circuit of the mammalian brain. The basal ganglia are a series of interconnected subcortical nuclei that integrate widespread cortical input with dopaminergic signaling to plan and execute relevant motor and cognitive patterns while suppressing unwanted or irrelevant patterns (Graybiel, A.M. *Curr. Biol.* **2000**, *10,* R509–R511 (2000).

Papaverine, a relatively specific PDE10A inhibitor, and PDE10A-knockout mice have been used to explore the physiology of this enzyme and the possible therapeutic utility of PDE10A inhibition. Inhibition of this enzyme pharmacologically or through gene disruption causes a reduction in activity and a reduced response to psychomotor stimulants. Inhibition also reduces the conditioned avoidance response, a behavioural response that is predictive of clinical antipsychotic activity (Siuciak, J.A.; et al., *Neuropharmacology* **2006**, *51* (2), 386-396; Siuciak, J.A.; et al., *Neuropharmacology* **2006**, *51* (2), 374-385).

In addition PDE10A inhibition bears the potential to improve the negative and cognitive symptoms associated to schizophrenia. Indeed papaverine have been shown to attenuate the deficits in the extra-dimensional shift learning induced in rats by sub-chronic treatment with PCP, an animal paradigm of NMDA receptor hypofunction (Rodefer, J,S., et al., *Eur. J. Neuroscience* **2005**, *2,*: 1070-1076).In addition increased social interaction in PDE10A2-deficient mice have been observed (Sano, H. *J. Neurochem.* **2008**, *105*, 546-556).

Diseases that can be treated with PDE10A inhibitors include~~, but are not limited to,~~ diseases thought to be mediated in part by dysfunction of the basal ganglia, of other parts of the central nervous system and of other PDE10A expressing tissues. In particular, diseases can be treated, where inhibition of PDE10A can have therapeutic effects.

These diseases include~~, but are not limited to,~~ certain psychotic disorders such as schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder or substance-induced psychotic disorder, anxiety disorders such as panic disorder, obsessive-compulsive disorder, acute stress disorder or generalized anxiety disorder, obsessive/compulsive disorders, drug addictions, movement disorders such as Parkinson's disease or restless leg syndrome, cognition deficiency disorders such as Alzheimer's disease or multi-infarct dementia, mood disorders such as depression or bipolar disorders, or

neuropsychiatric conditions such as psychosis, attention-deficit/hyperactivity disorder (ADHD) or related attentional disorders.

The compounds of the present invention are also suitable for the treatment of diabetes and related disorders such as obesity by regulating the cAMP signaling system.

PDE10A inhibitors might also be useful in preventing neurons from undergoing apoptosis by raising cAMP and cGMP levels and, thus, might possess anti-inflammatory properties. Neurodegenerative disorders treatable with PDE10A inhibitors include~~, but are not limited to,~~ as Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke or spinal cord injury.

The growth of cancer cells is inhibited by cAMP and cGMP. Thus by raising cAMP and cGMP, PDE10A inhibitors can also be used for the treatment of different solid tumors and hematological malignancies such as renal cell carcinoma or breast cancer.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

In this specification the term "lower" is used to mean a group consisting of one to seven, preferably of one to four carbon atom(s).

The term "halogen" refers to fluorine, chlorine, bromine and iodine, with fluorine, chlorine and bromine being preferred.

The term "alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent saturated aliphatic hydrocarbon radical of one to twenty carbon atoms, preferably one to sixteen carbon atoms, more preferably one to ten carbon atoms. Lower-alkyl groups as described below also are preferred alkyl groups.

The term "lower-alkyl", alone or in combination with other groups, refers to a branched or straight-chain monovalent alkyl radical of one to seven carbon atoms, preferably one to four

carbon atoms. This term is further exemplified by such radicals as methyl, ethyl, n-propyl, isopropyl, n-butyl, s-butyl, or t-butyl ~~and the like~~.

The term "cycloalkyl" refers to a monovalent carbocyclic radical of 3 to 10 carbon atoms, preferably 3 to 6 carbon atoms, such as cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

The term "fluoro-lower-alkyl" refers to lower-alkyl groups which are mono- or multiply substituted with fluorine. Examples of fluoro-lower-alkyl groups are e.g. CFH_2, CF_2H, CF_3, CF_3CH_2, $CF_3(CH_2)_2$, $(CF_3)_2CH$ and CF_2H-CF_2-.

The term "alkoxy" refers to the group R'-O-, wherein R' is an alkyl. The term "lower-alkoxy" refers to the group R'-O-, wherein R' is a lower-alkyl.

