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, 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, respectively changes in the affinity towards different target enzymes.

Therefore it is an objective of the ~~present invention~~embodiments disclosed herein 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 is accessible via PDE9A modulation.

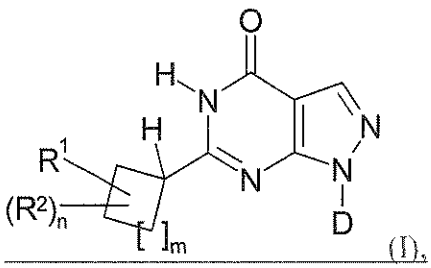
It is another objective of the ~~present invention~~embodiments disclosed herein to provide compounds that are useful for the manufacture of a medicament for the treatment of CNS disorders.

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

Another objective of the ~~present invention~~embodiments disclosed herein is to provide compounds that have a favourable selectively profile in favour of PDE9A inhibition over other PDE family members and other pharmacological targets and by this may provide an 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.

In a first aspect, there is provided a compound of formula (I)



(I),

wherein

R^1: is a 5 or 6 membered heteroaryl-group whereby 1, 2, 3 or 4 of the ring atoms are heteroatoms that are selected independently of each other from N, O or S,

whereby said 5 or 6 membered aromatic heteroaryl-group optionally may be substituted by 1, 2, 3 or 4, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, HO-, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- 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-, F_3C-, HF_2C- and FH_2C-;

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-, F_3C-, HF_2C- and FH_2C-;

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-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- and C_{3-7}-cycloalkyl,

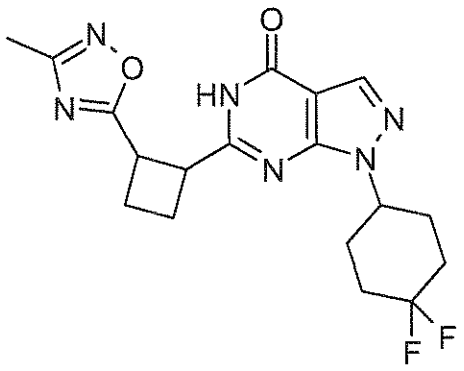
m: is selected from 1 or 2;

n: is selected from 0, 1 or 2,

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

or a pharmaceutically acceptable salt thereof;

with the proviso that the compound is not



be it in the form of any possible stereoisomer or a mixture of all or some thereof.

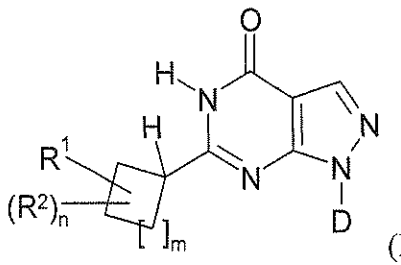
The present ~~invention further~~disclosure, in a second aspect, provides a pharmaceutical composition comprising a compound as herein described, in particular in the claims and a pharmaceutically acceptable carrier.

The present ~~invention~~disclosure 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~~disclosure 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):



(I),

wherein

R^1: is a 5 or 6 membered heteroaryl-group whereby 1, 2, 3 or 4, preferably 1, 2 or 3, of the ring atoms are heteroatoms that are selected independently of each other from N, O or S,

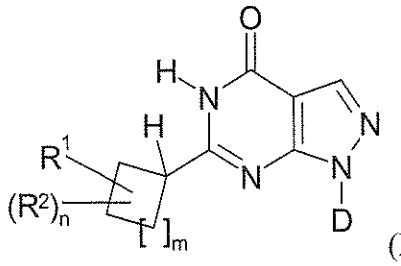
whereby said 5 or 6 membered aromatic heteroaryl-group optionally may be substituted by 1, 2, 3 or 4, preferably 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, HO-, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- and methyl, preferably fluorine, NC-, F_3C- and methyl;

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

Claims

1. A compound of formula (I)



(I),

wherein

R^1: is a 5 or 6 membered heteroaryl-group whereby 1, 2, 3 or ~~4, preferably 1, 2 or 3~~ of the ring atoms are heteroatoms that are selected independently of each other from N, O or S,

whereby said 5 or 6 membered aromatic heteroaryl-group optionally may be substituted by 1, 2, 3 or 4, ~~preferably 1 or 2 substituents,~~ whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, HO-, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- and methyl~~, preferably fluorine, NC-, F_3C- 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-, F_3C-, HF_2C- and FH_2C-;

