkoxy;

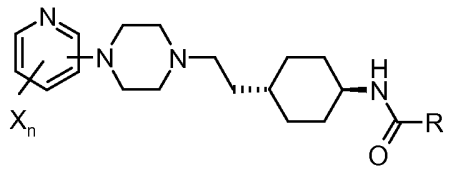
n is 1 or 2;

R is C_{1-6}-alkyl, wherein C_{1-6}-alkyl is optionally substituted by -$CONH_2$ or one 3 to 6 membered monocyclic cycloalkyl;

C_{1-6}-alkoxy;

as well as pharmaceutically acceptable salts thereof.

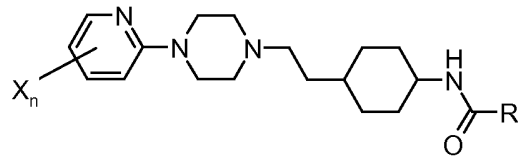
In a preferred embodiment the present invention relates e to a compound of formula I’,



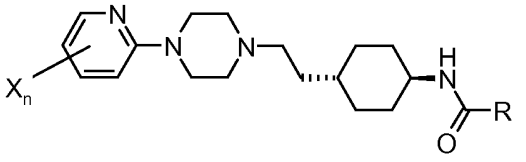
(I’)

wherein R, X and n are defined as given above.

Preference is given to compounds of formulae Ia or Ia’:



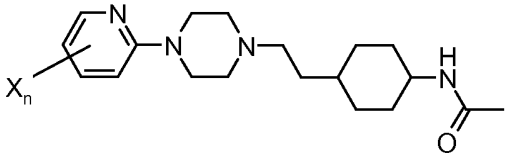
(Ia)



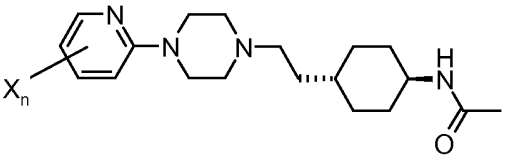
(Ia'),

wherein R, X and n are defined as given above.

Preference is given to compounds of formulae Ib or Ib':



(Ib)



(Ib')

wherein R, X and n are defined as given above.

Preference is given to compounds of formulae Ib or Ib', wherein X is independently of each other fluorine, chlorine, $-CF_3$ or $-OCH_3$; and n is 1 or 2.

Special preference is given to a compound of formula (I') selected from the group consisting of:

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-propionamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-2-cyclopropyl-acetamide;

N-(trans-4-{2-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(trans-4-{2-[4-(3,5-Dichloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(trans-4-{2-[4-(6-Trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-malonamide;

N-(trans-4-{2-[4-(3-Methoxy-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide; and

N-(trans-4-{2-[4-(2,3-Dichloro-pyridin-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is independently of each other halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl or C_{1-6}-alkoxy.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is halogen.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is fluorine.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is chlorine.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is C_{1-6}-alkyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is C_{1-6}-haloalkyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is $-CF_3$.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is C_{1-6}-alkoxy.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is $-OCH_3$.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein X is independently of each other chlorine, fluorine, $-CF_3$ or $-OCH_3$.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein n is 1 or 2.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein n is 1.

In one embodiment, the invention relates to compounds of formulae I, I', Ia, Ia', Ib, Ib' wherein n is 2.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is

- C_{1-6}-alkyl, wherein C_{1-6}-alkyl is optionally substituted by $-CONH_2$, or 3 to 6 membered monocyclic cycloalkyl; or
- C_{1-6}-alkoxy.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is methyl, methyl substituted by $-CONH_2$, methyl substituted by cyclopropyl, ethyl or ethyl substituted by $-OCH_3$.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is C_{1-6}-alkyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is methyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is ethyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is C_{1-6}-alkyl substituted by $-CONH_2$..

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is methyl substituted by $-CONH_2$..

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is C_{1-6}-alkyl substituted by 3 to 6 membered monocyclic cycloalkyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is methyl substituted by cyclopropyl.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is C_{1-6}-alkoxy.

In one embodiment, the invention relates to compounds of formulae I, I', Ia or Ia' wherein R is ethyl-OCH_3.

A further aspect of the present invention relates to a medicament containing the compounds of formulae I, I', Ia, Ia', Ib, Ib' and pharmaceutically acceptable excipients for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

A further aspect of the present invention relates to a medicament containing the compounds of formulae I, I, Ia, Ia', Ib, Ib' as well as its pharmaceutically acceptable salt for use in the treatment or prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

A further aspect of the present invention relates to a medicament containing the compounds of formulae I, I', Ia, Ia', Ib, Ib' as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

A further aspect of the present invention relates to pharmaceutical compositions containing the compounds of formulae I, I', Ia, Ia', Ib, Ib' for the treatment of schizophrenia, cognitive disorders and drug addiction.

A further aspect of the present invention relates to the process for the manufacture of compounds of formulae I, I', Ia, Ia', Ib, Ib' as defined above.

A further aspect of the present invention relates to a compound of formulae I, I', Ia, Ia', Ib, Ib' for use as therapeutically active substance.

A further aspect of the present invention relates to a compound of formulae I, I', Ia, Ia', Ib, Ib' for the treatment or prevention of diseases related to the D3 receptor.