The term "fluoro-lower-alkoxy" refers to the group R''-O-, wherein R'' is fluoro-lower-alkyl. Examples of fluoro-lower-alkoxy groups are e.g. CFH_2-O, CF_2H-O, CF_3-O, CF_3CH_2-O, $CF_3(CH_2)_2$-O, $(CF_3)_2CH$-O, and CF_2H-CF_2-O.

The term "hydroxy-lower-alkyl" refers to a lower-alkyl group as defined above, which is substituted by 1 to 3 hydroxy groups. Examples of hydroxy-lower-alkyl groups are e.g. hydroxy-methyl, hydroxy-ethyl, hydroxy propyl, 3-hydroxy-propyl, 2-hydroxy-propyl, 3-hydroxy-prop-2-yl, 2,3-dihydroxy-propyl and 1,3-dihydroxy-prop-2-yl.

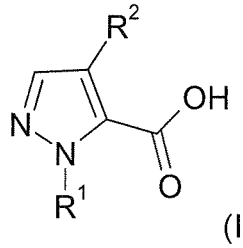
The term "hydroxy-lower-alkoxy" refers to a lower-alkoxy group as defined above, which is substituted by 1 to 3 hydroxy groups. Examples of hydroxy-lower-alkoxy groups are e.g. hydroxy-methoxy, hydroxy-ethoxy, hydroxy-propoxy, 3-hydroxy-propoxy, 2-hydroxy-propoxy, 3-hydroxy-prop-2-oxy, 2,3-dihydroxy-propoxy and 1,3-dihydroxy-prop-2-oxy.

The term "hydroxy-fluoro-lower-alkyl" refers to a fluoro-lower-alkoxy group as defined above, which is substituted by 1 to 3 hydroxy groups. Examples of hydroxy-fluoro-lower-alkoxy groups are e.g. 2,2,2-trifluoro-1-hydroxy-ethyl, 3,3,3-trifluoro-2-hydroxy-propyl.

The term "aryl", alone or in combination, relates to the phenyl or naphthyl group, preferably the phenyl group, which can optionally be substituted, unless specifically stated

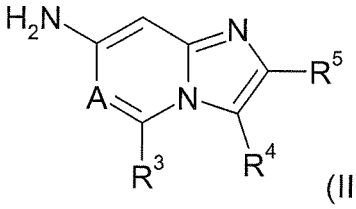
lower-alkyl, lower-alkoxy-lower-alkyl, amino-lower-alkyl, mono- or di-lower-alkyl-amino-lower-alkyl, morpholino-lower-alkyl, pyrrolidino-lower-alkyl, piperidino-lower-alkyl, piperazino-lower-alkyl, lower-alkyl-piperazino-lower-alkyl and aralkyl esters are examples of suitable esters. The methyl, ethyl, propyl, butyl and benzyl esters are preferred esters. The term "pharmaceutically acceptable esters" furthermore embraces compounds of formula (I) in which hydroxy groups have been converted to the corresponding esters with inorganic or organic acids such as, nitric acid, sulphuric acid, phosphoric acid, citric acid, formic acid, maleic acid, acetic acid, succinic acid, tartaric acid, methanesulphonic acid, or p-toluenesulphonic acid ~~and the like~~, which are non toxic to living organisms.

The invention further relates to a process for the manufacture of compounds of formula (I) as defined above, which process comprises reacting a compound of formula (II)



(II)

with a compound of formula (III)



(III),

wherein R^1, R^2, R^3, R^4, R^5 and A are as defined above.

The reaction of a compound of formula (II) with a compound of formula (III) can be carried out under conditions as described in the examples or under conditions well known to the person skilled in the art. For example, the reaction can be performed in solvents like dimethylformamide (DMF), tetrahydrofurane (THF), dioxane, dichloromethane, ethyl acetate~~,~~ or 1-methyl-2-pyrolidone (NMP) ~~and the like~~ at temperatures in the range of e.g. at -10 – 120 °C, but typically at 0 °C – room temperature, at atmospheric pressure or elevated pressure. The reaction can be carried out in one step or in several steps. If the reaction is carried out in one step, the conversion is usually accomplished with a coupling reagent, such as N,N'-dicyclohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC), 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)~~,~~ or propylphosphonic anhydride, ~~and the like~~ (a large number of chemically diverse coupling reagents are described in the literature). If the reaction is carried out in several steps, the acid (II) is usually transformed into a reactive species such as an acid chloride or an acid anhydride, for instance by reaction with thionyl chloride, sulphuryl chloride, phosphoroxychloride, oxalylchloride, or the like, with or without a solvent such as dichloromethane, with or without an additive such as DMF. This is then converted in another step by addition of the amine (III) into the product (I). The second step is typically carried out in a solvent such as dimethylformamide (DMF), tetrahydrofurane (THF), dioxane, dichloromethane, ethyl acetate~~,~~ or 1-methyl-2-pyrolidone (NMP) ~~and the like~~ at temperatures in the range of e.g. at -

such a compound with such a base. One possible method to form such a salt is e.g. by addition of 1/n equivalents of a basic salt such as e.g. $M(OH)_n$, wherein M = metal or ammonium cation and n = number of hydroxide anions, to a solution of the compound in a suitable solvent (e.g. ethanol, ethanol-water mixture, tetrahydrofuran-water mixture) and to remove the solvent by evaporation or lyophilisation.

