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

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

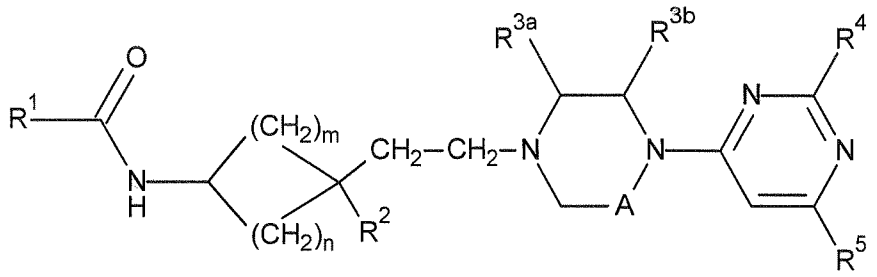
vi. no or only low blockade of the hERG channel: compounds which block the hERG channel may cause a prolongation of the QT interval and thus lead to serious disturbances of cardiac rhythm (for example so-called "torsade de pointes"). The potential of compounds to block the hERG channel can be determined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

vii. high free fraction in brain, i.e. the fraction of the compound bound to proteins should be low;

viii. low lipophilicity.

Brief Description of the Invention

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



(I)

where

m is 1 or 2,

n is 1 or 2,

A is selected from the group consisting of CH_2, CH_2CH_2, $CHFCH_2$ and CF_2CH_2,

R^1 is hydrogen or C_1-C_3-alkyl,

R^2 is selected from the group consisting of hydrogen and fluorine,

R^{3a} is selected from the group consisting of hydrogen and methyl,

R^{3b} is selected from the group consisting of hydrogen and methyl,

R^4 is branched C_4-C_6 alkyl or branched fluorinated C_4-C_6 alkyl, and

R^5 is an oxygen containing radical selected from the group consisting of C_1-C_2-alkoxy-C_1-C_4-alkyl, fluorinated C_1-C_2-alkoxy-C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, fluorinated hydroxy-C_1-C_4-alkyl, oxetanyl, fluorinated oxetanyl, oxolanyl, fluorinated oxolanyl,
C_3-C_5 cycloalkyl, fluorinated C_3-C_5 cycloalkyl, where the cycloalkyl moiety in the last two mentioned radicals carries 1 or 2 radicals selected from hydroxyl, C_1-C_2-alkoxy and fluorinated C_1-C_2-alkoxy and may additionally carry 1 or 2 radicals selected from C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl, C_3-C_5 cycloalkoxy-C_1-C_4-alkyl and fluorinated C_3-C_5 cycloalkoxy-C_1-C_4-alkyl, where the cycloalkoxy moiety in the last two mentioned radicals may carry 1 or 2 radicals selected from hydroxyl, C_1-C_2-alkoxy, fluorinated C_1-C_2-alkoxy, C_1-C_2-alkyl and fluorinated C_1-C_2-alkyl,

the N-oxides, the prodrugs and the pharmaceutically acceptable salts of these compounds.

In one aspect, there is provided a compound as disclosed herein for the use as a medicament.

In one aspect, there is provided a pharmaceutical composition comprising at least one compound as disclosed herein, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

In one aspect, there is provided a use of at least one compound as disclosed herein in the manufacture of a medicament for treating a medical disorder or condition susceptible to treatment with a dopamine D_3 receptor ligand.

The present ~~invention~~ disclosure is thus based on the object of providing compounds which selectively bind to the dopamine D3 receptor at low concentrations.

The compounds are further intended to display at least one of the properties i. to viii. mentioned above, in particular high selectivity with regard to dopamine D3 receptor

The present ~~invention~~ disclosure therefore relates to the compounds of the general formula I, the N-oxides and the pharmaceutically acceptable salts of the compounds of formula I, the prodrugs of the compounds of formula I and the pharmaceutically acceptable salts of said N-oxides and prodrugs of the compounds of formula I. The present ~~invention~~ disclosure in particular relates to the compounds of the general formula I and to their pharmaceutically acceptable salts.

The present ~~invention~~ disclosure therefore relates to the compounds of the general formula I, the N-oxides and the pharmaceutically acceptable salts of the compounds of formula I, the prodrugs of the compounds of formula I and the pharmaceutically acceptable salts of said N-oxides and prodrugs of the compounds of formula I for the use as a medicament.

The present ~~invention~~ disclosure also relates to the compounds of the general formula I, the N-oxides, the pharmaceutically acceptable salts of the compounds of formula I, the prodrugs of the compounds of formula I and the pharmaceutically acceptable salts of said N-oxides or prodrugs of the compounds of formula I for the use in the treatment of a medical disorder susceptible to treatment with a dopamine D3 receptor ligand, in particular from a disorder selected from neurological and psychiatric disorders which can be treated by modulation of the dopamine D_3 receptor, in particular by at least partially antagonizing the dopamine D3 receptor.

The compounds of the formula I, their pharmaceutically acceptable salts, their N-oxides and their prodrugs, and the pharmaceutically acceptable salts of said N-oxides or prodrugs selectively bind to the dopamine D_3 receptor even at low concentrations, and are in particular at least partial antagonists of the D3 receptor.

They are additionally distinguished by a high selectivity in relation to binding to the dopamine D3 receptor vis-à-vis binding to dopamine D2 receptor or adrenergic or serotonergic receptors such as alpha-1, alpha-2, 5HT1 and 5HT2. The compounds of the invention may additionally have one or more of the above mentioned properties ii. to viii.