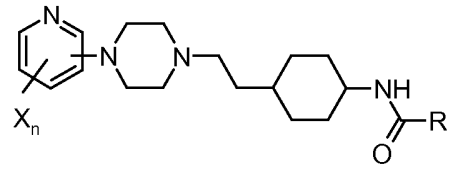
A further aspect of the present invention relates to a method for the therapeutic and/or prophylactic treatment of a disorder or condition mediated by the D3 receptor binding site, or that can be treated via modulation of the D3 receptor binding site,

particularly for the therapeutic and/or prophylactic treatment of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder, which method comprises administering a compound formulae I, I', Ia, Ia', Ib, Ib' to a human being or animal.

The preparation of compounds of formula I of the present invention may be carried out in sequential or convergent synthetic routes. Syntheses of the invention are shown in the following schemes. The skills required for carrying out the reaction and purification of the resulting products are known to those skilled in the art. The substituents and indices used in the following description of the processes have the significance given herein before unless indicated to the contrary.

In more detail, the compounds of formula I can be manufactured by the methods given below, by the methods given in the examples or by analogous methods. Appropriate reaction conditions for the individual reaction steps are known to a person skilled in the art. Starting materials are either commercially available or can be prepared by methods analogous to the methods given below, by methods described in references cited in the description or in the examples, or by methods known in the art.

A preferred embodiment of the process for preparing a compound of formula I,

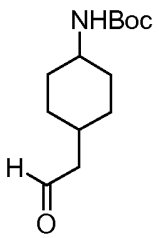


(I)

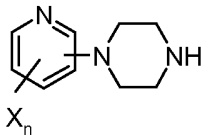
wherein R, X and n have meanings as given above,

comprises one of the following steps:

a) reductive amination of aldehyde of formula (I-1) with piperazine derivative of formula (I-2) in the presence of a reducing agent, and

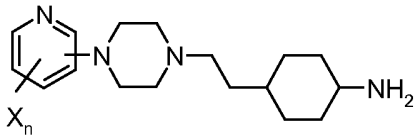


(I-1)



(I-2)

removing the protecting group Boc under acidic conditions to yield amine intermediate of formula (I-3)



(I-3)

b) coupling of amine intermediate of formula (I-3) with a carboxylic acid R-COOH or acid chloride R-COCl to yield compound of formula I.

The ability of the compounds to bind to the D_3 receptors was determined using radioligand binding to cloned receptors selectively expressed in HEK-293 EBNA cells.

Biological Data

Membrane preparation for human D_3 receptors

HEK-293 EBNA cells were transiently transfected with expression plasmids encoding for the human D_3 dopamine receptor. The cells were harvested 48 h post-transfection, washed three times with cold PBS and stored at -80°C prior to use. The pellet was suspended in cold 50 mM Tris-HCl buffer containing 10 mM EDTA (pH 7.4) and homogenized with a Polytron (Kinematica AG, Basel, Switzerland) for 20-30 sec at 12.000 rpm. After centrifugation at 48.000 X g for 30 min at 4°C, the pellet was resuspended in cold 10 mM Tris-HCl buffer containing 0.1 mM EDTA (pH 7.4), homogenized, and centrifuged as above. This pellet was further resuspended in a smaller volume of ice cold 10 mM Tris-HCl buffer containing 0.1 mM EDTA (pH 7.4) and homogenized with a Polytron for 20-30 sec at 12.000 rpm. The protein content of this homogenate was determined with the Bio-Rad (Bradford) Protein Assay (Biorad Laboratories GmbH, München, Germany) according to the instructions of the manufacturer using gamma globulin as the standard.

This homogenate was stored at -80°C in aliquots and thawed immediately prior to use.

Radioligand binding assay conditions

Aliquots of membrane preparations were thawed at RT, resuspended in assay buffer (50 mM Tris-HCl, 120 mM NaCl, 5 mM $MgCl_2$, 1 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, pH=7.4), homogenized with a Polytron for 20-30 sec at 12.000 rpm and adjusted to a final concentration of approximately 7.5 µg protein / well.

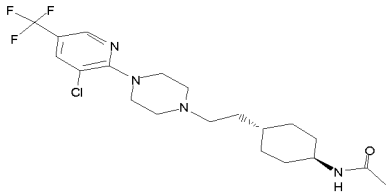
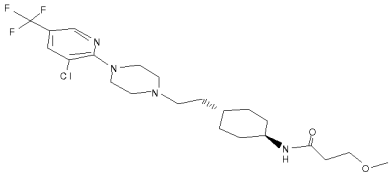
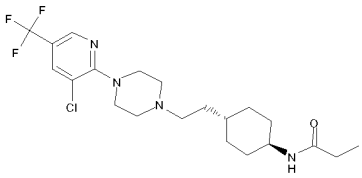
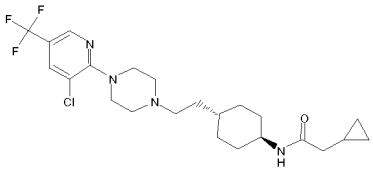
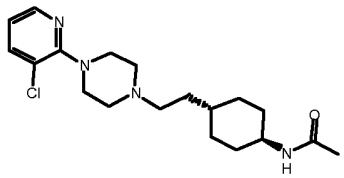
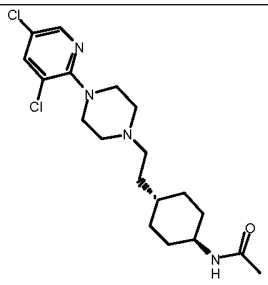
The binding affinity (Ki) of the compounds was determined using radioligand binding. Membranes were incubated in a total volume of 200 µl with a fixed concentration of radioligand (final concentration approximately 0.5 nM [^{3}H]-spiperone) and ten concentrations of test compound in ranging between 10 µM –0.1 nM for 1 h at RT. At the end of the incubation, the reaction mixtures were filtered on to unifilter 96-well white microplates with bonded GF/C filters (Packard BioScience, Zürich, Switzerland; preincubated for 1 h in 0.1% polyethylenimine (PEI) in assay buffer) with a Filtermate 196 harvester (Packard BioScience) and washed 3 times with cold assay buffer. The nonspecific binding was determined with equally composed reaction mixtures in the presence of 10 µM unlabelled spiperone. Per well 45 µl of Microscint 40 (Perkin Elmer, Schwerzenbach, Switzerland) was added, plates for sealed, shaken for 20 min and counted for 3 min on a Topcount Microplate Scintillation Counter (Canberra Packard SA, Zürich, Switzerland) with quenching correction.