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-, F_3C-, HF_2C- and FH_2C- ;

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-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- and C_{3-7}-cycloalkyl,

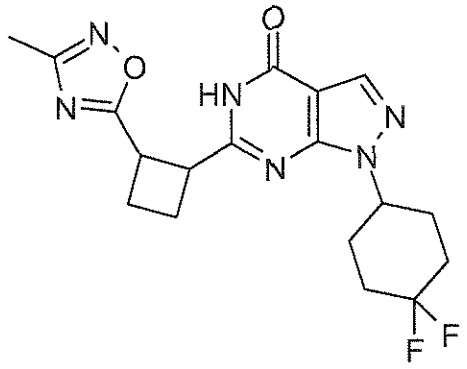
m: is selected from 1 or 2~~, preferably m is 1~~;

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

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

or a ~~and salts, preferably~~ pharmaceutically acceptable salts ~~thereof~~;

with the proviso that the compound is not



be it in the form of any possible stereoisomer or a mixture of all or some thereof.

2. ~~A~~ The compound according to claim 1,

wherein

R^1: is a 5 or 6 membered heteroaryl-group whereby ~~1, 2, 3 or 4 preferably~~ 1, 2 or 3 of the ring atoms are heteroatoms that are selected independently of each other from N, O or S,

whereby said 5 or 6 membered aromatic heteroaryl-group optionally may be substituted by ~~1, 2, 3 or 4, preferably~~ 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- and methyl~~, preferably fluorine, NC-, F_3C- 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, F_3C-, HF_2C- and FH_2C-;

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, F_3C-, HF_2C- and FH_2C- ;

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-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- and C_{3-7}-cycloalkyl.

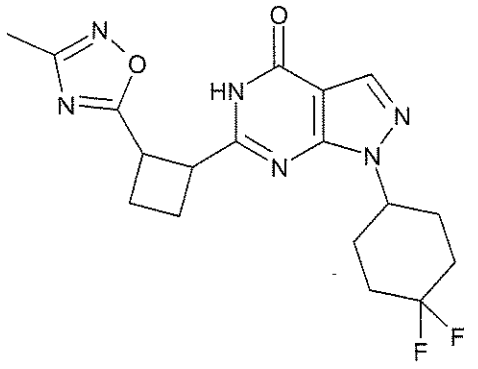
m: is selected from 1 or 2~~, preferably m is 1~~;

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

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

or a ~~and salts, preferably~~ pharmaceutically acceptable salts thereof;

with the proviso that the compound is not



be it in the form of any possible stereoisomer or a mixture of all or some thereof.

3. ~~A~~ The compound according to claim 2,

wherein

R^1: is a heteroaryl-group selected from the group consisting of thiadiazolyl, oxadiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyridyl and pyrimidinyl,

whereby said heteroaryl-group optionally may be substituted by ~~1, 2, 3 or 4, preferably~~ 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-; or a pharmaceutically acceptable salt thereof.

4. ~~A~~ The compound according to claim 1,

wherein

R^1: is a 5 or 6 membered heteroaryl-group selected from the group consisting of thiadiazolyl, 1,2,3-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyridyl and pyrimidinyl~~, preferably said group consisting of thiadiazolyl, isoxazolyl, thiazolyl, oxazolyl, pyridyl and pyrimidinyl~~,

whereby said heteroaryl-group optionally may be substituted by ~~1, 2, 3 or 4, preferably~~ 1 or 2 substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F_3C-, HF_2C-, FH_2C-, methyl, H_2N- and $(CH_3)_2N$-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- and methyl~~, preferably fluorine, NC-, F_3C- 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, F_3C-, HF_2C- and FH_2C-;

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, F_3C-, HF_2C- and FH_2C- ;

whereby pyridyl optionally may be substituted by 1, 2, 3 or 4~~, preferably 1 or 2~~ substituents, whereby said substituents may be selected independently of one another from the group consisting of fluorine, chlorine, bromine, NC-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2-, C_{1-6}-alkyl- and C_{3-7}-cycloalkyl.

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

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

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

or a ~~and salts, preferably~~ pharmaceutically acceptable salts thereof.

5. ~~A~~ The compound according to ~~any of~~ claims ~~1 to 4~~, whereby R^1 is ~~no~~ not oxadiazolyl, neither unsubstituted nor substituted, or a pharmaceutically acceptable salt thereof.

