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(71) Applicant (for all designated States except US):

BOEHRINGER INGELHEIM INTERNATIONAL GMBH [DE/DE]; Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HEINE, Niklas**

[DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE). **GIOVANNINI, Riccardo** [IT/IT]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Strasse 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **HAMMANN, Heinz** et al.; Binger Str. 173,

55216 Ingelheim Am Rhein (DE).

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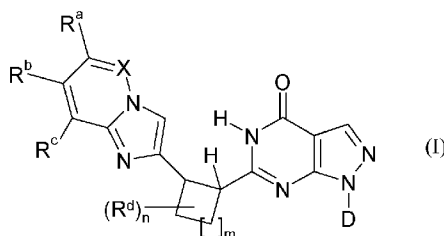
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(54) Title: 6-CYCLOALKYL-PYRAZOLOPYRIMIDINONES FOR THE TREATMENT OF CNS DISORDERS

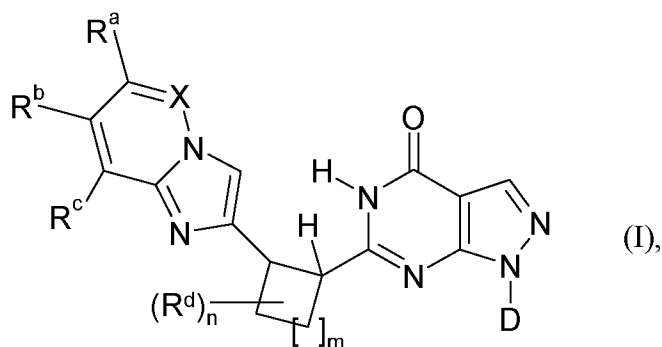


(57) Abstract: The invention relates to novel pyrazolopyrimidinones according to formula (I), wherein X is CR^e or unsubstituted N, D is optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl or 2-, 3- or 4-pyridyl, R^a, R^b, R^c, R^d, R^e are either H or optional substituents, m= 1 or 2 and n is 0, 1 or 2. The new compounds are for use as the active entity of medicaments or for the manufacture of medicaments respectively, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. Such conditions may for example be associated with Alzheimer's disease, schizophrenia and other diseases. The new compounds are also for example for the manufacture of medicaments and/or for use in the treatment of these diseases, in particular for cognitive impairment associated with such disease. The compounds of the invention show PDE9 inhibiting properties.

WO 2012/110441 A1

6-Cycloalkyl-pyrazolopyrimidinones for the Treatment of CNS Disorders

The invention relates to novel pyrazolopyrimidinones according to formula (I)



whereby X is CR^e or unsubstituted N, D is optionally substituted cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl or 2-, 3- or 4-pyridyl, R^a, R^b, R^c, R^d, R^e are either H or optional substituents, m= 1 or 2 and n is 0, 1 or 2.

The new compounds are for use as active entities of medicaments or for the manufacture of medicaments, in particular medicaments for the treatment of conditions concerning deficits in perception, concentration, learning or memory. Such conditions may for example be associated with Alzheimer's disease, schizophrenia and other diseases, in particular cognitive impairment associated with such diseases. The compounds of the invention show PDE9 inhibiting properties.

BACKGROUND OF THE INVENTION

The inhibition of phosphodiesterase 9A (PDE9A) is one of the current concepts to find new access paths to the treatment of cognitive impairments due to CNS disorders like Alzheimer's

disease, schizophrenia and other diseases or due to any other neurodegenerative process of the brain. With the present invention, new compounds that follow this concept are presented.

Phosphodiesterase 9A is one member of the wide family of phosphodiesterases. These enzymes modulate the levels of the cyclic nucleotides 5'-3' cyclic adenosine monophosphate (cAMP) and 5'-3' cyclic guanosine monophosphate (cGMP). These cyclic nucleotides (cAMP and cGMP) are important second messengers and therefore play a central role in cellular signal transduction cascades. Each of them reactivates inter alia, but not exclusively, protein kinases. The protein kinase activated by cAMP is called protein kinase A (PKA) and the protein kinase activated by cGMP is called protein kinase G (PKG). Activated PKA and PKG are able in turn to phosphorylate a number of cellular effector proteins (e.g. ion channels, G-protein-coupled receptors, structural proteins, transcription factors). It is possible in this way for the second messengers cAMP and cGMP to control a wide variety of physiological processes in a wide variety of organs. However, the cyclic nucleotides are also able to act directly on effector molecules. Thus, it is known, for example, that cGMP is able to act directly on ion channels and thus is able to influence the cellular ion concentration (review in: Wei *et al.*, *Prog. Neurobiol.*, **1998**, 56, 37-64). The phosphodiesterases (PDE) are a control mechanism for the activity of cAMP and cGMP and thus in turn for the corresponding physiological processes. PDEs hydrolyse the cyclic monophosphates to the inactive monophosphates AMP and GMP. Currently, 11 PDE families have been defined on the basis of the sequence homology of the corresponding genes. Individual PDE genes within a family are differentiated by letters (e.g. PDE1A and PDE1B). If different splice variants within a gene also occur, then this is indicated by an additional numbering after the letters (e.g. PDE1A1).

Human PDE9A was cloned and sequenced in 1998. The amino acid identity with other PDEs does not exceed 34% (PDE8A) and is never less than 28% (PDE5A). With a Michaelis-Menten constant (K_m) of 170 nanomolar (nM), PDE9A has high affinity for cGMP. In addition, PDE9A is selective for cGMP (K_m for cAMP=230 micromolar (μM)). PDE9A has no cGMP binding domain, suggesting that the enzyme activity is not regulated by cGMP. It was shown in a Western blot analysis that PDE9A is expressed in humans inter alia in testes, brain, small intestine, skeletal muscle, heart, lung, thymus and spleen. The highest expression was found in the brain, small intestine, kidney, prostate, colon and spleen (Fisher *et al.*, *J.*

Biol. Chem., **1998**, 273 (25), 15559-15564; Wang *et al.*, *Gene*, **2003**, 314, 15-27). The gene for human PDE9A is located on chromosome 21q22.3 and comprises 21 exons. 4 alternative splice variants of PDE9A have been identified (Guipponi *et al.*, *Hum. Genet.*, **1998**, 103, 386-392). Classical PDE inhibitors do not inhibit human PDE9A. Thus, IBMX, dipyridamole, SKF94120, rolipram and vinpocetine show no inhibition on the isolated enzyme in concentrations of up to 100 micromolar (μM). An IC₅₀ of 35 micromolar (μM) has been demonstrated for zaprinast (Fisher *et al.*, *J. Biol. Chem.*, **1998**, 273 (25), 15559-15564).

Murine PDE9A was cloned and sequenced in 1998 by Soderling *et al.* (*J. Biol. Chem.*, **1998**, 273 (19), 15553-15558). This has, like the human form, high affinity for cGMP with a K_m of 70 nanomolar (nM). Particularly high expression was found in the mouse kidney, brain, lung and liver. Murine PDE9A is not inhibited by IBMX in concentrations below 200 micromolar either; the IC₅₀ for zaprinast is 29 micromolar (Soderling *et al.*, *J. Biol. Chem.*, **1998**, 273 (19), 15553-15558). It has been found that PDE9A is strongly expressed in some regions of the rat brain. These include olfactory bulb, hippocampus, cortex, basal ganglia and basal forebrain (Andreeva *et al.*, *J. Neurosci.*, **2001**, 21 (22), 9068-9076). The hippocampus, cortex and basal forebrain in particular play an important role in learning and memory processes. As already mentioned above, PDE9A is distinguished by having particularly high affinity for cGMP. PDE9A is therefore active even at low physiological concentrations, in contrast to PDE2A (K_m=10 micromolar (μM); Martins *et al.*, *J. Biol. Chem.*, **1982**, 257, 1973-1979), PDE5A (K_m=4 micromolar (μM); Francis *et al.*, *J. Biol. Chem.*, **1980**, 255, 620-626), PDE6A (K_m=17 micromolar (μM); Gillespie and Beavo, *J. Biol. Chem.*, **1988**, 263 (17), 8133-8141) and PDE11A (K_m=0.52 micromolar (μM); Fawcett *et al.*, *Proc. Nat. Acad. Sci.*, **2000**, 97 (7), 3702-3707). In contrast to PDE2A (Murashima *et al.*, *Biochemistry*, **1990**, 29, 5285-5292), the catalytic activity of PDE9A is not increased by cGMP because it has no GAF domain (cGMP-binding domain via which the PDE activity is allosterically increased) (Beavo *et al.*, *Current Opinion in Cell Biology*, **2000**, 12, 174-179). PDE9A inhibitors may therefore lead to an increase in the baseline cGMP concentration.

This outline will make it evident that PDE9A engages in specific physiological processes in a characteristic and unique manner, which distinguishes the role of PDE9A from any of the other PDE family members.

WO 2004/099210 discloses 6-arylmethyl-substituted pyrazolopyrimidinones which are PDE9 inhibitors.

WO 2004/099211 discloses 6-cyclylmethyl- and 6-alkylmethyl-substituted pyrazolopyrimidines and their use for the improvement of cognition, concentration etc.

DE 102 38 722 discloses the use of PDE9A-inhibitors for the improvement of cognition, concentration.

WO 2004/018474 discloses phenyl-substituted pyrazolopyrimidines and their use for the improvement of perception, concentration learning and/or memory.

WO 2004/026876 discloses alkyl-substituted pyrazolopyrimidines and their use for the improvement of awareness, concentration learning capacity and/or memory performance.

WO 2004/096811 discloses heterocyclic bicycles as PDE9 inhibitors for the treatment of diabetes, including type 1 and type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, metabolic syndrome and/or cardiovascular disease.

WO2009068617 discloses PDE9 inhibiting compounds derived from pyrazolopyrimidinones with a substituted phenylmethyl- or pyridyl-methyl group in the 6-position.

WO2010112437 discloses PDE9 inhibiting compounds derived from pyrazolopyrimidinones with a phenyl or heteroaryl substituted arylmethyl- or heteroaryl-methyl group in the 6-position.

WO 2009/121919 discloses PDE9 inhibitors derived from pyrazolopyrimidinones with a non-aromatic heterocyclyl group in the 1-position, among which is tetrahydropyranyl.

WO 2010/026214 discloses PDE9 inhibitors derived from pyrazolopyrimidinones with a cycloalkyl or a cycloalkenyl group in the 1-position, among which is 4,4-difluorocyclohexyl.

Some references are directed to nucleoside derivatives. For example, WO 2002/057425 discloses nucleoside derivatives which are inhibitors of RNA-dependent RNA viral polymerase. WO 2001/060315 discloses nucleoside derivatives for the treatment of hepatitis C infection. EP679657 discloses compounds that serve as ribonucleoside analogues.

US2002058635 discloses purine L-nucleoside compounds, in which both the purine rings and the carbohydrate ring (pentose ring) are either modified, functionalized, or both, so the carbohydrate ring for example must show at least one esterified hydroxy group.

WO 2005/051944 discloses oxetane-containing nucleosides for the treatment of nucleoside analogue related disorders such as disorders involving cellular proliferation and infection.

WO 2006/084281 discloses inhibitors of the E1 activation enzyme that have a sulfonamide moiety.

WO 1998/40384 discloses pyrazolopyrimidinones which are PDE1, 2 and 5 inhibitors and can be employed for the treatment of cardiovascular and cerebrovascular disorders and disorders of the urogenital system.

CH396 924, CH396 925, CH396 926, CH396 927, DE1147234 and DE1149013, describe pyrazolopyrimidines which have a coronary-dilating effect and which can be employed for the treatment of disturbances of myocardial blood flow.

US3732225 describes pyrazolopyrimidines which have an anti-inflammatory and blood glucose-lowering effect.

DE2408906 describes styrylpyrazolopyrimidinones which can be employed as antimicrobial and anti-inflammatory agents for the treatment of, for example, oedema.

OBJECTIVE OF THE INVENTION

Changes in the substitution pattern of pyrazolopyrimidinones result in interesting changes concerning biological activity and changes in the affinity towards different target enzymes.

Therefore it is an objective of the present invention to provide compounds as herein described, in particular in the claims, that effectively modulate PDE9A for the purpose of the development of a medicament, in particular in view of diseases or conditions, the treatment of which are accessible via PDE9A modulation.

It is another objective of the present invention to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

Yet another objective of the present invention is to provide compounds which show a favourable safety profile.

Another objective of the present invention is to provide compounds that have a favourable selectivity profile in favour for PDE9A inhibition over other PDE family members and other pharmacological targets and by this may provide advantage.

Yet another objective is to provide a medicament that may not only serve for treatment but might also be used for the prevention or modification of the corresponding disease or condition.

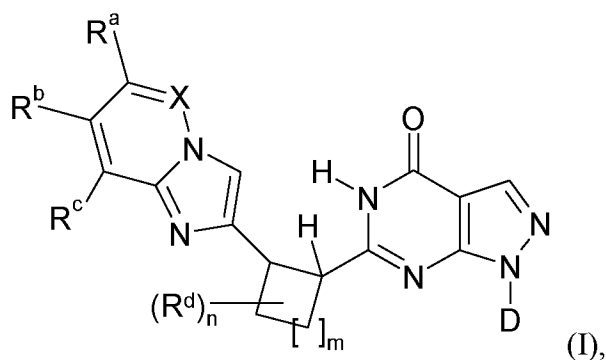
The present invention further provides a pharmaceutical composition comprising a compound as herein described, in particular in the claims, and a pharmaceutically acceptable carrier.

The present invention further provides a method for the treatment of any of the conditions as described herein in a mammal in need of such treatment, preferably a human, comprising administering to the mammal a therapeutically effective amount of a compound as herein described, in particular in the claims.

The present invention further provides a compound as herein described, in particular in the claims, for use in a method of treatment of the human or animal body by therapy.

DETAILED DESCRIPTION OF THE PRESENT INVENTION

The compounds of the present invention are characterised by general formula (I):



wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, CF₃-, CHF₂-, CH₂F-, NC- and halogen;

whereby C₁₋₆-alkyl- and C₁₋₆-alkyl-O- optionally may be substituted with halogen, preferably with fluoro

R^d: is selected from the group consisting of fluorine, NC-, -CF₃, -CHF₂, -CH₂F, and methyl;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, NC-, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, NC-, F₃C-, HF₂C- and FH₂C-;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably 1;

n: is selected from 0, 1 or 2, preferably, 0 or 1, more preferably 0,

whereby if n = 2, the two groups R^d are selected independently of one another;

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

This embodiment is **embodiment 1** of the present invention.