Data calculation

The CPM value for each duplicate of a concentration of competing compound was averaged (y1), then the % specific binding was calculated according to the equation (((y1 - non-specific)/(total binding-non-specific))x100). Graphs were plotted with the % specific binding using XLfit, a curve fitting program that iteratively plots the data using Levenburg Marquardt algorithm. The single site competition analysis equation used was $y = A + ((B-A)/(1+((x/C)^D)))$, where y is the % specific binding, A is the minimum y, B is the maximum y, C is the IC_{50}, x is the $\log_{10}$ of the concentration of the competing compound and D is the slope of the curve (the Hill Coefficient). From these curves the IC_{50} (inhibition concentration at which 50% specific binding of the radioligand was displaced) and Hill coefficient were determined. The affinity constant (Ki) was calculated using the Cheng-Prusoff equation $Ki = (IC_{50}/1+([L]/Kd)$, where [L] is the concentration of radioligand and Kd is the dissociation constant of the radioligand at the receptor as determined by the saturation isotherm.

The compounds of the present invention are potent modulators of the dopamine D_3 receptors as this is shown with the activity table hereinafter which gives the Ki values in µM for the dopamine D_3 receptors for some examples of the compounds of the present invention:

Ex.	Compound	Name	Ki dopamine D3 receptor: Human (D3)

Ex.	Compound	Name	Ki dopamine D3 receptor: Human (D3)
1		N-(trans-4-{2-[4-(3,5-Dichloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.00964
2		N-(trans-4-{2-[4-(6-Trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.005658
3		N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-malonamide	0.016784
4		N-(trans-4-{2-[4-(3-Methoxy-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.010146
5		N-(trans-4-{2-[4-(2,3-Dichloro-pyridin-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.001702
6		N-(trans-4-{2-[4-(3,5-Dichloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.00964

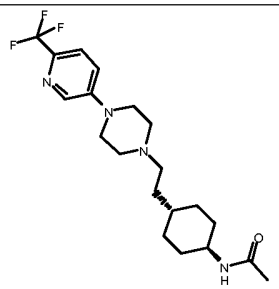
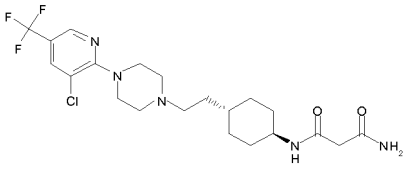
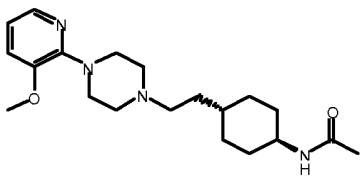
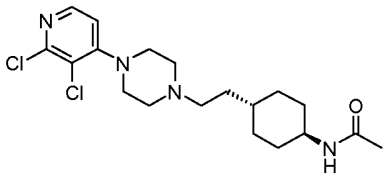
Ex.	Compound	Name	Ki dopamine D3 receptor: Human (D3)
7		N-(trans-4-{2-[4-(6-Trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.005658
8		N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-malonamide	0.016784
9		N-(trans-4-{2-[4-(3-Methoxy-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.010146
10		N-(trans-4-{2-[4-(2,3-Dichloro-pyridin-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide	0.001702

Table 1: acticity table: human Ki values of selected examples

The compounds of formula I and pharmaceutically acceptable salts thereof can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. However, the administration can also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and pharmaceutically acceptable salts thereof can be processed with pharmaceutically inert, inorganic or organic carriers for the production of pharmaceutical preparations. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts and the like can be used, for example, as such as carriers for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carriers for soft gelatine capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like; depending on the nature of the active substance no carriers are, however, usually required in the case of soft gelatine capsules.

