

Thus, PDE1 is a therapeutic target for regulation of intracellular signalling pathways, preferably in the nervous system and PDE1 inhibitors can enhance the levels of the second messengers cAMP/cGMP leading to modulation of neuronal processes and to the expression of neuronal plasticity-related genes, neurotrophic factors, and neuroprotective molecules. These neuronal plasticity enhancement properties together with the modulation of synaptic transmission make PDE1 inhibitors good candidates as therapeutic agents in many neurological and psychiatric conditions. The evaluation of PDE1 inhibitors in animal models (for reviews see e.g. Blokland et al. Expert Opinion on Therapeutic Patents (2012), 22(4), 349-354; and Medina, A. E. Frontiers in Neuropharmacology (2011), 5(Feb.), 21) have suggested the potential for the therapeutic use of PDE1 inhibitors in neurological disorders, like e.g. Alzheimer's, Parkinson's and Huntington's Diseases and in psychiatric disorders like e.g. Attention Deficit hyperactivity Disorder (ADHD), restless leg syndrome, depression, narcolepsy, cognitive impairment and cognitive impairment associated with schizophrenia (CIAS). There have also been patent applications claiming that PDE1 inhibitors are useful in diseases that may be alleviated by the enhancement of progesterone-signalling such as female sexual dysfunction.

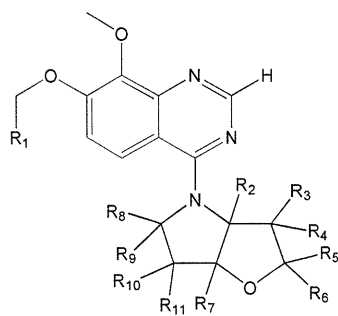
The compounds of the invention may offer alternatives to current marketed treatments for neurodegenerative and/or psychiatric disorders, which are not efficacious in all patients. Hence, there remains a need for alternative methods of treatment.

SUMMARY OF THE INVENTION

PDE1 enzymes are expressed in the Central Nervous System (CNS), making this gene family an attractive source of new targets for the treatment of psychiatric and neurodegenerative disorders.

The objective of the present ~~invention~~ disclosure is to provide compounds that are PDE1 inhibitors, and as such are useful to treat neurodegenerative disorders and psychiatric disorders. In a preferred embodiment the compounds are selective PDE1 inhibitors.

In one aspect, there is provided a compound having the structure



Compound (I)

wherein

R₁ is selected from the group consisting of H, F, C₃-C₆ cycloalkyl and C₁-C₄ alkyl,
R₂ to R₁₁ selected from the group consisting of H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl,
fluorine, hydroxy and C₁-C₆ alkoxy,
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).

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

In a further aspect, there is provided the use of the compound as disclosed herein in
the manufacture of a medicament for the treatment of a neurological or psychiatric
disorder.

In yet another aspect, there is provided the use of the compound as disclosed herein
in the manufacture of a medicament for the treatment of schizophrenia.

In another aspect, there is provided the use of the compound as disclosed herein in
the manufacture of a medicament for the treatment of cognitive impairment in
association with schizophrenia.

In a further aspect, there is provided the use of the compound as disclosed herein in the manufacture of a medicament for the treatment of Attention Deficit hyperactivity Disorder (ADHD).

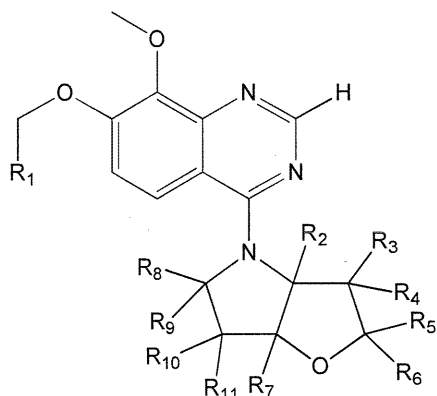
In yet another aspect, there is provided the use of the compound as disclosed herein in the manufacture of a medicament for the treatment of Alzheimer's disease.

In another aspect, there is provided the use of the compound as disclosed herein in the manufacture of a medicament for the treatment of Parkinson's disease.

In a further aspect, there is provided the use of the compound as disclosed herein in the manufacture of a medicament for the treatment of Huntington's disease.

In yet another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as disclosed herein, and one or more pharmaceutically acceptable carriers, diluents or excipients.

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



(I)

wherein

- 5 R₁ is selected from the group consisting of H, F, C₃-C₆ cycloalkyl, and C₁-C₄ alkyl, wherein the alkyl and the cycloalkyl optionally may be substituted one, two or three times with fluorine;
- R₂ to R₁₁ selected from the group consisting of H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, fluorine, hydroxy and C₁-C₆ alkoxy,
- 10 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).

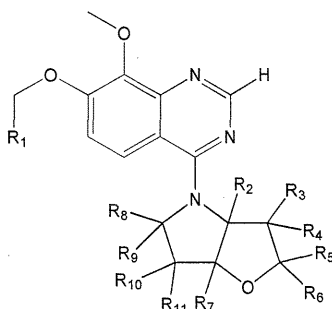
15 DETAILED DESCRIPTION OF THE INVENTION

EMBODIMENTS OF THE INVENTION

In a first embodiment (E1) the present invention relates to compounds of formula (I) (Compound (I))

Claims

1. A compound having the structure



Compound (I)

wherein

R₁ is selected from the group consisting of H, F, C₃-C₆ cycloalkyl and C₁-C₄ alkyl.

R₂ to R₁₁ selected from the group consisting of H, C₁-C₃ alkyl, C₃-C₆ cycloalkyl, fluorine, hydroxy and C₁-C₆ alkoxy, 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).

2. The compound of claim 1 wherein R₁ to R₁₁ are H.
3. The compound of claim 1, wherein the compound is (3aS,6aS)-4-(7,8-dimethoxyquinazolin-4-yl)hexahydro-2H-furo[3,2-b]pyrrole.
4. The compound of claim 1, wherein the compound is (3aR,6aR)-4-(7,8-dimethoxyquinazolin-4-yl)hexahydro-2H-furo[3,2-b]pyrrole.
5. The compound of any of claims 1-4 for use as a medicament.
6. Use of the compound of any of claims 1-4 in the manufacture of a medicament for use in the treatment of a neurological or psychiatric disorder.
7. Use of the compound of any of claims 1-4 in the manufacture of a medicament for use in the treatment of schizophrenia.
8. Use of the compound of any of claims 1-4 in the manufacture of a medicament for use in the treatment of cognitive impairment in association with schizophrenia.

9. Use of t~~The compound of any of claims 1-4 in the manufacture of a medicament for use in~~ the treatment of Attention Deficit hyperactivity Disorder (ADHD).
10. Use of t~~The compound of any of claims 1-4 in the manufacture of a medicament for use in~~ the treatment of Alzheimer's disease.
11. Use of t~~The compound of any of claims 1-4 in the manufacture of a medicament for use in~~ the treatment of Parkinson's disease.
12. Use of t~~The compound of any of claims 1-4 in the manufacture of a medicament for use in~~ the treatment of Huntington's disease.
13. A pharmaceutical composition comprising a therapeutically effective amount of a compound of claim 1, and one or more pharmaceutically acceptable carriers, diluents or excipients.