Embodiment 2 of the present invention: Another embodiment of the invention concerns a compound according to general formula (I), wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, C₁₋₃-alkyl-, C₁₋₃-alkyl-O-, -CF₃, -CHF₂, -CH₂F, NC- and halogen;

whereby C₁₋₆-alkyl- and C₁₋₆-alkyl-O- optionally may be substituted with halogen, preferably fluoro

R^d: is selected from the group consisting of fluorine, NC-, -CF₃, -CHF₂, -CH₂F and methyl;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably m is 1;

n: is 0, 1 or 2, preferably n is 0 or 1, more preferably n is 0,

whereby if n = 2, these two groups R^d are selected independently of one another;

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

Embodiment 3 of the present invention: Another embodiment of the invention concerns a compound according to general formula (I), wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, methyl, ethyl, methoxy, ethoxy, -CF₃, -CHF₂, -CH₂F, NC- and halogen; preferably R^a, R^b, R^c, R^e are selected independently from the group consisting of H, methyl, ethyl, methoxy, ethoxy, -CF₃ and NC-,

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably m is 1;

n is 0,

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

Embodiment 4 of the present invention: Another embodiment of the invention concerns a compound according to general formula (I), wherein

X is N or CR^e,

R^b, R^c, R^d, R^e are each H,

R_a is selected from the group consisting of H, methyl, ethyl, methoxy, ethoxy, -CF₃, -CHF₂, -CH₂F and F;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably m is 1;

n is 0,

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

Embodiments 5 to 9 of the present invention: Other embodiments of the invention concern a compound according to each of embodiments 1 to 4, wherein m is 1,

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

Embodiments 10 to 18 of the present invention: Other embodiments of the invention concern a compound according to each of embodiments 1 to 9, wherein

D is either 4,4-difluorocyclohexyl or tetrahydropyran-4-yl or 4-methyl-3-pyridyl and none of these two groups has further substituents and

m is 1.

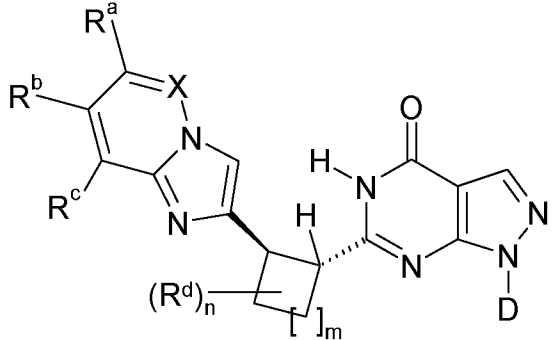
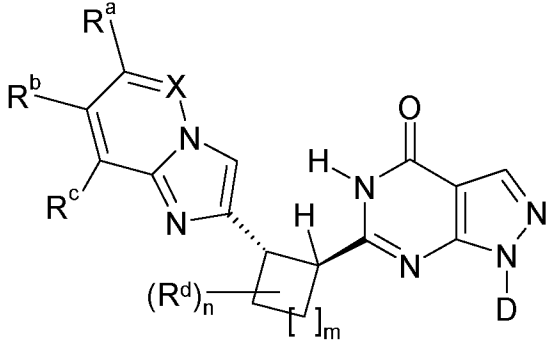
and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

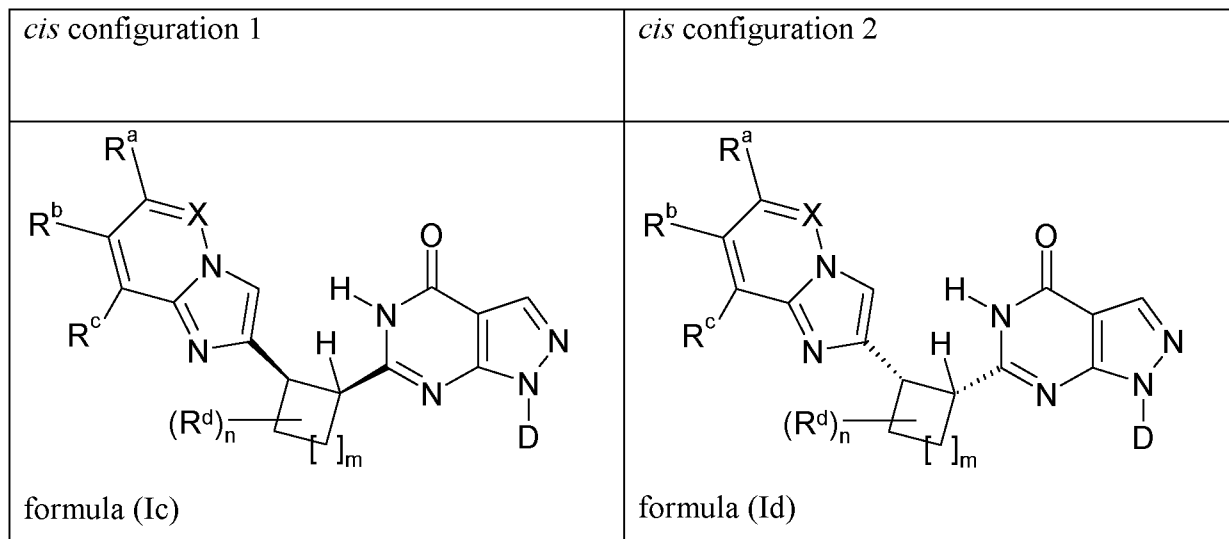
Embodiments 19 to 36 of the present invention concern a compound according to each of embodiments 1 to 18, wherein X = N.

Embodiments 37 to 56 of the present invention concern a compound according to each of embodiments 1 to 18, wherein X = CR^c.

For all embodiments 1 to 56: the configuration of the cycloalkyl group at position 6 of the pyrazolopyrimidinones group with respect to said pyrazolopyrimidinones group and the substituent R¹ may be *cis* or *trans*.

In this respect the compounds of the invention may have the following configurations:

<i>trans</i> configuration 1	<i>trans</i> configuration 2
 <p>formula (Ia)</p>	 <p>formula (Ib)</p>



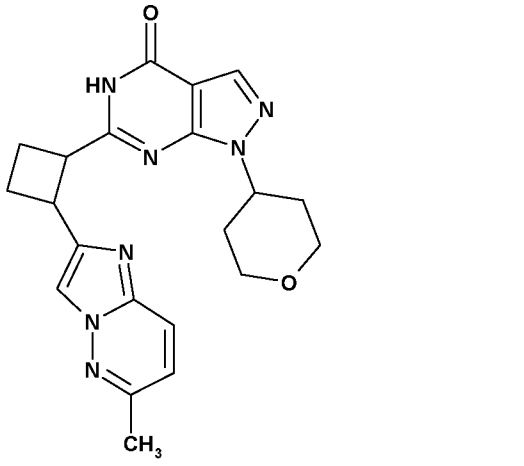
whereby R^a , R^b , R^c , R^d , D , m and n are as defined in any of the embodiments 1 to 56.

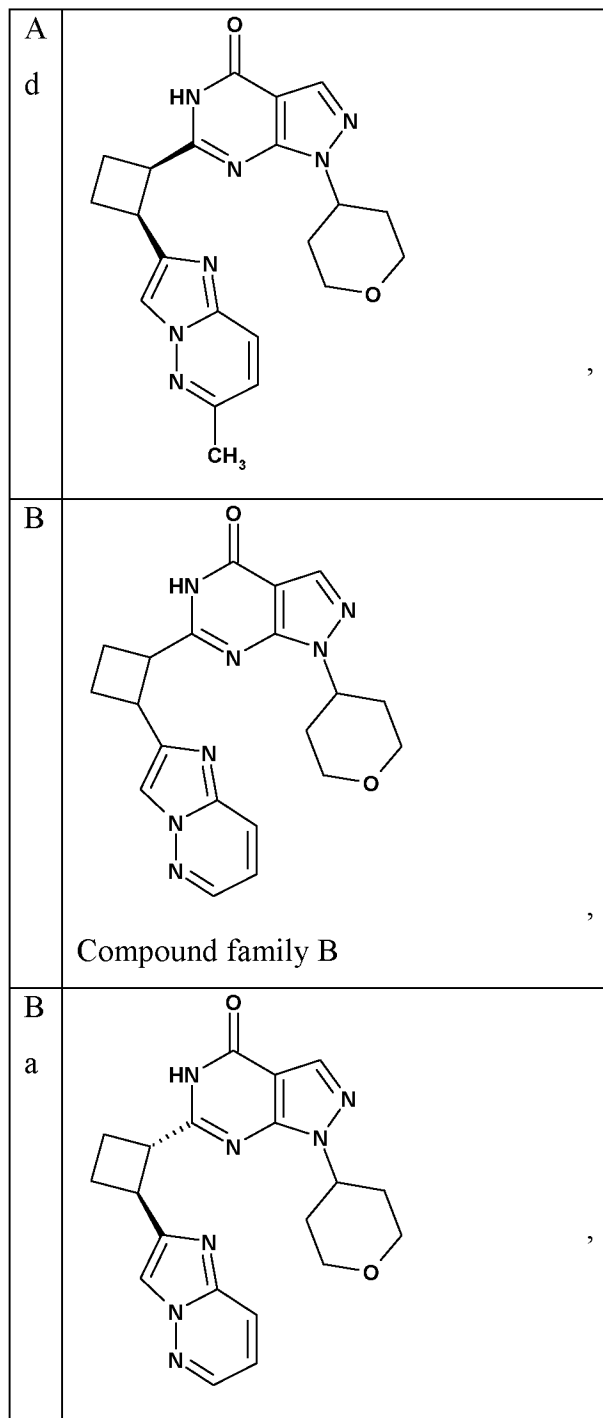
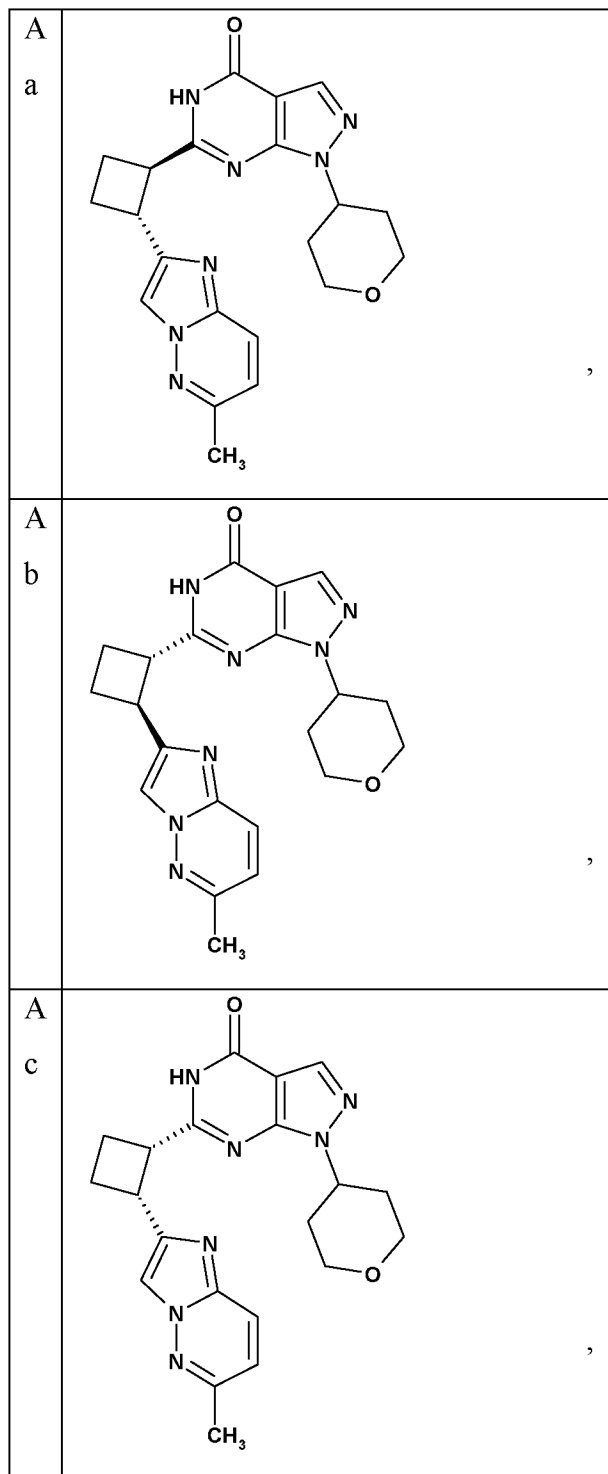
These stereochemically defined embodiments are a further aspect of the invention.

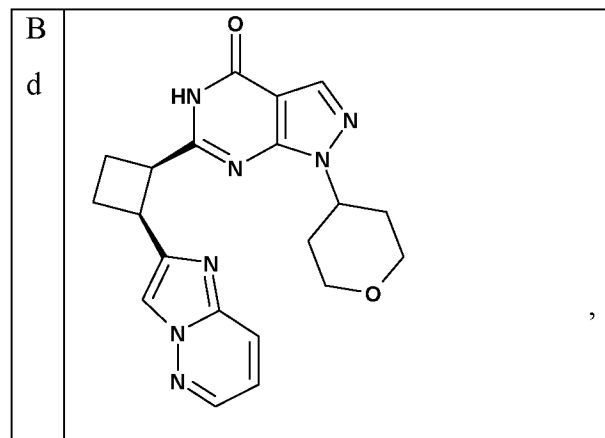
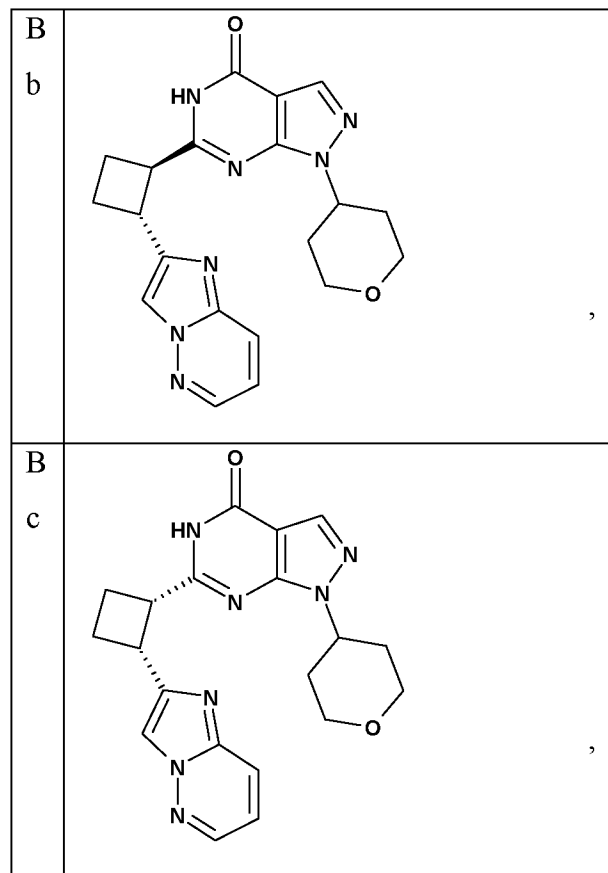
Embodiment 57 of the present invention:

Within the context of the present invention one or more compound(s) is (are) preferred that are selected from the group of specifically defined species as listed in the following table 1. These compounds represent compounds according to general formula (I) wherein X is N . The left column contains a letter code to identify the compound family, which is the group of compounds that have the same general chemical structural formula if no stereochemical properties are considered.