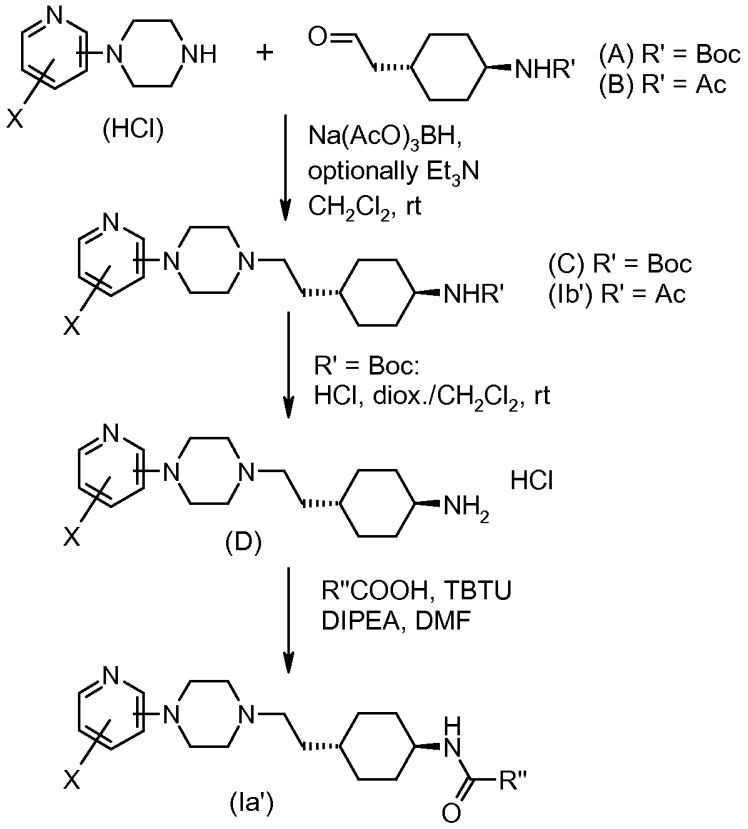
Suitable carriers for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar, glucose and the like. Adjuvants, such as alcohols, polyols, glycerol, vegetable oils and the like, can be used for aqueous injection solutions of water-soluble salts of compounds of formula I, but as a rule are not necessary. Suitable carriers for suppositories are, for example, natural or hardened oils, waxes, fats, semi-liquid or liquid polyols and the like.

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

As mentioned earlier, medicaments containing a compound of formula I or pharmaceutically acceptable salts thereof and a therapeutically inert excipient are also an object of the present invention, as is a process for the production of such medicaments which comprises bringing one or more compounds of formula I or pharmaceutically acceptable salts thereof and, if desired, one or more other therapeutically valuable substances into a galenical dosage form together with one or more therapeutically inert carriers.

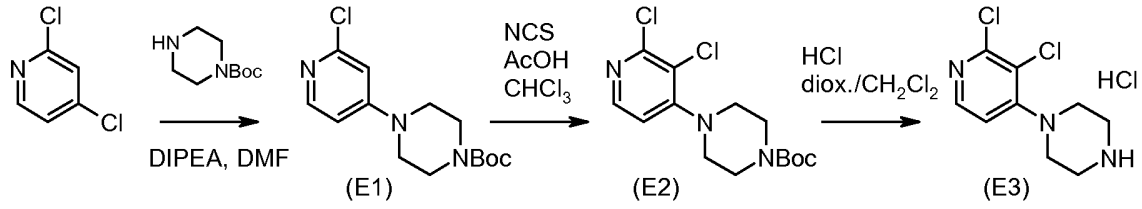
The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, the effective dosage for oral or parenteral administration is between 0.01-20 mg/kg/day, with a dosage of 0.1-10 mg/ kg/day being preferred for all of the indications described. The daily dosage for an adult human being weighing 70 kg accordingly lies between 0.7-1400 mg per day, preferably between 7 and 700 mg per day.

Synthesis



Scheme 1: General synthesis route for compounds Ia'

The starting materials are commercially available or the synthesis is described in the literature. Compound (E3) can be prepared as shown hereinafter in Scheme 2.



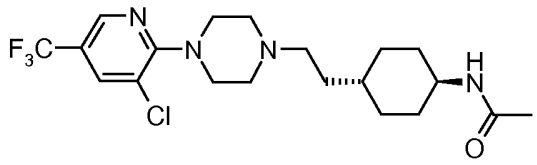
Scheme 2: General synthesis route to intermediate E3

Experimental Part

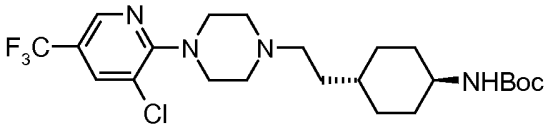
The following examples are provided to further elucidate the invention.

Example 1

N-(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide

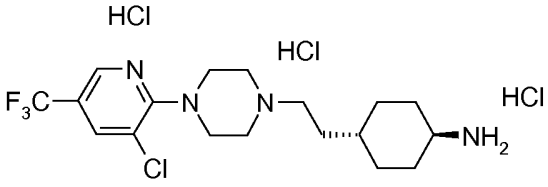


Step 1: (*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester (Intermediate C)



1-(2,3-Dichlorophenyl)-piperazine hydrochloride (1.g, 3.8 mmol) was dissolved in CH_2Cl_2) and [*trans*-4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (Intermediate A, 908 mg, 3.8 mmol) was added. After 3 h $Na(AcO)_3BH$ (1.44 g, 6.8 mmol) was added and stirring continued over night at 25 °C. Sat. aq. $NaHCO_3$ was added and the product was extracted with 3 portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and the solvent was evaporated. Flash chromatography (50 g SiO_2; Hept:EtOAc 80:20 -> 0:100) afforded 1.67 g (90%) of pure title compound as a white solid. *m/z*: 391.0 ($[M+H]^+$).