6. ~~A~~ The compound according to claim 4,

wherein

R^1: is a 5 or 6 membered heteroaryl-group selected from the group consisting of [1,3,4]thiadiazol-2-yl, isoxazol-5-yl, thiazol-5-yl-, oxazol-2-yl, pyridin-2-yl and pyrimidin-2-yl,

whereby said heteroaryl-group 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, chlorine, bromine, CN-, methyl and H_2N-;

R^2: is selected from the group consisting of fluorine, NC-, F_3C-, HF_2C-, FH_2C- and methyl, preferably fluorine, NC-, F_3C- and methyl;

D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuranyl, ~~thereof preferably tetrahydrofuran-3yl,~~ tetrahydropyranyl, and ~~thereof preferably tetrahydropyran-4yl,~~ 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, F_3C-, HF_2C- and FH_2C-; ~~preferably fluorine;~~

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, F_3C-, HF_2C- and FH_2C-;

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-, F_3C-, HF_2C-, FH_2C-, F_3C-CH_2- and methyl;

~~whereby preferably D is selected from the group of 4,4-difluorocyclohex-1-yl, tetrahydropyranyl, preferably tetrahydropyran-4-yl, and 4-methy-3-pyridyl;~~

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

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

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

or a ~~and salts, preferably~~ pharmaceutically acceptable salt~~s~~ thereof.

7. The compound according to claim 6, wherein

R^2: is selected from the group consisting of fluorine, NC-, F_3C- and methyl;

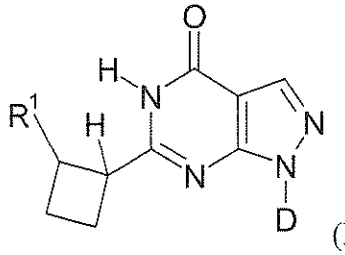
D: is selected from the group consisting of cyclopentyl, cyclohexyl, tetrahydrofuran-3-yl, tetrahydropyran-4-yl, 2-pyridyl, and 4-pyridyl,

m: is 1; and

n: is 0,

or a pharmaceutically acceptable salt thereof.

~~7~~8. ~~A~~ The compound according to claim 1, characterised in that it is a compound according to formula (II)



(II),

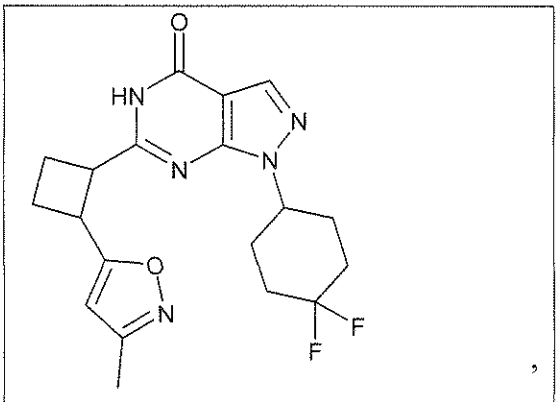
wherein

R^1: is as defined in any of claims 1, 2, 3, 4, 5 or 6;

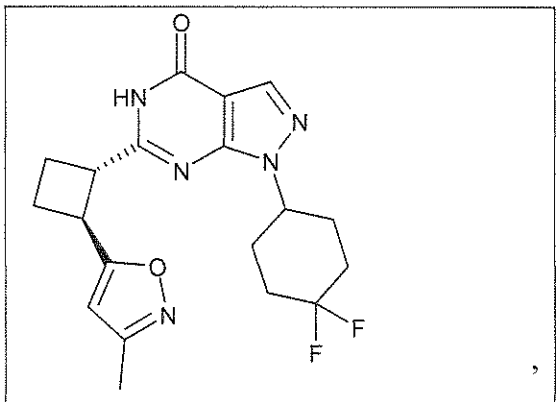
D: is selected from the group consisting of 4,4-difluorocyclohexyl, tetrahydropyran-4-yl and 4-methy-3-pyridyl whereby neither 4,4-difluorocyclohexyl nor tetrahydropyran-4-yl has additional substituents;

or a ~~and salts, preferably~~ pharmaceutically acceptable salts ~~thereof~~.