Table 1 of species:

<p>A</p> 	<p>Compound family A</p>
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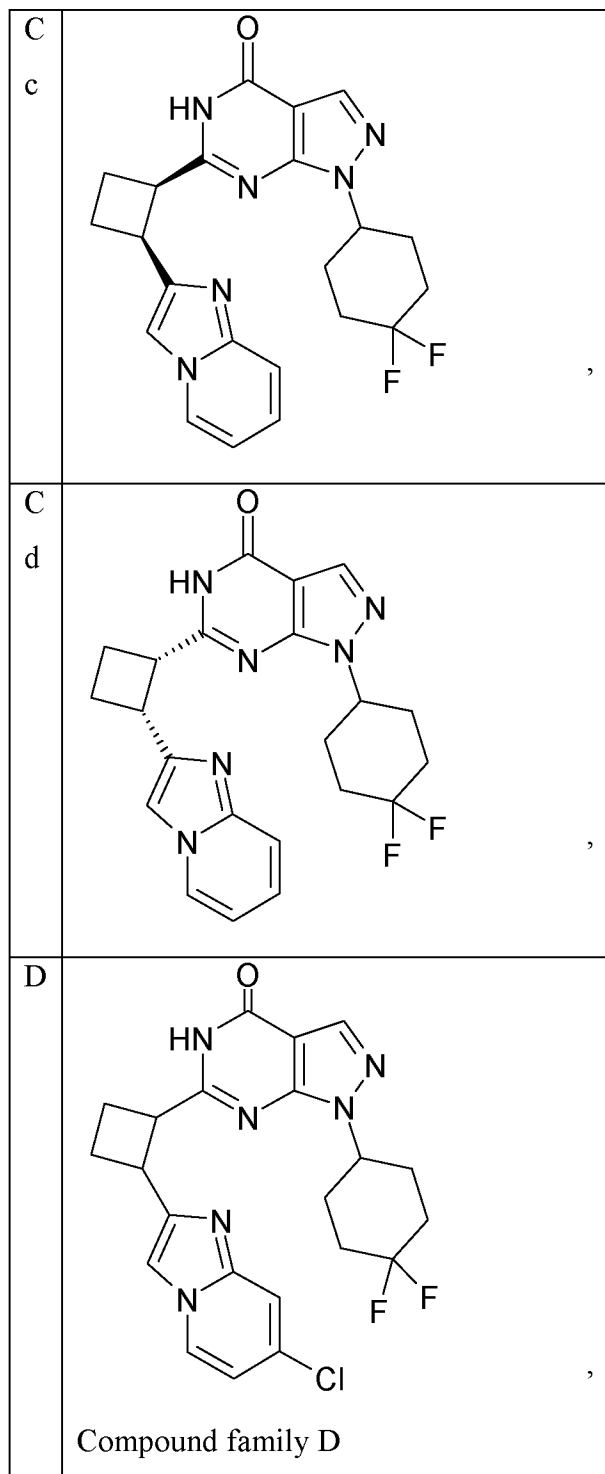
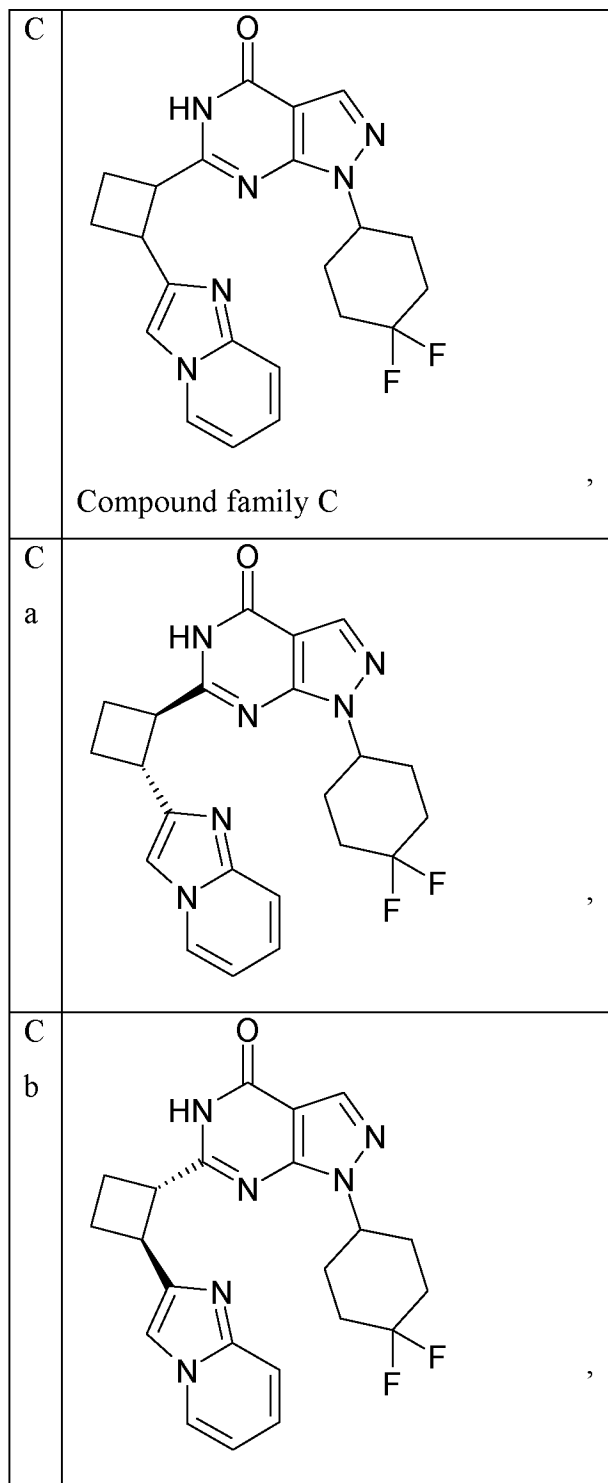


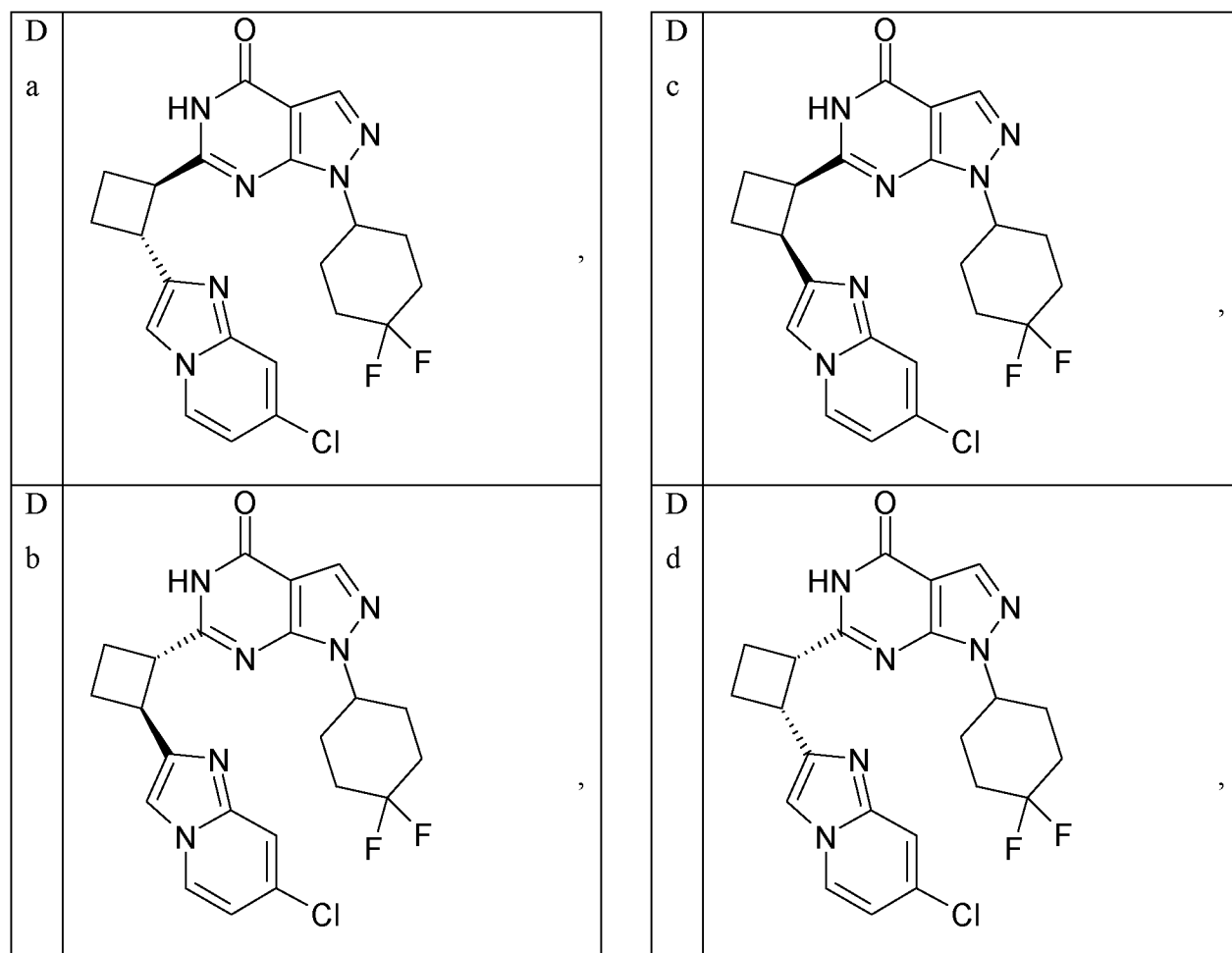
and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

Embodiment 58 of the present invention:

Another embodiment of the present invention concerns one or more compound(s) is (are) that are selected from the group of specifically defined species as listed in the following table 2. These compounds represent compounds according to general formula (I) wherein X is CR^e and R^e is H. The left column contains a letter code to identify the compound family, which is the group of compounds that have the same general chemical structural formula if no stereochemical properties are considered.

Table 2 of species:





and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

- 5 Within the latter group of compounds according to tables 1 and 2 (i.e. embodiments 57 and 58), compounds that show *trans* configuration with respect to the substitution at the cyclobutyl-group may be preferred over compounds with *cis* configuration. Of the possible *trans* configured compounds one may show advantages in efficacy. The more efficacious a compound, the more it is among the preferred compounds. Other criterion which may
- 10 differentiate preferred compounds according to the invention are the balance of efficacy and safety, and selectivity vs. other PDE family members such as PDE1C.

The different stereoisomers are subject to individual embodiments according to the invention:

For each of the embodiments 1 to 56: whenever D may be tetrahydrofuranyl, it is preferably tetrahydrofuran-3-yl; whenever D may be tetrahydropyranyl it is preferable tetrahydropyran-3-yl or tetrahydropyran-4-yl, more preferably tetrahydropyran-4-yl.

5 TERMS AND DEFINITIONS

Terms not specifically defined herein should be given the meanings that would be given to them by a person skilled in the art in light of the disclosure and the context. Examples include that specific substituents or atoms are presented with their 1 or 2 letter code, like H for
10 hydrogen, N for nitrogen, C for carbon, O for oxygen, S for sulphur and the like. Optionally but not mandatory the letter is followed or preceded by a hyphen to indicate a bond. As used in the specification, unless specified to the contrary, the following terms have the meaning indicated and the following conventions are adhered to.

In the groups, radicals, or moieties defined below, the number of carbon atoms is often
15 specified preceding the group, for example, C₁₋₆ alkyl means an alkyl group or alkyl radical having 1 to 6 carbon atoms. In general, for groups comprising two or more subgroups, the last named group is the radical attachment point, for example, "alkyl-O-" means a monovalent radical of the formula alkyl-O-, which is attached via the oxygen atom thereof (i.e. a alkoxy-substituent). If the term of a substituent starts or ends with a minus sign or hyphen, i.e. -, this
20 sign emphasises the attachment point like in the aforementioned example Alkyl-O-, where the O is linked to the group of which the alkoxy-group is a substituent. Unless otherwise specified below, conventional definitions of terms control and conventional stable atom valences are presumed and achieved in all formulas and groups.

25 In general, if terms are specifically defined with a given context, such specific definitions shall prevail over the more general definitions as outlined in this paragraph.

In general, all "**tautomeric forms and isomeric forms and mixtures**", whether individual geometric isomers or optical isomers or racemic or non-racemic mixtures of isomers of a
30 chemical structure or compound are intended, unless the specific stereochemistry or isomeric form is specifically indicated in the compound name or structure. Specific definitions prevail.

“**Substitution**”: The term "**substituted**" as used herein explicitly or implicitly, means that any one or more hydrogen(s) on the designated atom is replaced with a member of the indicated group of substituents, provided that the designated atom's normal valence is not exceeded. In case a substituent is bound via a double bond, e.g. an oxo substituent, such substituent replaces two hydrogen atoms on the designated atom. The substitution shall result in a stable compound. “Stable” in this context preferably means a compound that from a pharmaceutical point of view is chemically and physically sufficiently stable in order to be used as an active pharmaceutical ingredient of a pharmaceutical composition. If a substituent is not defined, it shall be hydrogen. By the term "**optionally substituted**" is meant that either the corresponding group is substituted or it is not. A characterisation that substituents of the same group may be “**selected independently of one another**” shall mean that the corresponding substituents may be the same or may be different.

The phrase "**pharmaceutically acceptable**" is employed herein to refer to those compounds, materials, compositions and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

"**pharmaceutically acceptable salt(s)**" of the compounds according to the invention are subject of the present invention as well. The term "**pharmaceutically acceptable salt(s)**" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof, preferably addition salts. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues/parts of the compounds of the present invention such as aminofunctions; acidic residues/parts within compounds of the present invention may form salts with alkali or organic bases. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid and the like; and the salts prepared from organic acids such as acetic acid, propionic acid, succinic acid, glycolic acid, stearic acid, lactic acid,

malic acid, tartaric acid, citric acid, ascorbic acid, pamoic acid, maleic acid, hydroxymaleic acid, phenylacetic acid, glutamic acid, benzoic acid, salicylic acid, sulfanilic acid, 2-acetoxybenzoic acid, fumaric acid, toluenesulfonic acid, methanesulfonic acid, ethane disulfonic acid, oxalic acid, isethionic acid and the like.

5 Physiologically acceptable salts with bases also may include salts with conventional bases such as, by way of example and preferably, alkali metal salts (e.g. sodium and potassium salts), alkaline earth metal salts (e.g. calcium and magnesium salts) and ammonia, organic amines having 1 to 16 C atoms, such as, by way of example and preferably, ethylamine, diethylamine, triethylamine, ethyldiisopropylamine, monoethanolamine, diethanolamine,
10 triethanolamine, dicyclohexylamine, dimethylaminoethanol, procaine, dibenzylamine, N-methyl-morpholine, dehydroabietylamine, arginine, lysine, ethylenediamine and methylpiperidine and the like.