Step 2: *trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexylamine trihydrochloride (Intermediate D)



(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-carbamic acid tert-butyl ester (1.67 g, 3.4 mmol) was dissolved in CH_2Cl_2 (15 ml). 4 N HCl in dioxane (17 ml, 68 mmol) was slowly added and the resulting mixture was stirred over night at 25 °C. $^iPr_2O$ (20 ml) was added and the solid product was collected by filtration and it was washed with more $^iPr_2O$ (20 ml).

Drying at 50 °C for 1 h on the high vacuum afforded 1.46 g (85%) of the title compound as a white solid. *m/z*: 391.2 ($[M+H]^+$).

Step 3: N-(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide

A solution of *trans*-4-{2-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexylamine trihydrochloride_(150 mg, 0.3 mmol), acetic acid (25 mg, 0.42 mmol), $^{i}Pr_2NEt$ (0.18 ml, 1.0 mmol) and TBTU (135 mg, 0.42 mmol) in DMF was stirred 2 h at 25 °C. Sat. aq. $NaHCO_3$ was added and the product was extracted with 3 portions of CH_2Cl_2. The organic phases were combined and passed through a column (20 g SiO_2; EtOAc/MeOH 100:0 -> 80:20) to yield 84 mg (63 %) of title compound as a white solid. *m/z*: 433.2 ($[M+H]^+$).

Examples 2-4

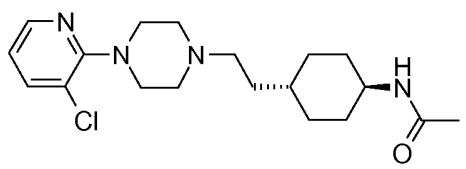
Examples 2-4 were prepared in analogy to example 1 starting from *trans*-4-{2-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexylamine trihydrochloride (Intermediate D) and an appropriate carboxylic acid.

Ex.	Compound	Carboxylic acid	*m/z* ($[M+H]^+$)
2	N-(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide	from 3-methoxy-propionicacid	477.0
3	N-(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-propionamide	from propionic acid	447.3
4	N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-2-cyclopropyl-acetamide	from cyclopropylacetic acid	473.2

Table 2: examples 2-4

Example 5

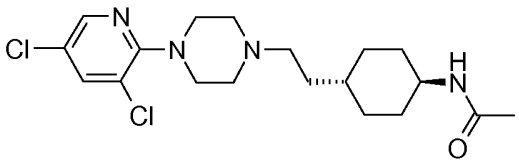
N-(*trans*-4-{2-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide



A solution in CH_2Cl_2 (5 ml) of 1-(3-chloro-pyridin-2-yl)-piperazine hydrochloride (50 mg, 0.21 mmol, *J. Med. Chem.* **2005**, 48(6), 1857-1872), N-[*trans*-4-(2-oxo-ethyl)-cyclohexyl]-acetamide (Intermediate B, 47 mg, 0.26 mmol) Et_3N (26 mg, 0.26 mmol) and $Na(AcO)_3BH$ (81 mg, 0.38 mmol) was stirred 3 h at 25 °C. Sat. aq. $NaHCO_3$ was added and the product was extracted with CH_2Cl_2 (2x20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated. Flash chromatography (10 g SiO_2; CH_2Cl_2:MeOH 100:0 -> 85:15) afforded 42 mg (54%) of the title compound as a white solid. *m/z*: 365.3 ($[M+H]^+$).

Example 6

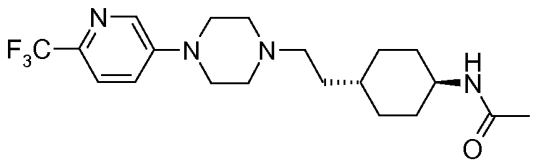
N-(*trans*-4-{2-[4-(3,5-Dichloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide



The title compound was prepared in analogy to Example 5 starting from 1-(3,5-dichloro-pyridin-2-yl)-piperazine. No Et_3N was used for this reaction. White solid. *m/z*: 399.2 ($[M+H]^+$).

Example 7

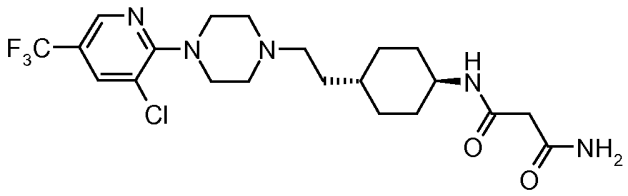
N-(*trans*-4-{2-[4-(6-Trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide



The title compound was prepared in analogy to Example 5 starting from 1-(6-trifluoromethyl-pyridin-3-yl)-piperazine (WO2005014563(A1)). No Et_3N was used for this reaction. White solid. *m/z*: 399.2 ($[M+H]^+$).