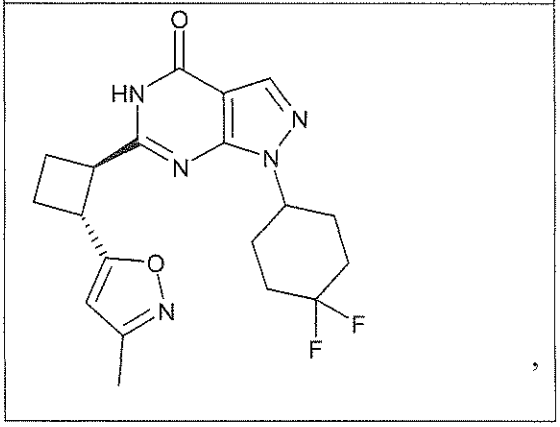
~~8~~9. ~~A~~ The compound according to claim ~~7~~8, wherein the compound is selected from the group consisting of



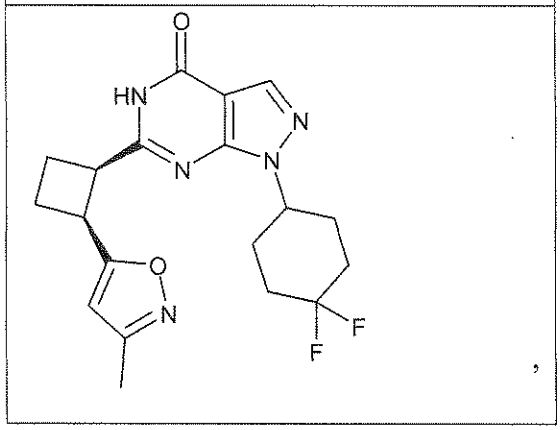
,



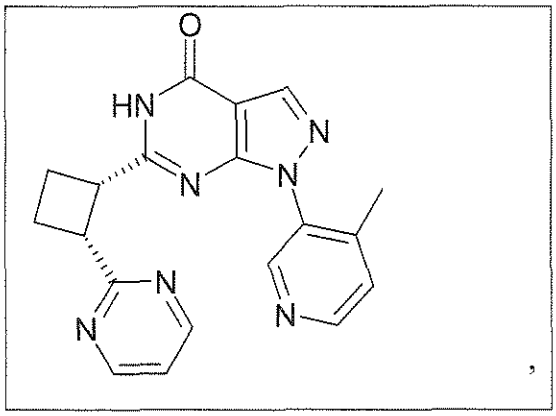
,



,

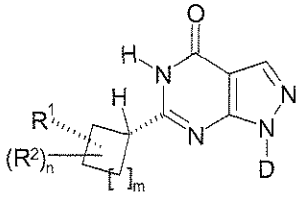


,

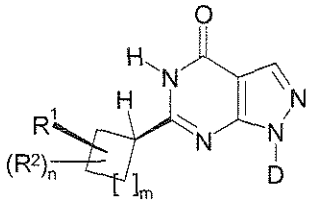


and the ~~salts, preferably~~ pharmaceutically acceptable salts thereof.

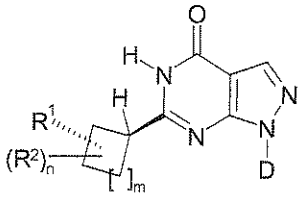
9<u>10</u>. ~~A~~ <u>The</u> compound according to ~~any one of~~ claims 1-~~6~~, whereby the compound is selected from the group <u>consisting</u> of a compound according to formula (Ia), formula (Ib), formula (Ic) and formula (Id)



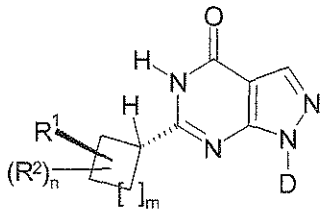
(Ia),



(Ib),



(Ic),

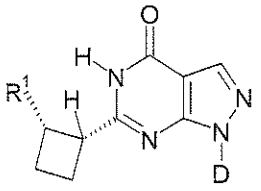


(Id),

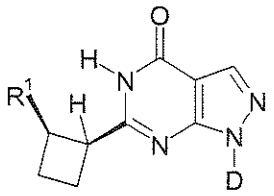
with R^1, R^2, D, n and m as defined <u>in</u> ~~or presented in any of~~ claims 1 ~~to 6~~

<u>or a</u> ~~and salts, preferably~~ pharmaceutically acceptable salts thereof.