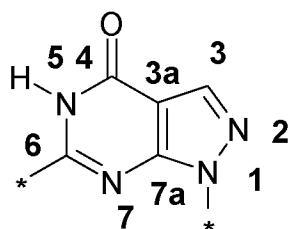
The pharmaceutically acceptable salts of the present invention can be synthesized from the
15 parent compound with basic or acidic properties by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base form of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

20 A “**Prodrug**” is considered a compound that is designed to release a biologically active compound according to the present invention *in-vivo* when such prodrug is administered to a mammalian subject. Prodrugs of compounds according to the present invention are prepared by modifying functional groups present in the compound of the invention in such a way that
25 these modifications are retransformed to the original functional groups under physiological conditions. It will be appreciated that prodrugs of the compounds according to the present inventions are subject to the present invention as well.

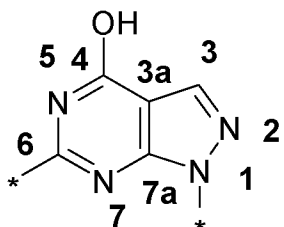
30 “**Metabolites**” are considered derivatives of the compounds according to the present invention that are formed *in-vivo*. Active metabolites are such metabolites that cause a pharmacological effect. It will be appreciated that metabolites of the compounds according to the present inventions are subject to the present invention as well, in particular active metabolites.

Some of the compounds may form “**solvates**”. For the purposes of the invention the term “solvates” refers to those forms of the compounds which form, in the solid or liquid state, a complex by coordination with solvent molecules. Hydrates are a specific form of solvates in which the coordination takes place with water. According to the present invention, the term preferably is used for solid solvates, such as amorphous or more preferably crystalline solvates.

“**Scaffold**”: The scaffold of the compounds according to the present invention is represented by the following core structure. The numeration of the positions of the ring member atoms is indicated in bold:



It will be evident for the skilled person in the art, that this scaffold can be described by its tautomeric “enol” form

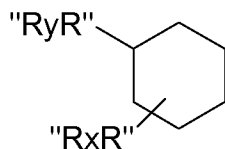


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In the context of the present invention both structural representations of the scaffold shall be considered the subject of the present invention, even if only one of the two representatives is presented. Without meant to be limiting or bound, it is believed that for the majority of compounds under ambient conditions and therewith under conditions which are the relevant conditions for a pharmaceutical composition comprising said compounds, the equilibrium of the tautomeric forms lies on the side of the pyrazolopyrimidin-4-one representation. Therefore,

all embodiments are presented as pyrazolopyrimidin-4-one-derivatives or more precisely as pyrazolo[3,4-d]pyrimidin-4-one derivatives.

5 “**Bonds**”: If within a chemical formula of a ring system or a defined group a substituent is directly linked to an atom or a group like “RyR” in the formula below, this shall mean that the substituent is only attached to the corresponding atom. If however from another substituent like “RxR” a bond is not specifically linked to an atom of the ring system but drawn towards the centre of the ring or group this means that this substituent “RxR” may be linked to any meaningful atom of the ring system / group unless stated otherwise.



10

The bond symbol “-“ (= minus sign) or the symbol “- *” (= minus sign followed by an asterisk sign) stands for the bond through which a substituent is bound to the corresponding remaining part of the molecule / scaffold. In cases in that the minus sign does not seem to be sufficiently clear, there may be added an asterisk to the bond symbol “-“ in order to determine the point of attachment of said bond with the corresponding main part of the molecule / scaffold.

15

The term “**C₁₋₆-alkyl**” denotes a saturated, branched or unbranched hydrocarbon group with 1 to 6 C atoms. Examples of such groups include methyl, ethyl, *n*-propyl, *iso*-propyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *tert*-pentyl, *n*-hexyl, *iso*-hexyl. This definition applies for the use of “**alkyl**” in any reasonable context within the present description in the absence of a further definition.

20

The term “**C₃₋₇-cycloalkyl**” denotes a saturated monocyclic group with 3 to 7 C ring atoms. Preferred are 5 or 6 membered cycloalkyl-groups. There are no other ring atoms than carbon atoms. Examples of such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl. This definition applies for “**cycloalkyl**” in any reasonable context within the present description in the absence of a further definition.

25

The terms “**halogen**” stands for fluoro (F), chloro (Cl) and bromo (Br) substituents, preferably F and Cl and more preferably F.

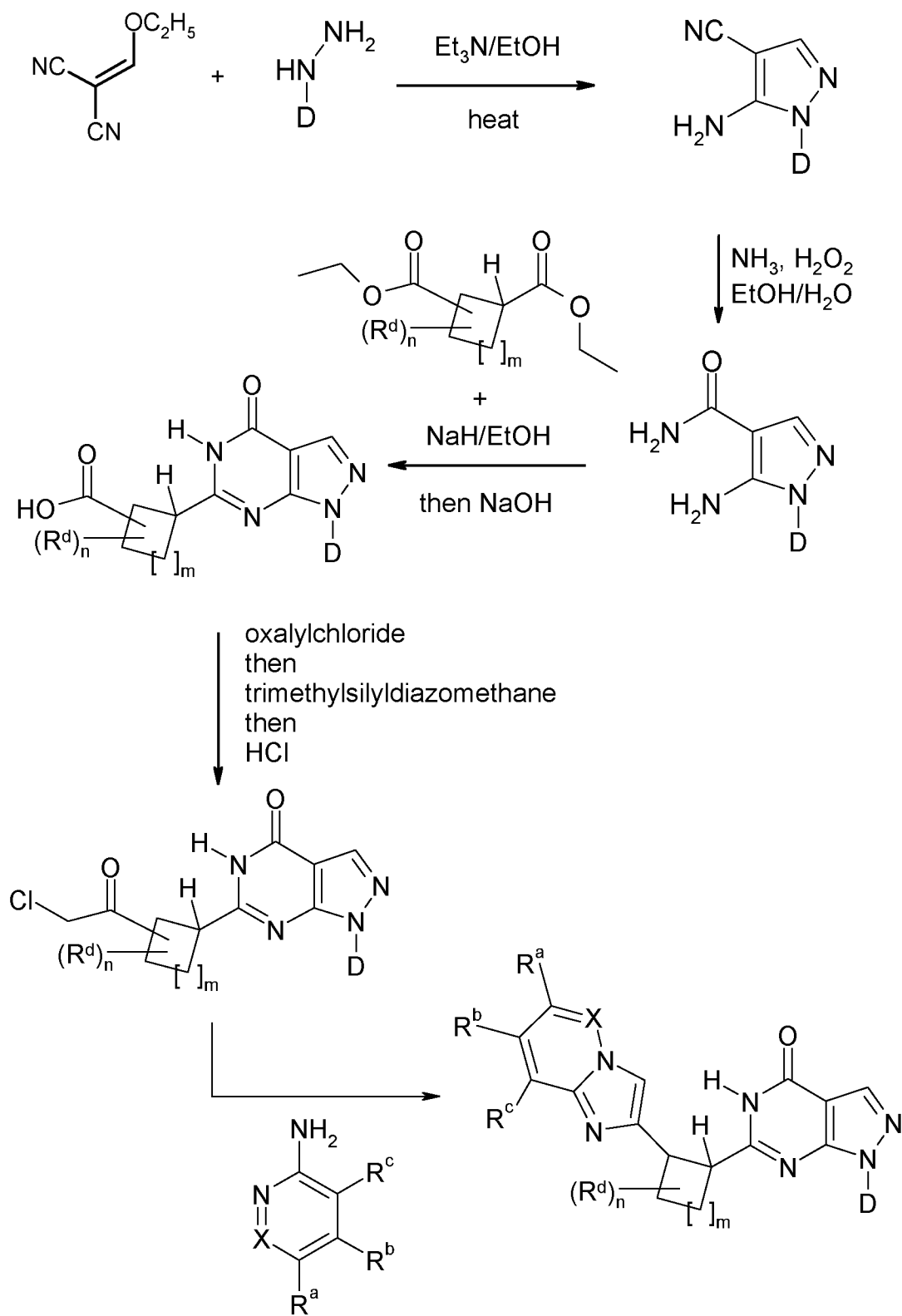
5 The terms “**pyridyl**” defines a pyridine-substituent, sometimes also called pyridinyl.

Expressions like "**prevention**", "**prophylaxis**", "**prophylactic treatment**" or "**preventive treatment**" used herein should be understood synonymous and in the sense that the risk to develop a condition mentioned hereinbefore is reduced, especially in a patient having elevated risk for said conditions or a corresponding anamnesis. Thus the expression "prevention of a disease" as used herein means the management and care of an individual at risk of developing the disease prior to the clinical onset of the disease. The purpose of prevention is to combat the development of the disease, condition or disorder and includes the administration of the active compounds to prevent or delay the onset of the symptoms or complications and to prevent or delay the development of related diseases, conditions or disorders. Success of said preventive treatment is reflected statistically by reduced incidence of said condition within a patient population at risk for this condition in comparison to an equivalent patient population without preventive treatment.

20 The expression "**treatment**" or "**therapy**" preferably means therapeutic treatment of (e.g. preferably human) patients having already developed one or more of said conditions in manifest, acute or chronic form, including symptomatic treatment in order to relieve symptoms of the specific indication or causal treatment in order to reverse or partially reverse the condition or to delay the progression of the indication as far as this may be possible, depending on the condition and the severity thereof. Thus the expression "treatment of a disease" as used herein means the management and care of a patient having developed the disease, condition or disorder. The purpose of treatment is to combat the disease, condition, disorder or a symptom thereof. Treatment includes the administration of the active compounds to eliminate or control the disease, condition or disorder as well as to alleviate the symptoms or complications associated with the disease, condition or disorder.

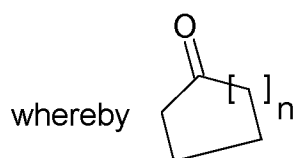
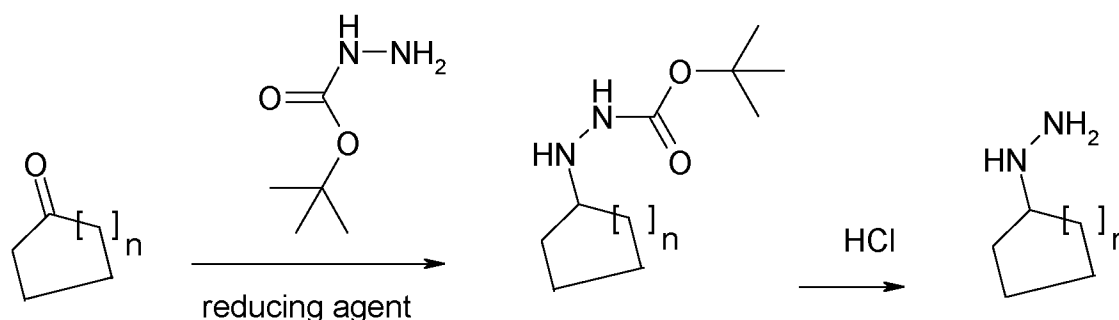
The following schemes shall illustrate generally how to manufacture the compounds of the present invention by way of example. The abbreviated substituents may be as defined for the embodiments of formula (I) if not defined otherwise within the context of the schemes:

Scheme 1



Scheme 1: In a first step 2-ethoxymethylene-malononitrile is condensed with mono-substituted hydrazines by heating in an appropriate solvent like ethanol in the presence of a base (e.g. triethylamine) to form the corresponding 5-amino-1H-pyrazole-4-carbonitriles. These compounds are converted in a second step to the corresponding amides, e.g. by treatment of an ethanolic solution with ammonia (25 % in water) and hydrogen peroxide (35 % in water). In a third step, heating with dicarboxylic acid diesters under basic conditions (e.g. sodium hydride in ethanol) followed by the addition of aqueous sodium hydroxide leads to 4-oxo-4,5-dihydro-1H-pyrazolo[3,4-d]pyrimidin-6-yl substituted carboxylic acids. Successive reaction with oxalylchloride, trimethylsilyldiazomethane and hydrochloric acid, followed by reaction with the corresponding 2-aminopyridazine(s), or the corresponding 2-amino-pyridine(s) respectively, leads to the final product(s).

Scheme 2



is cyclopentyl or cyclohexyl optionally substituted as defined in formula (I). Consequently, $n = 1$ or 2

15

Scheme 2: The mono-substituted hydrazine derivatives, that are used in step 1 of scheme 1 can be prepared by reductive amination of a ketone with hydrazinecarboxylic acid tert-butyl ester followed by a deprotection step as shown in scheme 4 for an D being cyclopentyl or cyclohexyl as defined in general formula (I) [cf., for example, J.W. Timberlake *et al.*, "Chemistry of

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Hydrazo-, Azo- and Azoxy Groups"; Patai, S., Ed.; 1975, Chapter 4; S. C. Hung et al., *Journal of Organic Chemistry* 1981, 46, 5413-5414].

Further information also can be found in:

- 5 - WO 2004/099210 (in particular page 9, last paragraph to page 14, line 8, incorporated by reference),
- with respect to the general manufacture of compounds with D being tetrahydropyranyl more information can be found in WO2009/121919, particularly on page 120 to 125 and the experimental part thereof (herewith incorporated by reference),
- 10 - with respect to D being 4,4-difluorocyclohexyl more information can be found in WO 2010/026214, particularly on page 59 to 63 and the experimental part thereof (herewith incorporated by reference),
- and in the experimental section (exemplary embodiments) of this description.

15

METHOD OF TREATMENT

The present invention refers to compounds, which are considered effective in the treatment of diseases. The compounds according to the invention effectively inhibit phosphodiesterase 9A and show preference in for PDE9A compared with other PDE family members. Therefore the

20 compounds are effective and selective inhibitors of PDE9A and can be used for the development of medicaments. Such medicaments shall preferably be used for the treatment of diseases in which the inhibition of PDE9A can result in a therapeutic, prophylactic or disease modifying effect. Preferably the medicaments shall be used to improve perception, concentration, cognition, learning or memory, in particular in situations/diseases/syndromes

25 such as:

mild cognitive impairment, age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's

disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy, temporal lobe epilepsy, schizophrenia, schizophrenia (with dementia), Korsakoff's psychosis or cognitive impairment associated with depression or bipolar disorder.

Another aspect of the present invention concerns the treatment of a disease which is accessible by PDE9A modulation, in particular sleep disorders like insomnia or narcolepsy, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, including type 1 or type 2 diabetes, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

Thus the medical aspect of the present invention can be summarised in that it is considered that a compound according to formula (I) or (II) as herein defined, in particular the specifically defined species compounds is used as a medicament.

Such a medicament preferably is for the treatment of a CNS disease.

In an alternative use, the medicament is for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9.

In an alternative use, the medicament is for the treatment of a disease that is accessible by the inhibition of PDE9, specifically PDE9A.

In an alternative use, the medicament is for the treatment, amelioration and / or prevention of cognitive impairment being related to perception, concentration, cognition, learning or memory, preferably if such cognitive impairment is associated with a disease or condition as described in this section.

In an alternative use, the medicament is for the treatment amelioration and / or prevention of cognitive impairment being related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems,

Alzheimer's disease, Lewy body dementia, dementia with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy,
5 temporal lobe epilepsy, schizophrenia (with dementia), Korsakoff's psychosis or cognitive impairment associated with depression or bipolar disorder.