Example 8

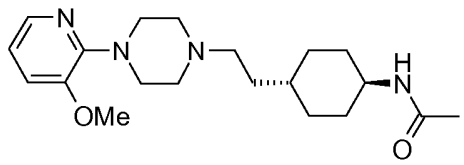
N-(*trans*-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-malonamide



Methyl malonate monoamide (42 mg, 0.36 mmol) was dissolved in CH_2Cl_2 (2 ml) and potassiumtrimethylsilanolate (66 mg, 0.51 mmol) was added. The reaction mixture was stirred 3 h at 25 °C, then the solvent was evaporated. The residue was dissolved in dioxane (5 ml) and *trans*-4-{2-[4-(3-chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexylamine trihydrochloride (100 mg, 0.20 mmol), $^{i}Pr_2NEt$ (0.17 ml, 1.0) and TBTU (99 mg, 0.31 mmol) were added. After stirring 2 h at 25 °C the solvent was evaporated, sat. aq. $NaHCO_3$ was added and the product was extracted with 2 portions of CH_2Cl_2. The organic phases were combined, dried (Na_2SO_4) and the solvent evaporated. Flash chromatography (20 g SiO_2; CH_2Cl_2/MeOH 100:0 -> 80:20) yielded 17 mg (18 %) of the title compound as a white solid. *m/z*: 476.2 ($[M+H]^+$).

Example 9

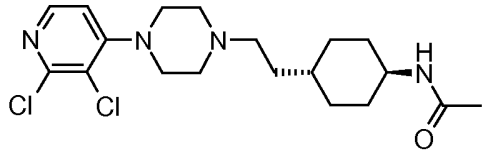
N-(*trans*-4-{2-[4-(3-Methoxy-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide



The title compound was prepared in analogy to Example 5 from 1-(3-methoxy-pyridin-2-yl)-piperazin dihydrochloride. Off-white solid. *m/z*: 361.2 ($[M+H]^+$).

Example 10

N-(*trans*-4-{2-[4-(2,3-Dichloro-pyridin-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide

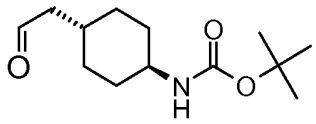


The title compound was prepared in analogy to Example 5 from 1-(2,3-dichloro-pyridin-4-yl)-piperazine hydrochloride (Intermediate E3). Off-white solid. *m/z*: 399.2 ($[M+H]^+$).

Synthesis of intermediates

Intermediate A

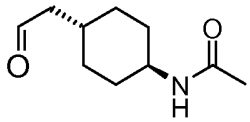
[*trans*-4-(2-oxo-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester



The title compound was prepared as described in WO2007/093540.

Intermediate B

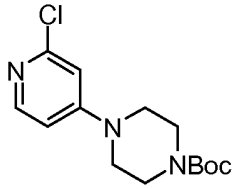
N-[*trans*-4-(2-oxo-ethyl)-cyclohexyl]-acetamide



The title compound was prepared as described in WO2007/093540.

Intermediate E1

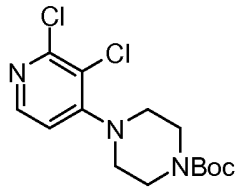
4-(2-Chloro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester



2,4-Dichloropyridine (1.00 g, 6.7 mmol) and piperazine-1-carboxylic acid *tert*-butyl ester (1.64 g, 8.8 mmol) were suspended in DMF (10 ml) and $^{i}Pr_2NEt$ (2.30 ml, 14 mmol) was added. After stirring over night at 120 °C the reaction mixture was diluted with H_2O and extracted with EtOAc. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. The residue was purified by flash chromatography (SiO_2 50 g, *n*Hept/EtOAc 5 to 100%) to yield 1.02 g (51 %) of product and 450 mg (22%) of the regioisomer as byproduct. Light yellow solid. *m/z*: 298.4 ($[M+H]^+$).

Intermediate E2

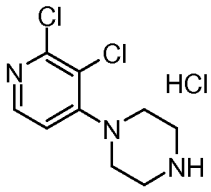
4-(2,3-Dichloro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester



A stirred solution of 4-(2-chloro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (900 mg, 3.0 mmol) in $CHCl_3$ (20 ml) was treated with AcOH (4 ml) and N-chlorosuccinimide (605 mg, 4.5 mmol). The reaction mixture was stirred 6 h under reflux, the it was poured on ice and the pH was raised to 7 by addition of solid $NaHCO_3$. The product was extracted with 2 portions of CH_2Cl_2. After drying (Na_2SO_4) and evaporation of the solvent, the residue was purified by flash chromatography (SiO_2 50 g, *n*Hept/EtOAc 5 to 100%) to yield 400 mg (40 %) of title compound as white solid. *m/z*: 332.2/334.3 ($[M+H]^+$).

Intermediate E3

1-(2,3-Dichloro-pyridin-4-yl)-piperazine hydrochloride



4-(2,3-Dichloro-pyridin-4-yl)-piperazine-1-carboxylic acid *tert*-butyl ester (380 mg, 1.1 mmol) was dissolved in CH_2Cl_2 (5 ml). 4 N HCl in dioxane (5.72ml, 23 mmol) was added and the resulting mixture was stirred 5 h at 25 °C. $^iPr_2O$ (10 ml) was added and the solid product was collected by filtration. Drying on the high vacuum finally yielded 350 mg (quant.) of the title compound as white solid. *m/z*: 232.2/234.1 ($[M+H]^+$).