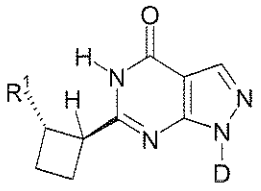
10 1<u>0</u>11. ~~A~~ <u>The</u> compound according to ~~any one of~~ claims ~~7 and 8~~, whereby the compound is selected from the group <u>consisting</u> of a compound according to formula (IIa), formula (IIb), formula (IIc) and formula (IId)



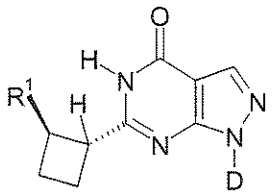
(IIa),



(IIb),



(IIc),



(IId),

with R^1 and D as defined in ~~any of~~ claims 7 ~~to 8~~

or a ~~and salts, preferably~~ pharmaceutically acceptable salts thereof.

~~11. A compound according to any one of claims 1 to 10 for use as a medicament or for the use as pharmaceutically active ingredient in a medicament, preferably a medicament for use in a therapeutic or prophylactic method, preferably in a therapeutic method.~~

~~12. A compound according to any one of claims 1 to 10 for use in a therapeutic or prophylactic, preferably a therapeutic method~~

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

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

~~(c) for the treatment of or for the amelioration of or for the prevention of, preferably for 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 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 with degeneration of the frontal lobes, including Pick's syndrome, Parkinson's disease, progressive nuclear palsy, dementia with corticobasal degeneration, amyotropic 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,

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

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

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

(g) for 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, brain, small intestine, skeletal muscle, heart, lung, thymus or spleen.

13. A compound according to any one of claims 1 to 10 for use in a method for the treatment or prophylaxis of cognitive impairment, preferable cognitive impairment related to perception, concentration, learning or memory.

14. A compound according to any one of claims 1 to 10 for use in a method for the treatment or prophylaxis of cognitive impairment, preferable cognitive impairment related to perception, concentration, learning or memory, as symptoms of anther base laying disease.

15. A compound according to any one of claims 1 to 10 for use in a method for the improvement of cognitive skills related to perception, concentration, learning or memory.

16. Pharmaceutical composition comprising a compound according to any one of claims 1 to 10 and a pharmaceutical carrier.

17. Method for the treatment of a disease or condition as defined in any of claims 12 to 15 in a patient in need of such treatment comprising administering to said patient a therapeutically active amount of a compound according to any one or more of claims 1 to 10.

18. Use of a compound according to any one of claims 1 to 10 for the manufacture of a medicament for the treatment of a disease or condition as defined in any of claims 12 to 15.

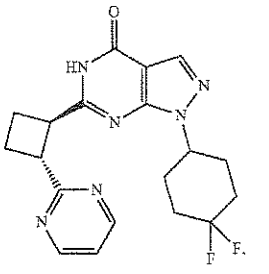
19. Combination of a compound according to any one of claims 1 to 10 with another active agent, whereby

- said combination preferably is useful for the treatment of a disease or condition as defined in any of claims 12 to 15 or
- said combination preferably being for the use in a therapeutic or prophylactic method, preferably a therapeutic method, for the treatment of a condition or disease as defined in any of claims 12 to 15 or
- said combination being for the manufacture of a medicament which preferably is for the treatment of a condition or disease as defined in any of claims 12 to 15.

12. A pharmaceutical composition comprising a compound according to claim 1 and a pharmaceutical carrier.

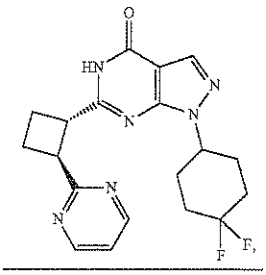
13. A pharmaceutical composition comprising a combination of a compound according to claim 1 with another active agent selected from the group of beta-secretase inhibitors, gamma-secretase inhibitors, gamma-secretase modulators, amyloid aggregation inhibitors, neuroprotective substances, anti-oxidants, anti-inflammatory substances, HMG-CoA reductase inhibitors, acetylcholine esterase inhibitors, NMDA receptor antagonists, AMPA receptor agonists, AMPA receptor positive modulators, AMPkines, glycine transporter 1 inhibitors, monoamine receptor reuptake inhibitors, substances modulating the concentration or release of neurotransmitters, substances inducing the secretion of growth hormone, CB-1 receptor antagonists or inverse agonists, antibiotics, 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 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 and metabotropic glutamate receptor 2 positive allosteric modulators.