In an alternative use, the medicament is for the treatment of Alzheimer's disease, schizophrenia or cognitive impairment associated with Alzheimer's disease or associated with schizophrenia.

10 In an alternative use, the medicament is for the treatment of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

15 In a further aspect of the invention, the present invention relates to the method of treatment or prevention of a condition or disease selected from the above listed groups of conditions and diseases, whereby the method comprises the administration of a therapeutically effective amount of a compound according to the invention in a human being in need thereof.

20 **PHARMACEUTICAL COMPOSITIONS**

Medicaments for administration, which are also subject to the present invention, comprise a compound according to the present invention in a therapeutically effective amount and a pharmaceutical carrier. By "therapeutically effective amount" it is meant that if the medicament is applied via the appropriate regimen adapted to the patient's condition, the
25 amount of said compound of formula (I) will be sufficient to effectively treat, to prevent or to decelerate the progression of the corresponding disease, or otherwise to ameliorate the state of a patient suffering from such a disease. It may be the case that the "therapeutically effective amount" in a mono-therapy will differ from the "therapeutically effective amount" in a combination therapy with another medicament.

30

The dose range of the compounds of general formula (I) applicable per day may be usually from 0.1 to 5000 mg, preferably from 0.1 to 1000 mg, preferably from 2 to 500 mg, more

preferably from 5 to 250 mg, most preferably from 10 to 100 mg. A dosage unit (e.g. a tablet) preferably may contain between 2 and 250 mg, particularly preferably between 10 and 100 mg of the compounds according to the invention.

- 5 The actual pharmaceutically effective amount or therapeutic dosage will depend on factors known by those skilled in the art such as age, weight, gender or other condition of the patient, route of administration, severity of disease and the like.

The compounds according to the invention may be administered by oral, parenteral
10 (intravenous, intramuscular etc.), intranasal, sublingual, inhalative, intrathecal, topical or rectal route. Suitable preparations for administering the compounds according to the present invention include for example patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like. The content of
15 the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium
20 stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac,
25 gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

30 Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose,

wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions may be prepared in the usual way, e.g. with the addition of isotonic agents,
5 preservatives such as p-hydroxybenzoates or stabilisers such as alkali metal salts of ethylene-diamine-tetra-acetic acid, optionally using emulsifiers and/or dispersants, while if water shall be used as diluent, for example, organic solvents may optionally be used as solubilisers or dissolving aids and the solutions may be transferred into injection vials or ampoules or infusion bottles.

10

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

15 Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable oils (e.g. groundnut or
20 sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates), sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and
25 polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

For oral use the tablets may contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatine and the like. Lubricants such as
30 magnesium stearate, sodium laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated.

COMBINATIONS WITH OTHER ACTIVE SUBSTANCES

5 In another aspect, the present invention relates to a combination therapy in which a compound according to the present invention is administered together with another active compound. Accordingly, the invention also refers to pharmaceutical formulations that provide such a combination of active ingredients, whereby one of which is a compound of the present invention. Such combinations may be fixed dose combinations (the active ingredients that are
10 to be combined are subject of the same pharmaceutical formulation) or free dose combinations (active ingredients are in separate pharmaceutical formulations).

Consequently, a further aspect of the present invention refers to a combination of each of the compounds of the present invention, preferably at least one compound according to the
15 present invention, with another active compound for example selected from the group of beta-secretase inhibitors; gamma-secretase inhibitors; gamma-secretase modulators; amyloid aggregation inhibitors such as e.g. alzhemed; directly or indirectly acting neuroprotective and/or disease-modifying substances; anti-oxidants, such as e.g. vitamin E , ginko biloba or ginkgolide; anti-inflammatory substances, such as e.g. Cox inhibitors, NSAIDs additionally or
20 exclusively having A β (Abeta) lowering properties; HMG-CoA reductase inhibitors, such as statins; acetylcholine esterase inhibitors, such as donepezil, rivastigmine, tacrine, galantamine; NMDA receptor antagonists such as e.g. memantine; AMPA receptor agonists; AMPA receptor positive modulators, AMPkines, glycine transporter 1 inhibitors; monoamine receptor reuptake inhibitors; substances modulating the concentration or release of
25 neurotransmitters; substances inducing the secretion of growth hormone such as ibutamoren mesylate and capromorelin; CB-1 receptor antagonists or inverse agonists; antibiotics such as minocyclin or rifampicin; PDE1, PDE2, PDE4, PDE5 and / or PDE10 inhibitors, GABAA receptor inverse agonists; GABAA alpha5 receptor inverse agonists; GABAA receptor antagonists; nicotinic receptor agonists or partial agonists or positive modulators; alpha4beta2
30 nicotinic receptor agonists or partial agonists or positive modulators; alpha7 nicotinic receptor agonists or partial agonists; histamine receptor H3 antagonists; 5-HT4 receptor agonists or partial agonists; 5-HT6 receptor antagonists; alpha2-adrenoreceptor antagonists, calcium antagonists; muscarinic receptor M1 agonists or partial agonists or positive modulators;

muscarinic receptor M2 antagonists; muscarinic receptor M4 antagonists; metabotropic glutamate receptor 5 positive allosteric modulators; metabotropic glutamate receptor 2 antagonists, metabotropic glutamate receptor 2/3 agonists, metabotropic glutamate receptor 2 positive allosteric modulators and other substances that modulate receptors or enzymes in a manner such that the efficacy and/or safety of the compounds according to the invention is increased and/or unwanted side effects are reduced.

This invention further relates to pharmaceutical compositions containing one or more, preferably one active substance. At least one active substance is selected from the compounds according to the invention and/or the corresponding salts thereof. Preferably the composition comprises only one such active compound. In case of more than one active compound the other one can be selected from the aforementioned group of combination partners such as alzhemed, vitamin E, ginkgolide, donepezil, rivastigmine, tacrine, galantamine, memantine, ibutamoren mesylate, capromorelin, minocyclin and/or rifampicin. Optionally the composition comprises further ingredients such as inert carriers and/or diluents.

The compounds according to the invention may also be used in combination with immunotherapies such as e.g. active immunisation with A β or parts thereof or passive immunisation with humanised anti-A β antibodies or antibody fragments for the treatment of the above mentioned diseases and conditions.

The compounds according to the invention also may be combined with Dimebon.

The compounds according to the invention also may be combined with antidepressants like amitriptyline imipramine hydrochloride (TOFRANIL), imipramine maleate (SURMONTIL), lofepramine, desipramine (NORPRAMIN), doxepin (SINEQUAN, ZONALON), trimipramine (SURMONTIL).

Or the compounds according to the invention also may be combined with serotonin (5-HT) reuptake inhibitors such as alaproclate, citalopram (CELEXA, CIPRAMIL) escitalopram (LEXAPRO, CIPRALEX), clomipramine (ANAFRANIL), duloxetine (CYMBALTA), femoxetine (MALEXIL), fenfluramine (PONDIMIN), norfenfluramine, fluoxetine (PROZAC), fluvoxamine (LUVOX), indalpine, milnacipran (IXEL), paroxetine (PAXIL, SEROXAT), sertraline (ZOLOFT, LUSTRAL), trazodone (DESYREL, MOLIPAXIN),

venlafaxine (EFFEXOR), zimelidine (NORMUD, ZELMID), bicifadine, desvenlafaxine (PRISTIQ), brasofensme and tesofensine.

5 The combinations according to the present invention may be provided simultaneously in one and the same dosage form, i.e. in form of a combination preparation, for example the two components may be incorporated in one tablet, e. g. in different layers of said tablet. The combination may be also provided separately, in form of a free combination, i.e. the compounds of the present invention are provided in one dosage form and one or more of the above mentioned combination partners is provided in another dosage form. These two dosage
10 forms may be equal dosage forms, for example a co-administration of two tablets, one containing a therapeutically effective amount of the compound of the present invention and one containing a therapeutically effective amount of the above mentioned combination partner. It is also possible to combine different administration forms, if desired. Any type of suitable administration forms may be provided.

15

The compound according to the invention, or a physiologically acceptable salt thereof, in combination with another active substance may be used simultaneously or at staggered times, but particularly close together in time. If administered simultaneously, the two active substances are given to the patient together; if administered at staggered times the two active
20 substances are given to the patient successively within a period of less than or equal to 12, particularly less than or equal to 6 hours.

The dosage or administration forms are not limited. In the context of the present invention any suitable dosage form may be used. For example, the dosage forms may be selected from solid
25 preparations such as patches, tablets, capsules, pills, pellets, dragees, powders, troches, suppositories, liquid preparations such as solutions, suspensions, emulsions, drops, syrups, elixirs, or gaseous preparations such as aerosols, sprays and the like.

The dosage forms are advantageously formulated in dosage units, each dosage unit being
30 adapted to supply a single dose of each active component being present. Depending from the administration route and dosage form the ingredients are selected accordingly.

The dosage for the above-mentioned combination partners may be expediently 1/5 of the normally recommended lowest dose up to 1/1 of the normally recommended dose.

5 The dosage forms are administered to the patient for example 1, 2, 3, or 4 times daily depending on the nature of the formulation. In case of retarding or extended release formulations or other pharmaceutical formulations, the same may be applied differently (e.g. once weekly or monthly etc.). It is preferred that the compounds of the invention be administered either three or fewer times, more preferably once or twice daily.

10 **EXAMPLES**

PHARMACEUTICAL COMPOSITIONS

Examples which might illustrate possible pharmaceutical formulations, without being meant to be limiting:

15

The term "active substance" denotes one or more compounds according to the invention including the salts thereof. In the case of one of the aforementioned combinations with one or more other active substances the term "active substance" may also include the additional active substances.

20

Example A

Tablets containing 100 mg of active substance

25 Composition: tablet

active substance	100.0 mg
lactose	80.0 mg
corn starch	34.0 mg
polyvinylpyrrolidone	4.0 mg
magnesium stearate	<u>2.0 mg</u>
	220.0 mg

Example BTablets containing 150 mg of active substance

5

Composition: tablet

active substance	150.0 mg
powdered lactose	89.0 mg
corn starch	40.0 mg
colloidal silica	10.0 mg
polyvinylpyrrolidone	10.0 mg
magnesium stearate	<u>1.0 mg</u>
	300.0 mg

Example C

10

Hard gelatine capsules containing 150 mg of active substance

active substance	150.0 mg
lactose	87.0 mg
corn starch (dried)	80.0 mg
magnesium stearate	<u>3.0 mg</u>
	320.0 mg

Example D

15

Composition: suppository

active substance	150.0 mg
polyethyleneglycol 1500	550.0 mg
polyethyleneglycol 6000	460.0 mg

polyoxyethylene sorbitan 840.0 mg
monostearate
2000.0 mg

Example E

Composition: ampoules containing 10 mg active substance

5 active substance 10.0 mg
0.01 N hydrochloric acid q.s.
double-distilled water ad 2.0 mL

10 Example F

Composition: ampoules containing 50 mg of active substance

active substance 50.0 mg
0.01 N hydrochloric acid q.s.
15 double-distilled water ad 10.0 mL

The preparation of any the above mentioned formulations can be done following standard procedures.

20

BIOLOGICAL ASSAY

The *in-vitro* effect of the compounds of the invention can be shown with the following biological assays.

25 PDE9A2 assay protocol:

The PDE9A2 enzymatic activity assay was run as scintillation proximity assay (SPA), in general according to the protocol of the manufacturer (GE Healthcare, former Amersham Biosciences, product number: TRKQ 7100).

5 As enzyme source, lysate (PBS with 1 % Triton X-100 supplemented with protease inhibitors, cell debris removed by centrifugation at 13.000 rpm for 30 min) of SF 9 cell expressing the human PDE9A2 was used. The total protein amount included in the assay varied upon infection and production efficacy of the SF9 cells and lay in the range of 0.1 – 100 ng.

In general, the assay conditions were as follows:

- 10
- total assay volume: 40 microlitre
 - protein amount: 0.1 – 50 ng
 - substrate concentration (cGMP): 20 nanomolar; ~1 mCi/l
 - incubation time: 60 min at room temperature
 - final DMSO concentration: 0.2 - 1 %

15

The assays were run in 384-well format. The test reagents as well as the enzyme and the substrate were diluted in assay buffer. The assay buffer contained 50 mM Tris, 8.3 mM MgCl₂, 1.7 mM EGTA, 0.1 % BSA, 0.05 % Tween 20; the pH of assay buffer was adjusted to 7.5. The reaction was stopped by applying a PDE9 specific inhibitor (e.g. compounds
20 according to WO 2004/099210 or WO 2004/099211, like one of the enantiomers of example 37, e.g. 1-(2-Chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methyl-propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one) in excess.

References:

25 Wunder F, Tersteegen A, Rebmann A, Erb C, Fahrig T, Hendrix M. Characterization of the first potent and selective PDE9 inhibitor using a cGMP reporter cell line. *Molecular Pharmacology*. 2005 Dec;68(6):1775-81.

30 van der Staay FJ, Rutten K, Bärfacker L, Devry J, Erb C, Heckroth H, Karthaus D, Tersteegen A, van Kampen M, Blokland A, Prickaerts J, Reymann KG, Schröder UH, Hendrix M. The novel selective PDE9 inhibitor BAY 73-6691 improves learning and memory in rodents. *Neuropharmacology*. 2008 Oct;55(5):908-18.

PDE1C assay protocol:

The assay was run in an analogous manner to the PDE9A2 assay, with the following differences: instead of PDE9A2 PDE1C has been used and the assay buffer contained in addition 50 nM Calmodulin, 3 mM CaCl₂. The reaction can be stopped by applying the same inhibitor as the one that is outlined above (1-(2-Chlorophenyl)-6-[(2R)-3,3,3-trifluoro-2-methyl-propyl]-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidine-4-one).

Determination of IC₅₀:

IC₅₀ can be calculated with GraphPadPrism or other suitable software setting the positive control as 100 and the negative control as 0. For calculation of IC₅₀, dilutions of the test compounds (substrates) are selected and tested following the aforementioned protocol.

Data

In the following IC₅₀ values for PDE9A2 inhibition [nanomolar (nM)] illustrate that the compounds according to the present invention inhibit PDE9, specifically PDE9A2. This shows that the compounds provide useful pharmacological properties. The examples are not meant to be limiting.

The table also provides selectivity values (Selectivity) that show a preference of the compounds for PDE9A versus PDE1C. Selectivity is the ratio (IC₅₀ for PDE1C inhibition [nanomolar (nM)]) / (IC₅₀ for PDE9A2 inhibition [nanomolar (nM)]).

The example numbers refer to the final examples as outlined in the section **Exemplary embodiments**.

All data can be measured according to the procedure described herein. The definition enantiomer 1 or enantiomer 2 is refers to the elution orders of enantiomers in chiral SFC and chiral HPLC.

