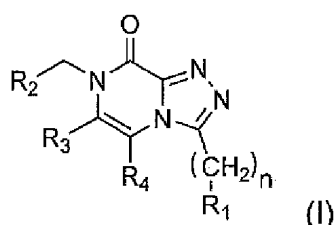


The objective of the present disclosure is to provide compounds that are PDE1 inhibitors, and as such are useful to treat neurodegenerative disorders and psychiatric disorders.

Accordingly, the present disclosure relates to compounds of formula (I)



wherein

n is 0 or 1;

R₁ is selected from the group consisting of linear or branched C₁-C₈ alkyl, such as C₁ to C₃ alkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl and saturated monocyclic C₃-C₈ cycloalkyl; or

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R₁ is selected from the group consisting oxetanyl, tetrahydrofuranyl, tetrahydropyranyl, saturated monocyclic C₃-C₈ cycloalkyl, each substituted one or two times with methyl or hydroxy, and linear or branched C₁-C₈ alkyl substituted one or more times, preferably one, two or three times, with fluorine; and

R₂ is selected from the group consisting of, linear or branched C₁-C₈ alkyl, phenyl, saturated monocyclic C₃-C₈ cycloalkyl, saturated bicyclic C₄-C₁₀ cycloalkyl, saturated tricyclic C₇-C₁₀ cycloalkyl, oxetanyl, tetrahydrofuranyl and tetrahydropyranyl; or

15

R₂ is selected from the group consisting of phenyl substituted with a substituent selected from the group consisting of halogen, linear or branched C₁-C₃ alkyl, difluoromethyl, trifluoromethyl and methoxy; saturated monocyclic C₃-C₈ cycloalkyl, substituted one or two times with substituents selected from the group consisting of fluorine and methyl; and oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each substituted one or two times with substituents selected from the group consisting of fluorine and methyl;

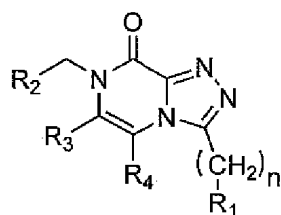
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R_3 is selected from the group consisting of linear or branched C_1 - C_4 alkyl, phenyl, substituted phenyl, halogen, tetrahydrofuranyl, benzyl, where the phenyl ring of the benzyl can be optionally substituted with one or more substituents chosen from halogen, methyl, alkoxy or the phenyl ring of the benzyl can be substituted with an aromatic ring or heteroaromatic ring like e.g. pyridine;

R_4 is selected from the group consisting of linear or branched C_1 - C_4 alkyl, halogen, and tetrahydrofuranyl.

Reference to Compound I includes the free base of Compound I, pharmaceutically acceptable salts of Compound I, such as acid addition salts of Compound I, racemic mixtures of Compound I, or the corresponding enantiomer and/or optical isomer of Compound I, and polymorphic and amorphous forms of Compound I as well as tautomeric forms of Compound I.

In one aspect, the present disclosure relates to a compound having the structure



Compound (I)

wherein

n is 0 or 1;

R_1 is selected from the group consisting of linear or branched C_1 - C_8 alkyl, oxetanyl, tetrahydrofuranyl, tetrahydropyranyl and saturated monocyclic C_3 - C_8 cycloalkyl; or

R_1 is selected from the group consisting of oxetanyl substituted one or two times with methyl or hydroxy; tetrahydrofuranyl substituted one or two times with methyl or hydroxy; tetrahydropyranyl substituted one or two times with methyl or hydroxy; saturated monocyclic C_3 - C_8 cycloalkyl substituted one or two times with methyl or hydroxy; and linear or branched C_1 - C_8 alkyl substituted one, two or three times with fluorine; and

R_2 is selected from the group consisting of linear or branched C_1 - C_8 alkyl, phenyl, saturated monocyclic C_3 - C_8 cycloalkyl, saturated bicyclic C_4 - C_{10} cycloalkyl, saturated tricyclic C_7 - C_{10} cycloalkyl, oxetanyl, tetrahydrofuranyl and tetrahydropyranyl; or

R_2 is selected from the group consisting of phenyl substituted with a substituent selected from the group consisting of halogen, methyl, difluoromethyl, trifluoromethyl and methoxy; saturated monocyclic C_3 - C_8 cycloalkyl, substituted one or two times with substituents selected from the group consisting of fluorine and methyl; and oxetanyl, tetrahydrofuranyl and tetrahydropyranyl, each substituted one or two times with substituents selected from the group consisting of fluorine and methyl;

- 10 R_3 is selected from the group consisting of linear or branched C_1 - C_4 alkyl, phenyl, substituted phenyl, halogen and tetrahydrofuranyl;

R_4 is selected from the group consisting of linear or branched C_1 - C_4 alkyl, halogen, and tetrahydrofuranyl;

- 15 and pharmaceutically acceptable acid addition salts of Compound I, racemic mixtures of Compound I, or the corresponding enantiomer and/or optical isomer of Compound I, and polymorphic forms of Compound I as well as tautomeric forms of Compound I;

- with the proviso that compound I is not 1,2,4-Triazolo[4,3-a]pyrazin-8(7H)-one, 7-[(4-chlorophenyl)methyl]-3-methyl- (CAS Registry Number: 946270-18-4) or 1,2,4-Triazolo[4,3-a]pyrazin-8(7H)-one, 7-[(4-chlorophenyl)methyl]-3-propyl- (CAS Registry Number: 946237-23-6).
- 20

In another aspect, the present disclosure relates to a compound as disclosed herein for use as a medicine.