The compounds of the formula I, their pharmaceutically acceptable salts, their N-oxides, their prodrugs, and the pharmaceutically acceptable salts of said N-oxides, and prodrugs are therefore particularly suitable for treating disorders and conditions in creatures, especially human creatures, which can be treated or controlled by modulation of the dopamine D3 receptor.

The diseases which respond to the influence of dopamine D3 receptor ligands or agonists include disorders and diseases of the central nervous system, in particular affective disturbances, neurotic disturbances, stress disturbances and somatoform disturbances and psychoses, and especially Parkinson's disease, schizophrenia, major depressive disorder (depression), motivation disturbances, bipolar disorder, disorders related to substance abuse (also termed drug abuse), eating disorders, cognitive dysfunction, in particular cognitive dysfunction associated with schizophrenia or dementia, anxiety, attention deficit disorder with or without hyperactivity and personality disorder. In addition, D3-mediated diseases may include disturbances of kidney function, i.e. renal function disorders, in particular kidney function disturbances which are caused by diabetes such as diabetes mellitus, also termed as diabetic nephropathy. It may also be possible to ameliorate pain by administering dopamine D3 receptor ligands.

The ~~invention~~ disclosure therefore also relates to the use of the compounds of the formula I, their N-oxides, prodrugs and their pharmaceutically acceptable salts and the pharmaceutically acceptable salts of said N-oxides or prodrugs, for the manufacture of a medicament, in particular of a medicament which is suitable for the treatment of a disorder or a condition which can be treated by modulation of the dopamine D3 receptor..

The ~~invention~~ disclosure further relates to a medicament, in particular a medicament which is suitable for the treatment of a disorder or a condition which can be treated by modulation of the dopamine D3 receptor and in particular by at least partially antagonizing the dopamine D3 receptor. The medicament comprises at least one compound of the formula I, as described herein, or an N-oxide, or a prodrug of said compound I, or a pharmaceutically acceptable salt of the compound of the formula I or a pharmaceutically acceptable salt of the N-oxide, or the prodrug of compound of the formula I.

Detailed Description of the Invention

The terms "compound of the formula I" and "compounds I" are used as synonyms.

The term "prodrugs" means compounds which are metabolized in vivo to the compounds I of the invention. Typical examples of prodrugs are described in C.G. Wermuth (editor): The Practice of Medicinal Chemistry, Academic Press, San Diego,

trans-N-[4-[2-[4-[2-tert-butyl-6-(2-hydroxyethyl)pyrimidin-4-yl]piperazin-1-yl]ethyl]cyclohexyl]formamide

trans-N-[4-[2-[(2R)-4-[2-tert-butyl-6-(2-methoxyethyl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]cyclohexyl]formamide

trans-N-[4-[2-[(3S)-4-[2-tert-butyl-6-(2-hydroxyethyl)pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclohexyl]acetamide

trans-N-[4-[2-[(2R)-4-[2-tert-butyl-6-(2-hydroxyethyl)pyrimidin-4-yl]-2-methyl-piperazin-1-yl]ethyl]cyclohexyl]acetamide

trans-N-[4-[2-[4-(2-tert-butyl-6-tetrahydrofuran-3-yl-pyrimidin-4-yl)piperazin-1-yl]ethyl]cyclohexyl]formamide

N-[3-[2-[(3S)-4-[2-tert-butyl-6-(2-methoxyethyl)pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclobutyl]formamide

trans-N-[4-[2-[(3R)-4-[2-tert-butyl-6-(2-hydroxyethyl)pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclohexyl]acetamide

trans-N-[3-[2-[(3S)-4-[2-tert-butyl-6-(2-methoxyethyl)pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclobutyl]acetamide

cis-N-[3-[2-[(3S)-4-[2-tert-butyl-6-(2-methoxyethyl)pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclobutyl]acetamide

trans-N-[4-[2-[(3S)-4-[2-tert-butyl-6-[2-(difluoromethoxy)ethyl]pyrimidin-4-yl]-3-methyl-piperazin-1-yl]ethyl]cyclohexyl]acetamide

and the N-oxides, the prodrugs and the pharmaceutically acceptable salts of these compounds.

28. A compound of any of claims 1 to 27 for the use as a medicament.

29. A pharmaceutical composition comprising at least one compound as claimed in any of claims 1 to 27, optionally together with at least one physiologically acceptable carrier or auxiliary substance.

~~30. A method for treating a medical disorder or condition susceptible to treatment with a dopamine D_3 receptor ligand, said method comprising administering an effective~~

30. ~~amount~~ Use of at least one compound as claimed in any of claims 1 to 27 in the manufacture of a medicament for treating a medical disorder or condition susceptible to treatment with a dopamine D_3 receptor ligand~~to a subject in need thereof~~.

31. The ~~method~~ use of claim 30, wherein the medical disorder is a disorder or condition of the central nervous system.

32. The ~~method~~ use of claim 30, wherein the medical disorder is a disorder or condition selected from the group of Parkinson's disease, schizophrenia, bipolar disorder, depression, motivation disturbances, anxiety, cognitive dysfunction, pain, disorder associated with drug abuse, and eating disorders.

33. The ~~method~~ use of claim 30, wherein the medical disorder is renal function disorders, such as diabetic nephropathy.