14. The compound according to claim 1, wherein the compound is



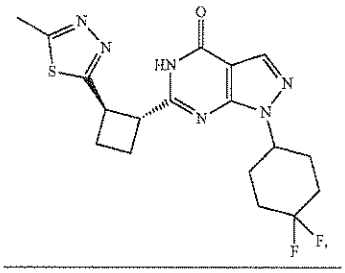
or a pharmaceutically acceptable salt therof.

15. The compound according to claim 1, wherein the compound is



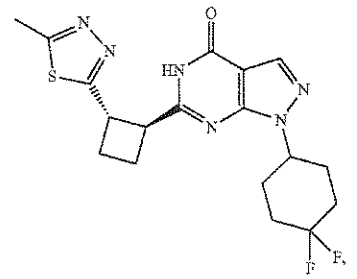
or a pharmaceutically acceptable salt thereof.

16. The compound according to claim 1, wherein the compound is



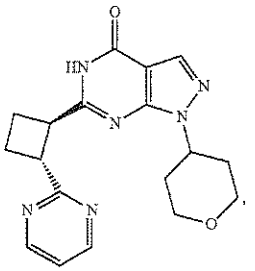
or a pharmaceutically acceptable salt thereof.

17. The compound according to claim 1, wherein the compound is



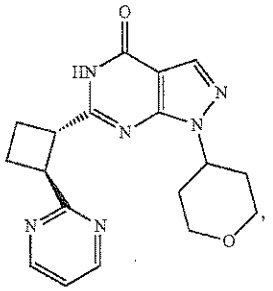
or a pharmaceutically acceptable salt thereof.

18. The compound according to claim 1, wherein the compound is



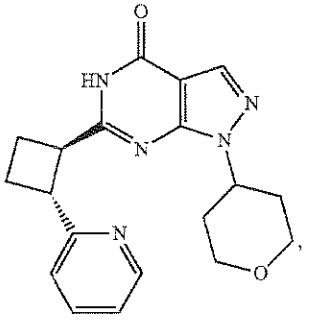
or a pharmaceutically acceptable salt thereof.

19. The compound according to claim 1, wherein the compound is



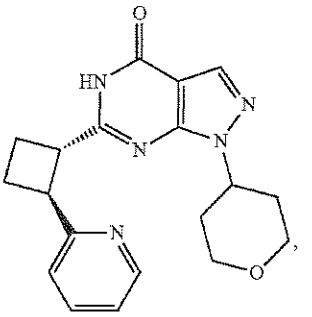
or a pharmaceutically acceptable salt thereof.

20. The compound according to claim 1, wherein the compound is



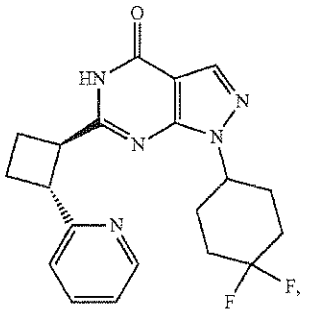
or a pharmaceutically acceptable salt thereof.

21. The compound according to claim 1, wherein the compound is



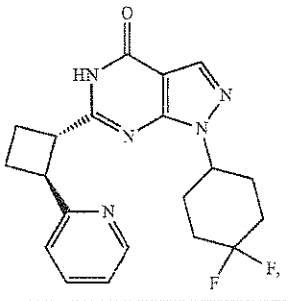
or a pharmaceutically acceptable salt thereof.

22. The compound according to claim 1, wherein the compound is



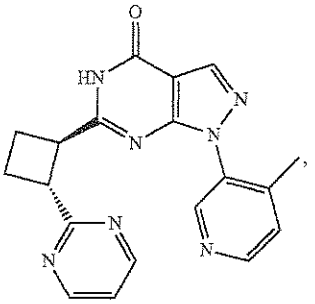
or a pharmaceutically acceptable salt thereof.

23. The compound according to claim 1, wherein the compound is



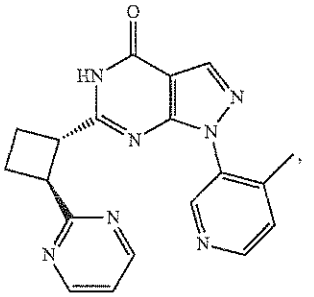
or a pharmaceutically acceptable salt thereof.

24. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.

25. The compound according to claim 1, wherein the compound is



or a pharmaceutically acceptable salt thereof.