Pharmaceutical Preparations

Example A

Film coated tablets containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per tablet	
Kernel:		
Compound of formula I	10.0 mg	200.0 mg
Microcrystalline cellulose	23.5 mg	43.5 mg

Ingredients	Per tablet	
Lactose hydrous	60.0 mg	70.0 mg
Povidone K30	12.5 mg	15.0 mg
Sodium starch glycolate	12.5 mg	17.0 mg
Magnesium stearate	1.5 mg	4.5 mg
(Kernel Weight)	120.0 mg	350.0 mg
Film Coat:		
Hydroxypropyl methyl cellulose	3.5 mg	7.0 mg
Polyethylene glycol 6000	0.8 mg	1.6 mg
Talc	1.3 mg	2.6 mg
Iron oxide (yellow)	0.8 mg	1.6 mg
Titanium dioxide	0.8 mg	1.6 mg

Table 3: Example of film coated tablets

The active ingredient is sieved and mixed with microcrystalline cellulose and the mixture is granulated with a solution of polyvinylpyrrolidone in water. The granulate is mixed with sodium starch glycolate and magnesiumstearate and compressed to yield kernels of 120 or 350 mg respectively. The kernels are lacquered with an aqueous solution / suspension of the above mentioned film coat.

Example B

Capsules containing the following ingredients can be manufactured in a conventional manner:

Ingredients	Per capsule
Compound of formula I	25.0 mg
Lactose	150.0 mg
Maize starch	20.0 mg
Talc	5.0 mg

Table 4: Example of capsules

The components are sieved and mixed and filled into capsules of size 2 or other suitable sizes..

Example C

Injection solutions can have the following composition:

Compound of formula I	3.0 mg
Gelatine	150.0 mg

Phenol	4.7 mg
Sodium carbonate	to obtain a final pH of 7
Water for injection solutions	ad 1.0 ml

Table 5: Example of injection solutions

Example D

Soft gelatin capsules containing the following ingredients can be manufactured in a conventional manner:

Capsule contents	
Compound of formula I	5.0 mg
Yellow wax	8.0 mg
Hydrogenated Soya bean oil	8.0 mg
Partially hydrogenated plant oils	34.0 mg
Soya bean oil	110.0 mg
Weight of capsule contents	165.0 mg
Gelatin capsule	
Gelatin	75.0 mg
Glycerol 85 %	32.0 mg
Karion 83	8.0 mg (dry matter)
Titanium dioxide	0.4 mg
Iron oxide yellow	1.1 mg

Table 6: Example of soft gelatin capsules

The active ingredient is dissolved in a warm melting of the other ingredients and the mixture is filled into soft gelatin capsules of appropriate size. The filled soft gelatin capsules are treated according to the usual procedures.

Example E

Sachets containing the following ingredients can be manufactured in a conventional manner:

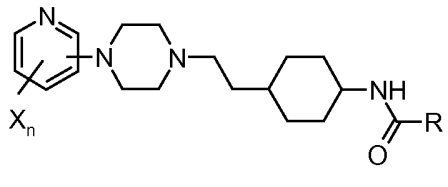
Compound of formula I	50.0 mg
Lactose, fine powder	1015.0 mg
Microcrystalline cellulose (AVICEL PH 102)	1400.0 mg
Sodium carboxymethyl cellulose	14.0 mg
Polyvinylpyrrolidone K 30	10.0 mg
Magnesium stearate	10.0 mg
Flavoring additives	1.0 mg

Table 7: Example of sachets

The active ingredient is mixed with lactose, microcrystalline cellulose and sodium carboxymethyl cellulose and granulated with a mixture of polyvinylpyrrolidone in water. The granulate is mixed with magnesium stearate and the flavoring additives and filled into sachets.

Claims

1. A compound of formula I:



(I)

wherein:

X is independently of each other halogen, C_{1-6}-alkyl, C_{1-6}-haloalkyl or C_{1-6}-alkoxy;

n is 1 or 2;

R is C_{1-6}-alkyl, wherein C_{1-6}-alkyl is optionally substituted by $-CONH_2$ or one 3 to 6 membered monocyclic cycloalkyl;

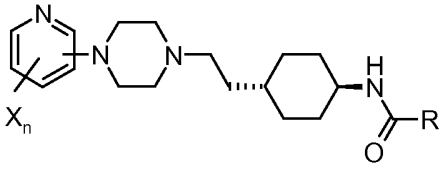
C_{1-6}-alkoxy;

as well as pharmaceutically acceptable salts thereof.

2. A compound of formula I, wherein X is independently of each other chlorine, fluorine, $-CF_3$ or $-OCH_3$.

3. A compound of formula I, wherein R is methyl, methyl substituted by $-CONH_2$, methyl substituted by cyclopropyl, ethyl or ethyl-OCH_3.

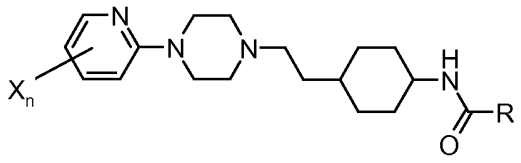
4. A compound of formula I' according to any of claims 1 - 3:

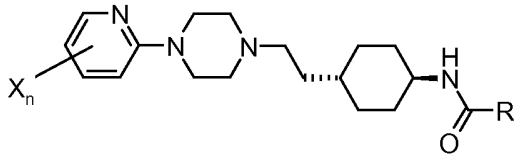


(I')

wherein R, X and n are defined as in claim 1.