Compound family	Example No.	IC ₅₀ PDE9A2 [nanomolar]	Selectivity
A	1*	1	288
A	2 (<i>trans</i> enantiomer 1)	0.5	532
A	3 (<i>trans</i> enantiomer 2)	19	85
C	4*	6	123
D	5*	10	40

* *trans* racemic mixture

***In-vivo* effect:**

It is believed that the positive *in-vitro* efficacy results of the compounds of the present invention translate in positive *in-vivo* efficacy.

The *in-vivo* effects of the compounds of this invention can be tested in the Novel Object Recognition test according to the procedure of Prickaerts *et al.* (*Neuroscience* **2002**, *113*, 351-361), the social recognition test or the T-maze spontaneous alternation test according to the procedures described by van der Staay *et al.* (*Neuropharmacology* **2008**, *55*, 908-918). For further information concerning biological testing one is also referred to these two citations.

Besides the inhibition property toward the target PDE9, compounds according to the present invention may provide further advantageous pharmacokinetic properties.

For example, compounds according to the invention may show one or more advantages in the area of safety, balanced metabolism, low risk of causing drug - drug interaction and/or balanced clearance.

Compounds also might show one or more additional or alternative advantages in the area of bioavailability, high fraction absorbed, blood brain transport properties, a favourable (e.g. high mean) residence time (mrt), favourable exposure in the effect compartment and so on.

CHEMICAL MANUFACTURE

Abbreviations:

5		
	APCI	Atmospheric pressure chemical ionization
	ACN	acetonitrile
	DCM	dichloromethane
	DEA	diethylamine
10	DIPEA	diisopropylethylamine
	DME	1,2-dimethoxyethane
	DMF	dimethylformamide
	EI	electronic impact
	ESI	electrospray ionization (in MS)
15	EtOH	ethanol
	Exp.	Example
	GC-MS	gas chromatography with mass spectrometric detection
	h	hour(s)
	HPLC	high performance liquid chromatography
20	HPLC-MS	coupled high performance liquid chromatography-mass spectrometry
	M	molar (mol/L)
	MeOH	methanol
	min	minutes
	MS	mass spectrometry
25	NMP	1-methyl-2-pyrrolidinone
	R _t	retention time (in HPLC)
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin-layer chromatography
30	UPLC	ultra performance liquid chromatography

UPLC-MS methods:**Method 1 (NH₄COOH)**

Instrument: LC/MS Waters Acquity UPLC System DAD, SQD single quadrupole. Column:
5 BEH C18 1.7 μm, 2.1 mm x 50 mm; eluent A: water + ammonium formate 5 mM + 10 %
acetonitrile; eluent B: acetonitrile; gradient: A 100 %, then to B 100% in 1.20 min for 0.25
min; flow rate: 0.7 mL/min; UV detection: 254 nm; ion source: ESI.

LC-MS methods:**Method 1**

10 MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695,
Waters 2996 diode array detector; column: Varian Microsorb 100 C18, 30 x 4.6 mm, 3.0 μm;
eluent A: water + 0.13 % TFA, eluent B: ACN; gradient: 0.0 min 5 % B → 0.18 min 5 % B
→ 2.0 min 98 % B → 2.2 min 98 % B → 2.3 min 5 % B → 2.5 min 5 % B; flow rate: 3.5
mL/min; UV detection: 210-380 nm.

15

Method 1E hydro

Instrument: LC/MS ThermoFinnigan. Hplc Surveyor DAD, MSQ Quadrupole; column:
Synergi Hydro-RP80A, 4 μm, 4.60 x 100 mm; eluent A: 90% water + 10%
acetonitrile+ammonium formate 10 mM; eluent B = ACN 90%+10% H₂O + NH₄COOH 10
20 mM; gradient: A(100) for 1.5 min, then to B (100) in 10 min for 1.5 min; flow rate: 1.2
mL/min; UV Detection: 254nm; Ion source: APCI.

Method 3

MS apparatus type: Waters Micromass ZQ; HPLC apparatus type: Waters Alliance 2695,
25 Waters 2996 diode array detector; column: Varian Microsorb C18, 20 x 4.6 mm, 5.0 μm;
eluent A: water + 0.15 % TFA, eluent B: MeOH; gradient: 0.0 min 5 % B → 0.25 min 5 % B
→ 1.90 min 100 % B → 2,05 min 100 % B → 2.15 min 5 % B → 2.25 min 5 % B; flow rate:
5.2 mL/min; UV detection: 210-400 nm.

GC/MS methods**Method 3A.2**

Instrument: GC/MS Finnigan Thermo Scientific. Trace GC Ultra, DSQ II single quadrupole.

- 5 Column: DB-5MS, 25 m x 0.25 mm x 0.25 μ m; carrier gas: helium, 1 mL/min constant flow; oven program: 50°C (hold 1 minute), to 100°C in 10°C/min, to 200°C in 20°C/min, to 300°C in 30°C/min eluent, detection: trace DSQ II, single quadrupole; ion source: EI. Scan range: 50-450 a

10 **Chiral HPLC methods:**

Chiral Method 1:

HPLC apparatus type: Agilent 1100; column: Daicel chiralcel OJ-H, 250 mm x 4.6 mm, 5.0 μ m; eluent: hexane/EtOH 80:20; flow rate: 1 mL/min, Temperature: 25°C; UV Detection: variable (200- 500 nm).

15

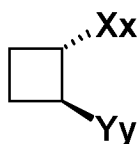
MICROWAVE HEATING:

- Discover® CEM instruments, equipped with 10 and 35 mL vessels.

20 **General comment concerning the presentation of the structures**

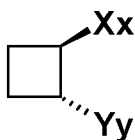
Some compounds have stereogenic centre(s). The structures depicted in the experimental section, below, will not necessarily show all the possible stereochemical possibilities of the compounds but only one. However, in such cases a term like “trans - racemic mixture” or “cis-racemic mixture” is added next to the depicted structure in order to indicate the other
25 stereochemical options.

An example is given below. The presented structural formula is

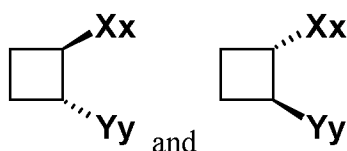


The added term “trans-racemic mixture” points to the second stereochemical option:

trans - racemic mixture

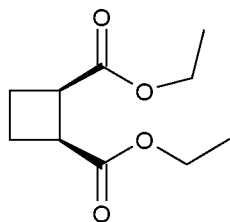


5 Thus, the manufactured compound is a mixture of



This principle applies to other depicted structures as well.

Example 1A (cis – racemic mixture)



10

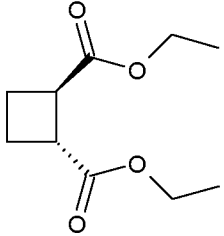
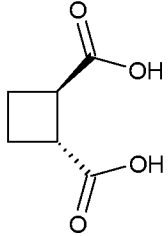
2.00 g (13.9 mmol) cis-cyclobutan-1,2-dicarboxylic acid were mixed with 15.5 mL EtOH at 0°C and 2.15 mL (29.5 mmol) thionylchloride were slowly added. The mixture was allowed to warm to room temperature and stirred for 2h. The solvent was removed under reduced pressure and the product was filtered through a pad of activated basic alumina that was afterwards washed with DCM. 2.70 g of the product were obtained.

15

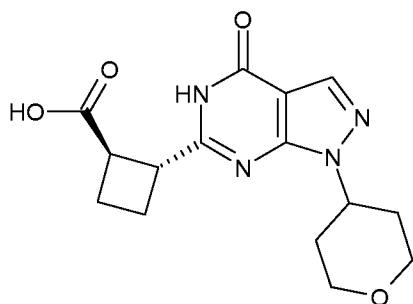
GC (Method 3A.2): R_t : 8.42 min

MS (EI): m/z: 155 (M-45)⁺, 127 (M-73)⁺

The following example was synthesized in analogy to the preparation of Example 1A, using the corresponding diacid as starting material.

Example	Structure	starting material	R _t [min]	MS (ESI pos, m/z)
Exp. 1B trans – racemic mixture			1.34 (Method 1)	201 (M+H) ⁺

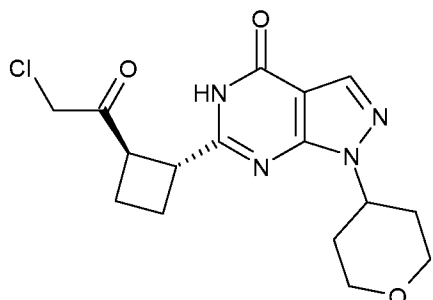
5 Example 2A (trans – racemic mixture)



1.17 g (5.5 mmol) 5-Amino-1-(tetrahydro-pyran-4-yl)-1H-pyrazole-4-carboxylic acid amide
 10 amide (see PCT patent application WO 09-121919) was mixed with 15 mL of anhydrous
 EtOH, 2.7 g (13.8 mmol) of Example 1A and 0.89 g (22.2 mmol) of sodium hydride (60 %
 suspension in mineral oil) were added. The reaction mixture was heated to 140°C for 40 min
 in a microwave oven (Power: 150 W). The mixture was cooled to room temperature, the
 solvent was removed under reduced pressure and the residue taken up with Citric Acid (5 ml
 15 of 10% solution in water); DCM was added and the organic phase was separated through a
 phase separator cartridge. The crude obtained after evaporation of solvents (2.18 g) was
 purified by flash-chromatography [Eluent: (DCM/MeOH/AcOH 90:10:1)/DCM] starting with
 DCM and eluting the final product with a 1/1 ratio of the above described eluent. 1.14g (64
 %) of the product were obtained.
 20 UPLC-MS (Method 1): R_t = 0.54

MS (ESI pos): $m/z = 319 (M+H)^+$

Example 3A (trans – racemic mixture)



5

0.50 g (1.76 mmol) of Example 2A were dissolved in THF (5 ml) under inert atmosphere; the temperature was lowered at 0°C before the addition of DMF (1 drop) and oxalyl chloride (0.167 ml, 1.94 mmol). The reaction mixture was stirred 2h at 0°C and afterwards trimethylsilyldiazomethane (2M solution in diethyl ether) was added (1.76 ml; 3.52 mmol).

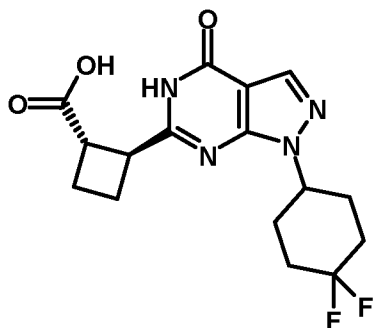
10 After 2h hydrochloric acid (4M solution in dioxane) was added (0.88 ml; 3.52 mmol) and the temperature increased to room temperature. The mixture was diluted with DCM and washed with NaHCO₃ saturated solution; the aqueous phase was extracted with DCM. The organic phases were collected and washed with NaCl saturated solution; the organic phase was dried and the residue obtained after evaporation of solvents (0.54 g) was used as such in the next

15 steps.

UPLC-MS (Method 1): $R_t = 0.82$

MS (ESI pos): $m/z = 351, 353 (M+H)^+$

20 **Example 4A (trans – racemic mixture)**

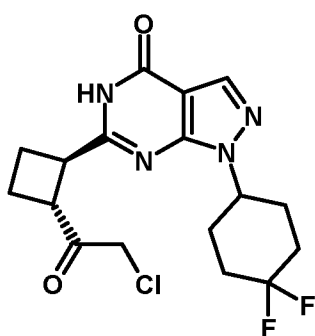
**trans - racemic mixture**

1.00 g (4.09 mmol) 5-Amino-1-(4,4-difluoro-cyclohexyl)-1H-pyrazole-4-carboxylic acid amide (see PCT patent application WO 2010/026214, example 8A) was mixed with 15 mL of anhydrous EtOH, 2.46 g (12.3 mmol) of Example 1B and 0.66 g (16.4 mmol) of sodium hydride (60 % suspension in mineral oil) were added. The reaction mixture was heated to 140°C for 30 min in a microwave oven. The mixture was cooled to room temperature and sodium hydroxide solution (4 M aqueous solution) was added. The solvent was removed under reduced pressure. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: MeOH). 0.70 g (49 %) of the product were obtained.

HPLC-MS (Method 1): $R_t = 1.24$ min

MS (ESI pos): $m/z = 353$ (M+H)⁺

Example 5A (trans – racemic mixture)



15 **trans - racemic mixture**

0.250 g (0.71 mmol) of Example 4A were mixed with 2 mL THF. The mixture was cooled with an ice bath and 0.060 mL (0.71 mmol) oxalylchloride and one drop of DMF were added. The reaction mixture was stirred at 0°C for 1 h. To the reaction mixture were added 4 mL ACN and 0.710 mL trimethylsilyldiazomethane (2.0 M in hexane, 1.42 mmol). The mixture

was stirred at 0°C for 2 h, then 0.355 mL HCl (4.0 M in dioxane) was slowly added. The reaction was stirred for 15 min. To the mixture were added ethylacetate and saturated sodium hydrogen carbonate solution. The organic layer was washed with water and brine and partially evaporated. The product was used for the next reaction without further purification.

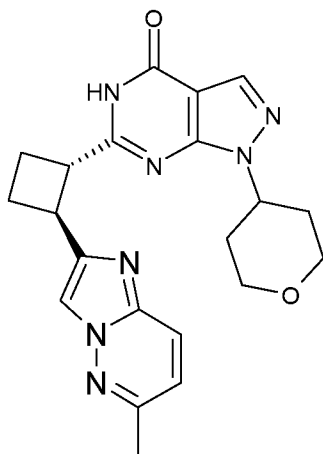
5 HPLC-MS (Method 1): $R_t = 1.40$ min

MS (ESI pos): $m/z = 385/387$ (Cl).

Exemplary embodiments

Example 1 (trans – racemic mixture)

10



Example 3A (1g, 2.85 mmol) was suspended in dimethoxyethane in a 50 ml Schlenk tube; 3-amino-6-methyl pyridazine was added; the Schlenk tube was closed with a stopper and the reaction mixture heated at 95°C during 14h.

15 The temperature was lowered, the solvent was removed under reduced pressure and the crude passed through a SPE “STRATA” 10g SCX cartridge eluting with MeOH and afterwards with a NH_3 solution in MeOH; the obtained residue was purified by flash chromatography [EluentS: Cyclohexane/EtOAc (from 1/1 to 100% EtOAc), then EtOAc/MeOH (9/1)], yielding 0.69g (59%) of the title compound.

20 HPLC-MS (Method 1Eh): $R_t = 7.62$

MS (APCI): $m/z = 406$ (M+H)⁺

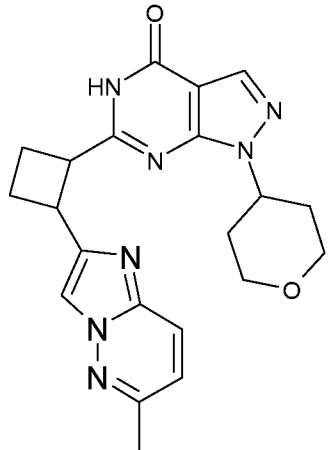
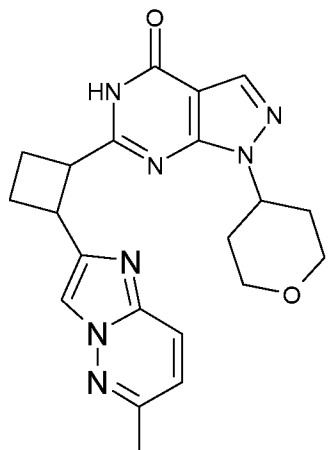
The enantiomers of Example 1 were separated by semipreparative chiral HPLC.