The conversion of compounds of formula (I) into pharmaceutically acceptable esters can be carried out e.g. by treatment of a suitable carboxy group present in the molecule with a suitable alcohol using e.g. a condensating reagent such as benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), N,N-dicylohexylcarbodiimide (DCC), N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDCI) or O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N,N-tetra-methyluronium-tetrafluoroborate (TPTU), or by direct reaction with a suitable alcohol under acidic conditions, as for example in the presence of a strong mineral acid like hydrochloric acid~~,~~ or sulfuric acid ~~and the like~~. Compounds having a hydroxyl group can be converted to esters with suitable acids by analogous methods.

Insofar as their preparation is not described in the examples, the compounds of formula (I) as well as all intermediate products can be prepared according to analogous methods or according to the methods set forth above. Starting materials are commercially available, known in the art or can be prepared by methods known in the art or in analogy thereto.

As described above, the novel compounds of the present invention have been found to inhibit PDE10A activity. The compounds of the present invention can therefore be used, either alone or in combination with other drugs, for the treatment and/or prophylaxis of diseases which are modulated by PDE10A inhibitors. These diseases include~~, but are not limited to,~~ certain psychotic disorders such as schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder or substance-induced psychotic disorder, anxiety disorders such as panic disorder, obsessive/compulsive disorders, acute stress disorder or generalized anxiety disorder, drug addictions, movement disorders such as Parkinson's disease or restless leg syndrome, cognition deficiency disorders such as Alzheimer's disease or multi-infarct dementia, mood disorders such as depression or bipolar disorders, or neuropsychiatric conditions such as psychosis, attention-deficit/hyperactivity disorder (ADHD) or related attentional disorders. Other disorders are diabetes and related disorders, such as type 2 diabetes mellitus, neurodegenerative disorders such as Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke or spinal cord injury, solid tumors and hematological malignancies such as renal cell carcinoma or breast cancer.

The invention therefore also relates to pharmaceutical compositions comprising a compound as defined above and a pharmaceutically acceptable carrier and/or adjuvant.

The invention likewise embraces compounds as described above for use as therapeutically active substances, especially as therapeutically active substances for the treatment and/or prophylaxis of diseases which are modulated by PDE10A inhibitors, particularly as therapeutically active substances for the treatment and/or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma and breast cancer.

The compounds of formula I and/or their pharmaceutically acceptable salts can be used as medicaments, e.g. in the form of pharmaceutical preparations for enteral, parenteral or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or suspensions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils. Oral administration is preferred.

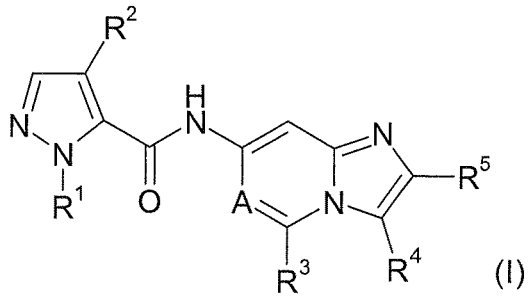
The production of the pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula I and/or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers might, however, be required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose~~,~~ or invert sugar ~~and the like~~. Suitable carrier materials for injection solutions are, for example, water, alcohols, polyols, glycerol and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as

Claims

1. Compounds of formula (I)



(I)

wherein

A is N or C(R^6);

R^1 is hydrogen, C_{1-7}-alkyl or fluoro-C_{1-7}-alkyl;

R^2 is halogen, C(O)NR^7R^8 or C(O)OR^9;

R^3 is hydrogen, $NR^{10}R^{11}$, C_{1-7}-alkyl, C_{1-7}-alkoxy, fluoro-C_{1-7}-alkyl or fluoro-C_{1-7}-alkoxy;

R^4 is hydrogen, C_{1-7}-alkyl, fluoro-C_{1-7}-alkyl, C_{1-7}alkoxy or fluoro-C_{1-7}-alkoxy;