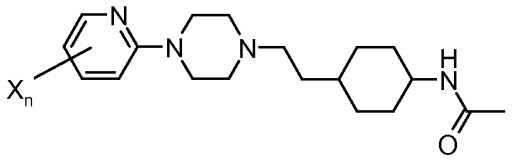
5. A compound of formulae Ia or Ia' according to any of claims 1 - 3:

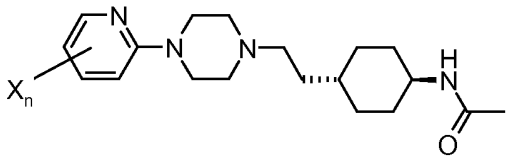

(Ia),


(Ia')

wherein R, X and n are defined as in claim 1.

6. A compound of formulae Ib or Ib' according to any of claims 1 - 3:


(Ib),


(Ib')

wherein:

X is independently of each other fluorine, chlorine, $-CF_3$ or $-OCH_3$; and

n is 1 or 2.

7. A compound of formula Ib' according to claim 6 selected from the group consisting of:

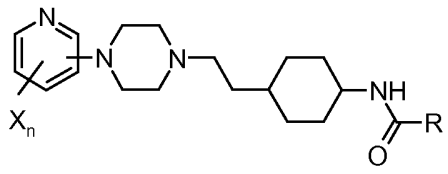
N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-3-methoxy-propionamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-propionamide;

N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-2-cyclopropyl-acetamide;
N-(trans-4-{2-[4-(3-Chloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-(trans-4-{2-[4-(3,5-Dichloro-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-(trans-4-{2-[4-(6-Trifluoromethyl-pyridin-3-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide;
N-(trans-4-{2-[4-(3-Chloro-5-trifluoromethyl-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-malonamide;
N-(trans-4-{2-[4-(3-Methoxy-pyridin-2-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide; and
N-(trans-4-{2-[4-(2,3-Dichloro-pyridin-4-yl)-piperazin-1-yl]-ethyl}-cyclohexyl)-acetamide.

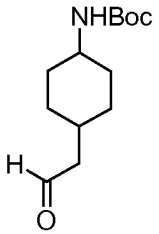
8. A process for preparing a compound of formula I



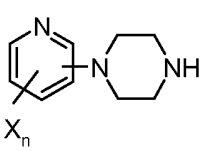
(I)

wherein R, X and n have meanings as given in claim 1,
comprising one of the following steps:

a) reductive amination of aldehyde of formula (I-1) with piperazine derivative of formula (I-2) in the presence of a reducing agent, and

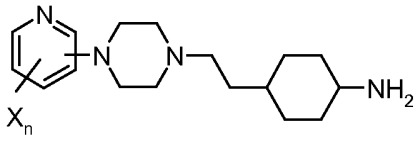


(I-1)



(I-2)

removing the protecting group Boc under acidic conditions to yield amine intermediate of formula (I-3)



(I-3)

b) coupling of amine intermediate of formula (I-3) with a carboxylic acid R-COOH or acid chloride R-COCl to yield compound of formula I.

9. A compound according to any of claims 1-7 for use as therapeutically active substance.

10. A compound according to any of claims 1-7 for the treatment or prevention of diseases related to the D3 receptor.

11. A medicament containing one or more compounds as claimed in any one of claims 1 to 7 and pharmaceutically acceptable excipients for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

12. A compound in accordance with any one of claims 1 to 7 as well as its pharmaceutically acceptable salt for use in the treatment or prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

13. The use of a compound in accordance with any one of claims 1 to 7 as well as its pharmaceutically acceptable salt for the manufacture of medicaments for the treatment and/or the prevention of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic

depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder.

14. A method for the therapeutic and/or prophylactic treatment of a disorder or condition mediated by the D3 receptor binding site, or that can be treated via modulation of the D3 receptor binding site, particularly for the therapeutic and/or prophylactic treatment of cognitive disorders, drug addiction, depression, anxiety, drug dependence, dementias, memory impairment, psychotic disorders comprising schizophrenia, schizoaffective disorders, bipolar disease, mania, psychotic depression, psychoses comprising paranoia and delusions, attention-deficit hyperactivity disorder, addiction and obsessive compulsive disorder, which method comprises administering a compound according to any of claims 1-7 to a human being or animal.

15. The invention as hereinbefore described.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/061911

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D213/74 A61K31/444 A61P25/30

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 A61K A61P

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, 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.
X	US 5 047 406 A (CAPRATHE BRADLEY W [US] ET AL) 10 September 1991 (1991-09-10) Abstract; column 3, line 11 to column 4, line 52; column 4, lines 53-66; claims; examples e.g. column 34, example 58.	1-15
X	WO 2007/148208 A (BIOPROJET SOC CIV [FR]; CAPET MARC [FR]; DANVY DENIS [FR]; LEVOIN NICO) 27 December 2007 (2007-12-27) Abstract; claims; examples e.g. page 113, example 65.	1-15

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

☒ See patent family annex.

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"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

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Date of the actual completion of the international search	Date of mailing of the international search report
15 December 2009	04/01/2010

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, Fax: (+31-70) 340-3016	Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/061911

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