Method for semipreparative enantioseparation:

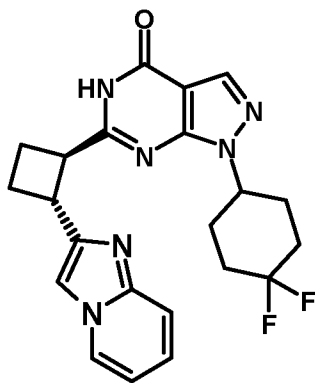
Semipreparative conditions:

HPLC semipreparative system: Waters 600 pump; column: Daicel chiralcel OJ-H, 5.0 μm , 250 mm x 20 mm; eluent: hexane/EtOH 80:20; flow rate: 15 mL/min, Temperature: 25°C; UV Detection: 230 nm.

5

Example	structure	R _t [min]
Exp. 2 trans - enantiomer 1		14.84 (Chiral Method 1)
Exp. 3 trans - enantiomer 2		17.51 (Chiral Method 1)

Example 4 (trans – racemic mixture)



To Example 5A (crude product synthesized from 0.250 g (0.71 mmol) of Example 4A) was added dropwise 0.118 g (1.24 mmol) pyridin-2-ylamine in 4 mL EtOH. The reaction mixture was stirred overnight. The EtOH was evaporated and the residue was mixed with 2 ml DMF and heated to 50°C for 2h. The residue was purified by preparative HPLC (eluent A: water + 0.13 % TFA, eluent B: MeOH). After freeze drying the residue was diluted with 2 ml 10% aqueous K₂CO₃ and extracted with DCM. Evaporation of the solvent and freeze drying from ACN/water yielded 44 mg of the product.

HPLC-MS: (Method 3): R_t = 1.20 min; MS (ESI pos): m/z = 425 (M+H)⁺

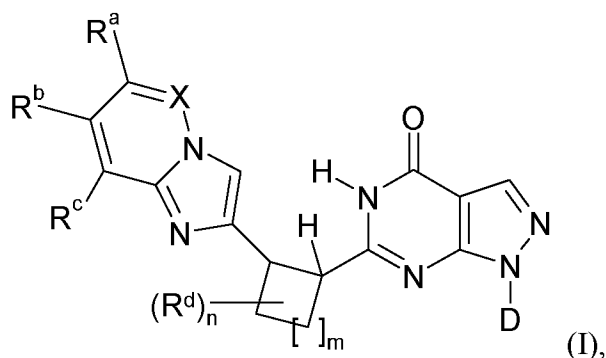
10

The following example was synthesized in analogy to the preparation of Example 4, using the corresponding amine as starting material.

Example	structure	starting material: amine	Rt [min]	MS (ESI pos, m/z)
Exp. 5 trans – racemic mixture		4-chlor-pyridin-2-ylamine	1,21 (Method 3)	459/61 (Cl) (M+H) ⁺

Claims

1. A compound of formula (I)



5 wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, C₁₋₆-alkyl-, C₁₋₆-alkyl-O-, -CF₃, -CHF₂, -CH₂F, NC- and halogen;

10 whereby C₁₋₆-alkyl- and C₁₋₆-alkyl-O- optionally may be substituted with halogen, preferably with fluoro

R^d: is selected from the group consisting of fluorine, NC-, -CF₃, -CHF₂, -CH₂F and methyl;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

15 whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, NC-, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, NC-, F₃C-, HF₂C- and FH₂C-;

20 whereby pyridyl optionally may be substituted by 1, 2, 3 or 4 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably 1;

25 n: is selected from 0, 1 or 2, preferably, 0 or 1, more preferably 0,

whereby if n = 2, the two groups R^d are selected independently of one another;

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

5 2. A compound according to claim 1,

wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, C₁₋₃-alkyl-, C₁₋₃-alkyl-O-, -CF₃, -CHF₂, -CH₂F, NC- and halogen;

10 whereby C₁₋₆-alkyl- and C₁₋₆-alkyl-O- optionally may be substituted with halogen, preferably with fluoro

R^d: is selected from the group consisting of fluorine, NC-, -CF₃, -CHF₂, -CH₂F and methyl;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

15 whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

20 whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

25 m: is selected from 1 or 2, preferably m is 1;

n: is selected from the group consisting 0, 1 or 2, preferably n is 0 or 1, more preferably n is 0, whereby if n = 2, the two groups R^d are selected independently of one another;

30 and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

3. A compound according to claim 2,

wherein

X is N or CR^e,

R^a, R^b, R^c, R^e are selected independently of each other from the group consisting of H, methyl, ethyl, methoxy, ethoxy, CF₃-, -CHF₂, -CH₂F, NC- and halogen; preferably R^a, R^b,

5 R^c, R^e are selected independently of each other from the group consisting of H, methyl, ethyl, methoxy, ethoxy, CF₃- and NC-,

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

10 whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

15 whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

m: is selected from 1 or 2, preferably m is 1;

20 n is 0,

and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

4. A compound according to claim 1,

25 wherein

X is N or CR^e,

R^b, R^c, R^d, R^e are each H,

R_a is selected from the group consisting of H, methyl, ethyl, methoxy, ethoxy, -CF₃, -CHF₂, -CH₂F and F; preferably R_a is selected from the group consisting of H, methyl, ethyl, methoxy, ethoxy and CF₃-;

30

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, tetrahydropyranyl, 2-, 3- and 4-pyridyl,

whereby cyclopentyl and cyclohexyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another

5 from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C-;

whereby tetrahydrofuranyl and tetrahydropyranyl optionally may be substituted by 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, F₃C-, HF₂C- and FH₂C- ;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4, preferably 1, 2 or 3, more preferably 1 or 2, substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F₃C-, HF₂C-, FH₂C-, F₃C-CH₂-, C₁₋₆-alkyl- and C₃₋₇-cycloalkyl;

10

m: is selected from 1 or 2, preferably m is 1;

n is 0,

15 and salts, preferably pharmaceutically acceptable salts thereof, solvates thereof and the solvates of the aforementioned salts thereof.

5. A compound according to any of claims 1 to 4, wherein m = 1.

20 6. A compound according to any of claims claim 1 to 5, wherein X = N.

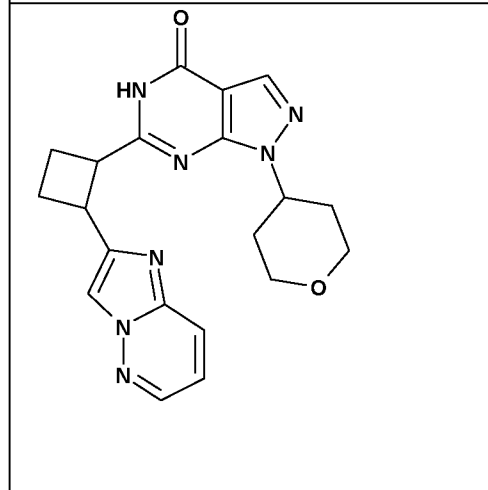
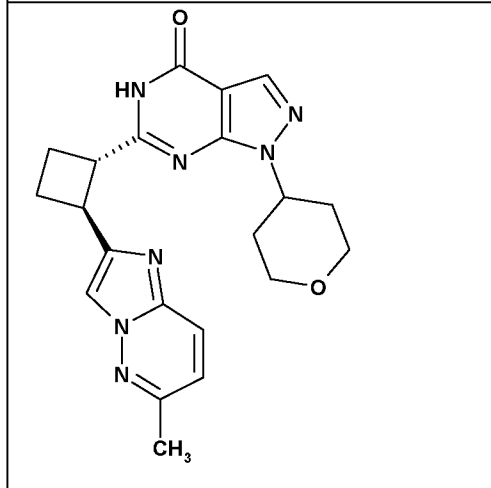
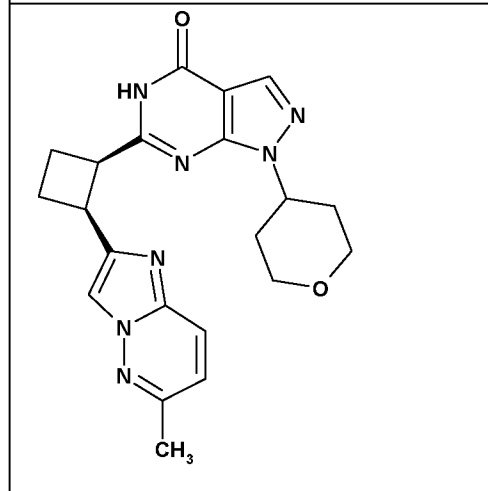
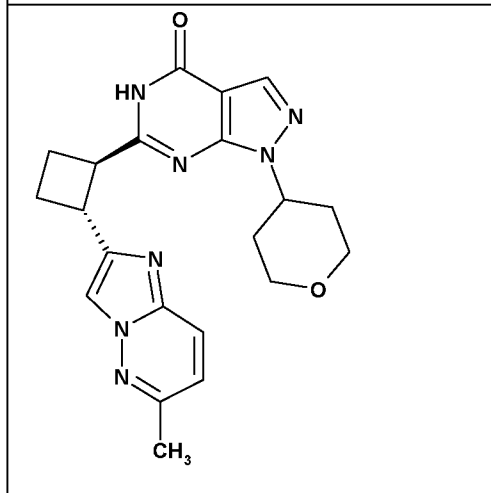
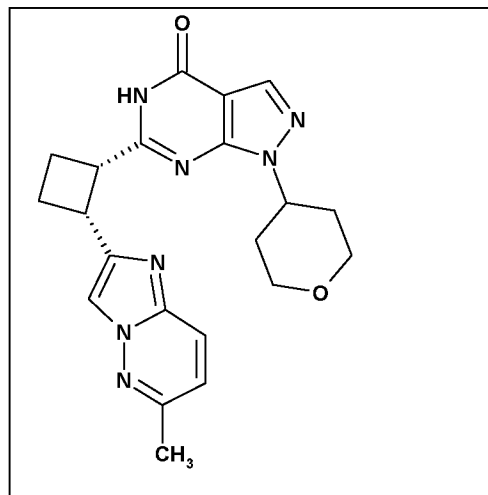
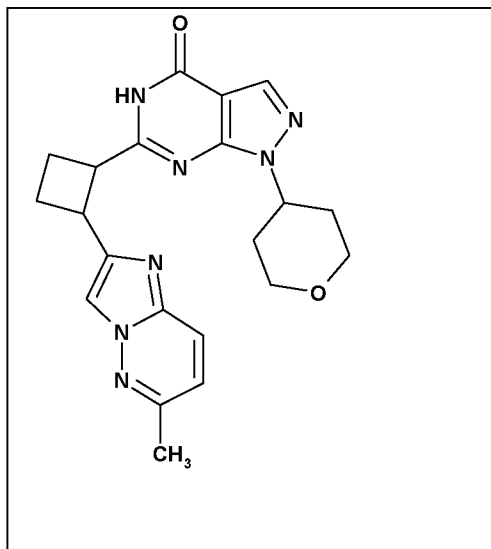
7. A compound according to any of claims claim 1 to 5, wherein X = CR^e.

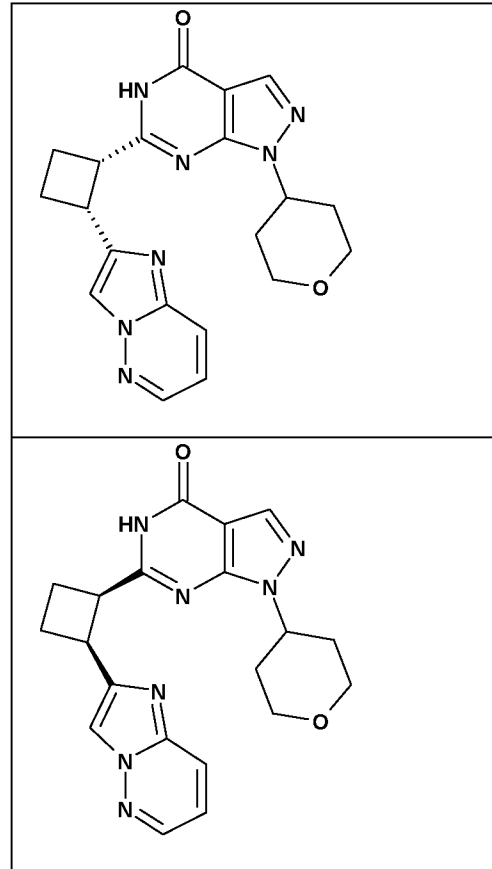
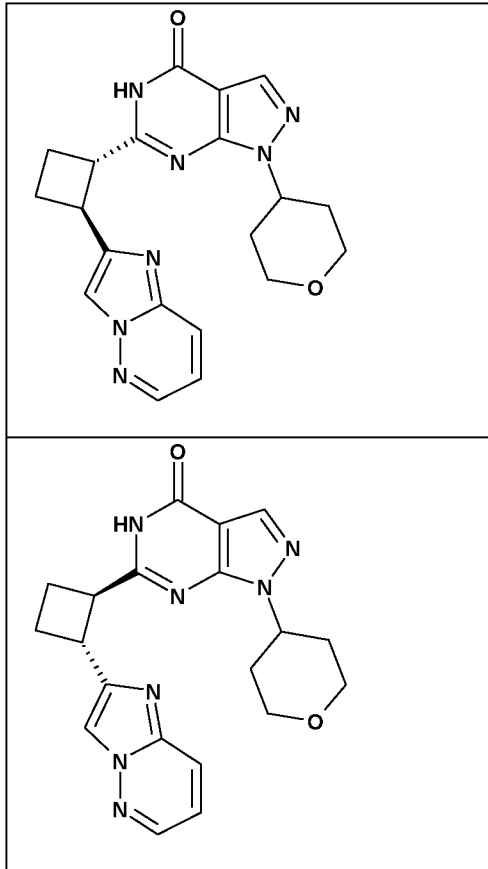
8. A compound according to any of claims claim 1 to 7, wherein D is either 4,4-difluorocyclohexyl or tetrahydropyran-4-yl or 4-methy-3-pyridyl and none of these two

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groups has further substituents and m = 1.