R^5 is aryl or-heteroaryl, said heteroaryl being aromatic 5 to 6 membered monocyclic ring or 9 to 10 membered bicyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, which can optionally be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-7}-alkyl, C_{1-7}-alkoxy, fluoro-C_{1-7}-alkyl, fluoro-C_{1-7}-alkoxy and hydroxy;

R^6 is hydrogen, halogen, CN, cycloalkyl, C_{1-7}-alkyl, cycloalkyl-C_{1-7}-alkyl, C_{1-7}-alkoxy, fluoro-C_{1-7}-alkyl or fluoro-C_{1-7}-alkoxy;

R^7 and R^8 independently from each other are selected from the group consisting of hydrogen, C_{1-7}-alkyl, C_{1-7}-alkoxy-C_{1-7}-alkyl, fluoro-C_{1-7}-alkyl, cycloalkyl, cycloalkyl-C_{1-7}-alkyl, NH_2-C_{1-7}-alkyl, N(H,C_{1-7}-alkyl)-C_{1-7}-alkyl, N(C_{1-7}-alkyl$_2$)-C_{1-7}-alkyl, hydroxy-C_{1-7}-alkyl, hydroxy-C_{1-7}-alkoxy-C_{1-7}-alkyl, NH_2C(O)-C_{1-7}-alkyl, N(H,C_{1-7}-alkyl)C(O)-C_{1-7}-alkyl, N(C_{1-7}-alkyl$_2$)C(O)-C_{1-7}-alkyl, C_{1-7}-alkoxy, hydroxy-C_{1-7}-alkyl-oxetanyl-C_{1-7}-alkyl, oxo-tetrahydrofuranyl, tetrahydrofuranyl-C_{1-7}-alkyl, oxo-tetrahydrofuranyl-C_{1-7}-alkyl, hydroxy-fluoro-C_{1-7}-alkyl,

tetrahydrofuranyl, aryl and heteroaryl, said heteroaryl being aromatic 5 to 6 membered monocyclic ring or 9 to 10 membered bicyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur, which aryl or heteroaryl, said heteroaryl being aromatic 5 to 6 membered monocyclic ring or 9 to 10 membered bicyclic ring which can comprise 1, 2 or 3 atoms selected from nitrogen, oxygen and/or sulphur can optionally be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-7}-alkyl, C_{1-7}-alkoxy, fluoro-C_{1-7}-alkyl, fluoro-C_{1-7}-alkoxy and hydroxy,

or R^7 and R^8, together with the nitrogen atom to which they are attached, form a heterocyclyl selected from the group consisting of pyrrolidinyl, azetidinyl, morpholinyl, 5,6-dihydro-8-H-[1,2,4]triazolo[4,3-a]pyrazinyl, 3,4-dihydro-1H-pyrrolo[1,2-a]pyrazinyl, 2-oxa-6-aza-spiro[3.3]heptyl, 5,6-dihydro-8H-imidazo[1,2-a]pyrazinyl, [1,4]oxazepanyl, piperazinyl, thiomorpholinyl and 2-oxa-5-aza-bicyclo[2.2.1]heptyl, which heterocyclyl can optionally be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-7}-alkyl, C_{1-7}-alkyl-C(O), C_{1-7}-alkoxy-C_{1-7}-alkyl, oxo, hydroxy, hydroxy-C_{1-7}-alkyl, N(C_{1-7}-alkyl$_2$), NH_2, N(H,C_{1-7}-alkyl), fluoro-C_{1-7}-alkyl, fluoro-C_{1-7}-alkyl-C(O), C_{1-7}-alkoxy and fluoro-C_{1-7}-alkoxy;

R^9 is hydrogen, C_{1-7}-alkyl, or fluoro-C_{1-7}-alkyl;

R^{10} and R^{11} independently from each other are hydrogen, C_{1-7}-alkyl or fluoro-C_{1-7}-alkyl,

or R^{10} and R^{11}, together with the nitrogen atom to which they are attached, form a heterocyclyl selected from the group consisting of piperidinyl, morpholinyl, pyrrolidinyl, azetidinyl and piperazinyl, which heterocyclyl can optionally be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C_{1-7}-alkyl, C_{1-7}-alkoxy, fluoro-C_{1-7}-alkyl and fluoro-C_{1-7}-alkoxy;

and pharmaceutically acceptable salts and thereof.

2. Compounds according to claim 1, wherein A is N.

3. Compounds according to claim 1, wherein A is C(R^6) and R^6 is as defined in claim 1.

4. Compounds according to any of claims 1 - 3, wherein R^1 is hydrogen or C_{1-7}alkyl.

5. Compounds according to any of claims 1 - 4, wherein R^1 is methyl.