- 25 In another aspect, the present disclosure relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound as disclosed herein and one or more pharmaceutically acceptable carriers, diluents and excipients.

In yet another aspect, the present disclosure relates to the pharmaceutical composition as disclosed herein for use in the treatment of a disease selected from the group consisting of attention-deficit/hyperactivity disorder (ADHD),

schizophrenia, cognitive impairment, depression, Parkinson's disease and Alzheimers disease.

In a further aspect, the present disclosure relates to the use of a compound as disclosed herein in the manufacture of a medicament for the treatment of a neurodegenerative disorder, such as Alzheimer's Disease, Parkinson's Disease and Huntington's Disease or for the treatment of a psychiatric disorder such as Attention Deficit hyperactivity Disorder (ADHD), schizophrenia, depression, narcolepsy, cognitive impairment and cognitive impairment associated with schizophrenia (CIAS) or a brain disease like restless leg syndrome.

In another aspect, the present disclosure relates to the use of the pharmaceutical composition as disclosed herein in the manufacture of a medicament for the treatment of a disease selected from the group consisting of attention-deficit/hyperactivity disorder (ADHD), schizophrenia, cognitive impairment, depression, Parkinson's disease and Alzheimers disease.

DETAILED DESCRIPTION OF THE INVENTION

EMBODIMENTS OF THE INVENTION

The following notation is applied: an embodiment of the invention is identified as E_i , where i is an integer indicating the number of the embodiment. An embodiment E_i' specifying a specific embodiment of a previously listed embodiment E_i is identified as $E_i'(E_i)$, e.g. $E_2(E_1)$ means "in an embodiment E_2 of embodiment E_1 ".

Where an embodiment is a combination of two embodiments the notation is similarly $E_i''(E_i \text{ and } E_i')$, e.g. $E_3(E_2 \text{ and } E_1)$ means "in an embodiment E_3 of any of embodiments E_2 and E_1 "

Where an embodiment is a combination of more than two embodiments the notation is similarly $E_i'''(E_i, E_i' \text{ and } E_i'')$, e.g. $E_4(E_1, E_2 \text{ and } E_3)$ means "in an embodiment E_4 of any of embodiments E_1, E_2 and E_3 "

In a first embodiment E_1 the present invention relates to compounds of formula (I) (Compound I):

(R)-7-(3-fluorobenzyl)-3-propyl-6-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 (S)-7-(3-fluorobenzyl)-3-propyl-6-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 7-(3-fluorobenzyl)-6-methyl-3-propyl-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 7-(3-fluorobenzyl)-6-ethyl-3-propyl-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 6-benzyl-7-(3-fluorobenzyl)-3-(tetrahydro-2H-pyran-4-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 (R)-7-(3-fluorobenzyl)-3-propyl-5-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 (S)-7-(3-fluorobenzyl)-3-propyl-5-(tetrahydrofuran-3-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 7-(3-fluorobenzyl)-3-propyl-5-methyl-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 7-(3-fluorobenzyl)-3-propyl-5-ethyl-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 5-bromo-7-(3-fluorobenzyl)-3-propyl-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one
 6-([1,1'-biphenyl]-4-ylmethyl)-7-(cyclohexylmethyl)-3-(tetrahydro-2H-pyran-4-yl)-[1,2,4]triazolo[4,3-a]pyrazin-8(7H)-one

and pharmaceutically acceptable salts thereof.

9. A compound of any one of claims 1 to 8 for use as a medicine.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1 to 8 and one or more pharmaceutically acceptable carriers, diluents and excipients.
11. The pharmaceutical composition of claim 10 for use in the treatment of a disease selected from the group consisting of attention-deficit/hyperactivity disorder (ADHD), schizophrenia, cognitive impairment, depression, Parkinson's disease and Alzheimers disease.
12. Use of a compound of any of claims 1-8 in the manufacture of a medicament for the treatment of a neurodegenerative disorder, such as Alzheimer's Disease, Parkinson's Disease and Huntington's Disease or for the treatment of a psychiatric disorder such as Attention Deficit hyperactivity Disorder (ADHD), schizophrenia, depression, narcolepsy, cognitive impairment and cognitive impairment associated with schizophrenia (CIAS) or a brain disease like restless leg syndrome.
13. Use of the pharmaceutical composition of claim 10 in the manufacture of a medicament for the treatment of a disease selected from the group consisting of attention-deficit/hyperactivity disorder (ADHD), schizophrenia, cognitive impairment, depression, Parkinson's disease and Alzheimers disease.