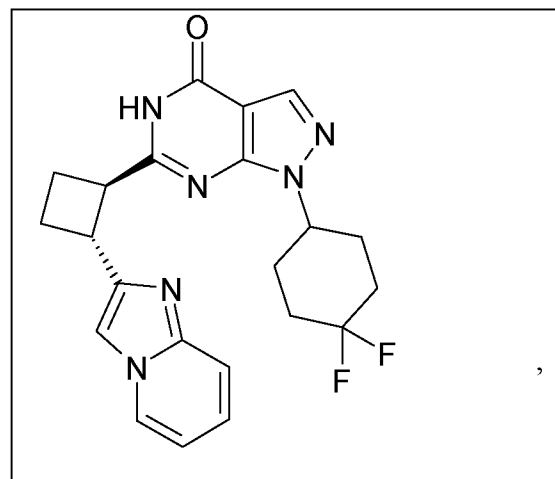
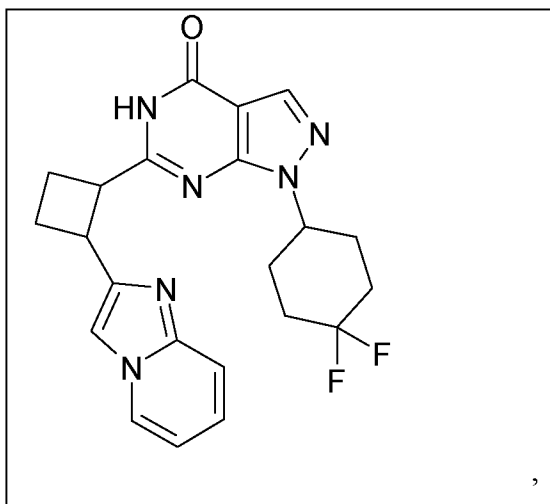
9. A compound according to claim 1, wherein the compound is selected from the group consisting of

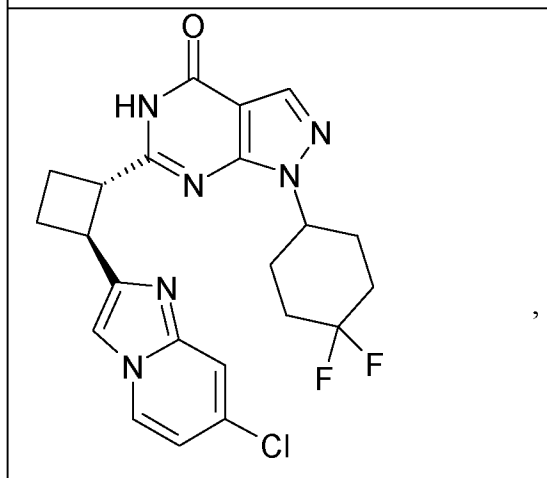
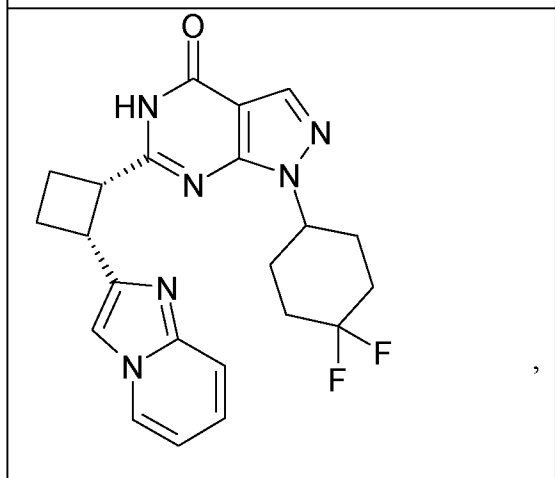
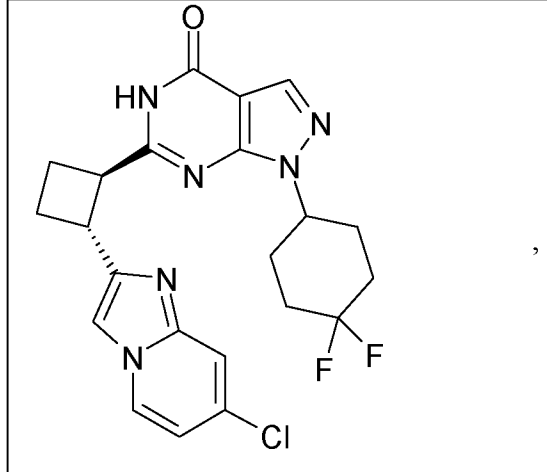
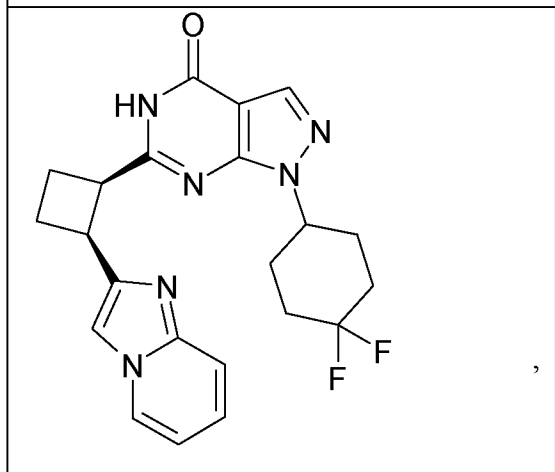
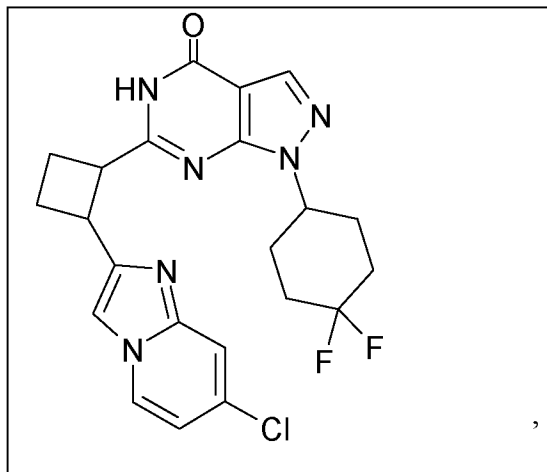
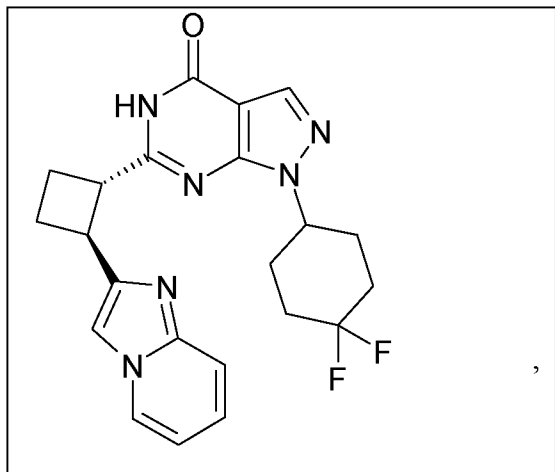


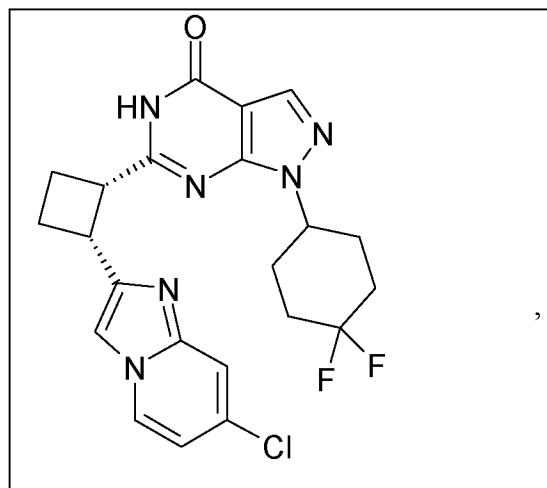
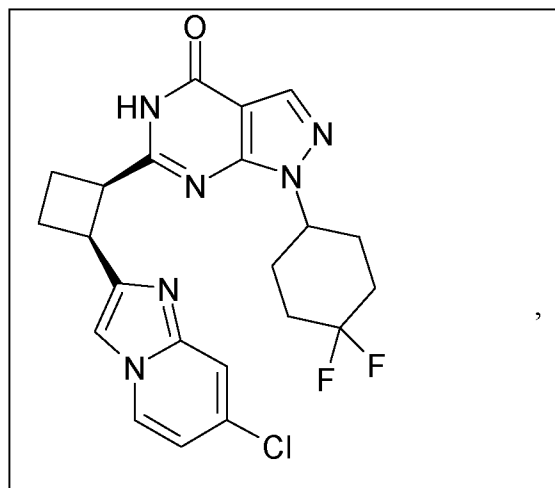


and salts, preferably pharmaceutically acceptable salts thereof.

10. A compound according to claim 1, wherein the compound is selected from the group
5 consisting of

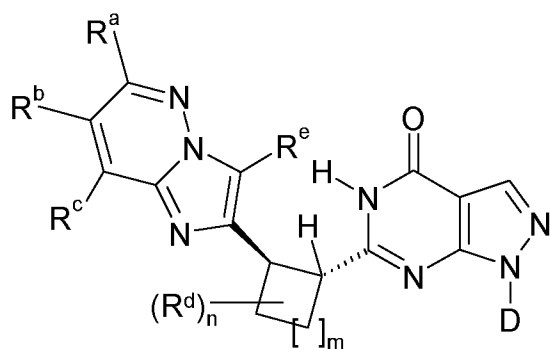




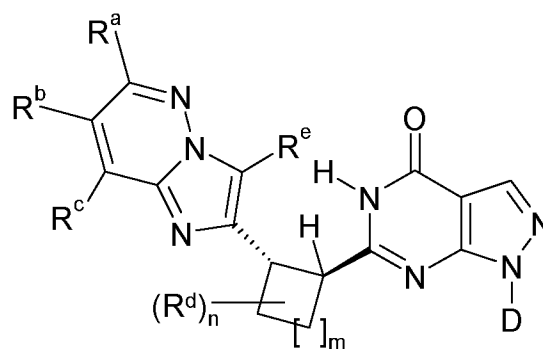


and salts, preferably pharmaceutically acceptable salts thereof.

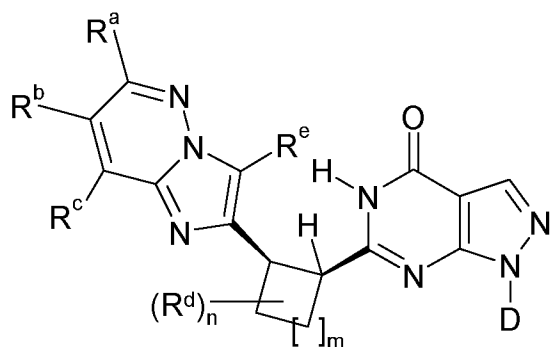
11. A compound according to any one of claims 1-6 or claim 8, wherein the compound is selected from the group consisting of a compound according to formula (Ia), formula (Ib),
5 formula (Ic) and formula (Id)



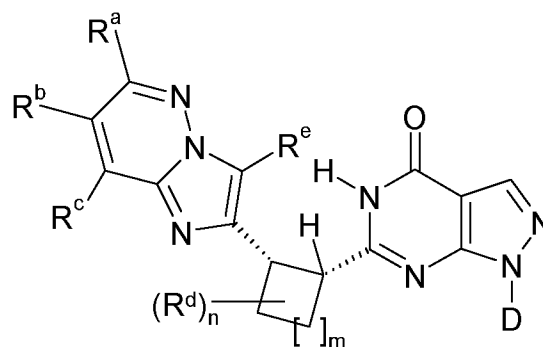
(Ia),



(Ib),



(Ic),



(Id),

wherein X, R^a, R^b, R^c, R^d, R^e, D, m and n are as defined in any of the embodiments 1 to 7.

and salts, preferably pharmaceutically acceptable salts thereof.

12. A compound according to any one of claims 1 to 11 for use in or as a medicament,
5 preferably a medicament for humans, whereby the use of the medicament or the medicament is for

(a) the treatment of a CNS disease, more preferably for use in a medicament for the treatment of a CNS disease, the treatment of which is accessible by the inhibition of PDE9,

10 (b) the treatment of a disease that is accessible by the inhibition of PDE9,

(c) the treatment, amelioration or prevention, preferably the treatment of a condition being selected from the group consisting of cognitive impairment being related to a disease or condition selected from the group of perception, concentration, cognition, learning or memory, whereby preferably the treatment, amelioration or prevention of
15 cognitive impairment is related to age-associated learning and memory impairments, age-associated memory losses, vascular dementia, craniocerebral trauma, stroke, dementia occurring after strokes (post stroke dementia), post-traumatic dementia, general concentration impairments, concentration impairments in children with learning and memory problems, Alzheimer's disease, Lewy body dementia, dementia
20 with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, multiple sclerosis, thalamic degeneration, Creutzfeld-Jacob dementia, HIV dementia, epilepsy, temporal lobe epilepsy, schizophrenia, schizophrenia (with dementia), Korsakoff's psychosis or cognitive
25 impairment associated with depression or bipolar disorder,

(d) the treatment of Alzheimer's disease or cognitive impairment associated with Alzheimer's disease,

(e) the treatment of schizophrenia or cognitive impairment associated with schizophrenia,

(f) the treatment of epilepsy or cognitive impairment associated with epilepsy,

(g) the treatment of a disease or condition being selected from the group consisting of sleep disorders, bipolar disorder, metabolic syndrome, obesity, diabetes mellitus, hyperglycemia, dyslipidemia, impaired glucose tolerance, or a disease of the testes,
5 brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 11 and a pharmaceutical carrier.

14. A method for the treatment of a disease or condition as defined in claim 12 in a patient comprising administering to said patient a therapeutically active amount of a compound
10 according to any one of claims 1 to 11.

15. Use of a compound according to any one of claims 1 to 11 for the manufacture of a medicament as defined in claim 12.

15 16. A combination comprising a compound according to any one of claims 1 to 11 with another active agent, that preferably is useful for the treatment of a disease or condition as defined in claim 12, said combination being for the treatment of a condition or disease as defined in claim 12 or said combination being for the manufacture of a medicament for the treatment of a condition or disease as defined in claim 12.

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INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2012/052379

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07D487/04 A61K31/519 A61P25/00
 ADD.

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

B. FIELDS SEARCHED

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

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

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

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/099211 A1 (BAYER HEALTHCARE AG [DE]; HENDRIX MARTIN [DE]; BAERFACKER LARS [DE]; E) 18 November 2004 (2004-11-18) cited in the application claim 1; table 1 -----	1-16
A	WO 2010/112437 A1 (BOEHRINGER INGELHEIM INT [DE]; GIOVANNINI RICCARDO [DE]; DORNER-CIOSSE) 7 October 2010 (2010-10-07) cited in the application claims 1, 12 -----	1-16
A	WO 03/093269 A2 (BAYER CROPSCIENCE AG [DE]; LINKER KARL-HEINZ [DE]; ANDREE ROLAND [DE];) 13 November 2003 (2003-11-13) cited in the application claims 1, 13 -----	1-16

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

<p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p>	<p>"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</p> <p>"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</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p>
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Date of the actual completion of the international search 23 March 2012	Date of mailing of the international search report 03/04/2012
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Bakboord, Joan
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2012/052379

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