

Summary

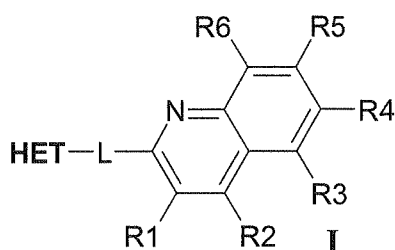
The objective of the present ~~invention~~-disclosure is to provide compounds that are selective PDE10A enzyme inhibitors.

5 A further objective of the present ~~invention~~-disclosure is to provide compounds which have such activity, and which have improved solubility, metabolic stability and/or bioavailability compared to prior art compounds.

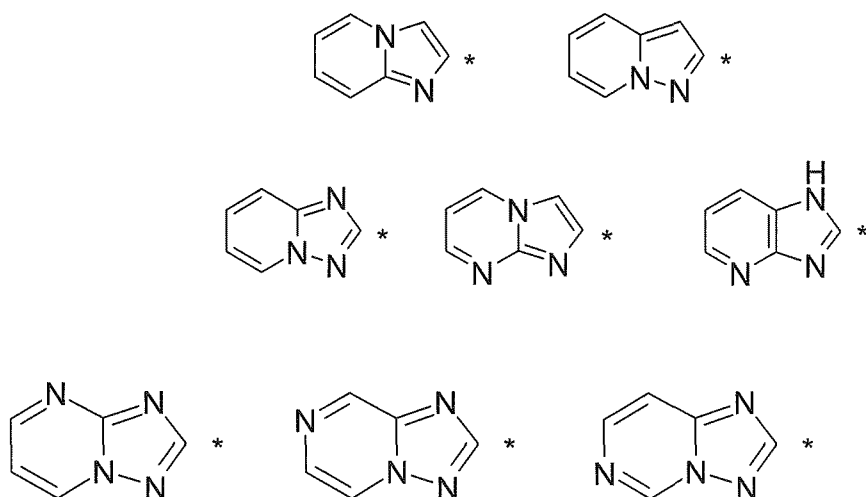
10 Another objective of the ~~disclosure~~ invention is to provide an effective treatment, in particular long-term treatment, of a human patient, without causing the side effects typically associated with current therapies for neurological and psychiatric disorders.

In one ~~aspect~~embodiment, there is provided a compound having the structure of formula I:

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wherein R₁, R₂, R₃, R₄, R₅ and R₆ are individually selected from the group consisting of hydrogen, hydroxyl, cyano, C₁-C₆ alkyl; C₁-C₆ alkoxy, halogen, methylenedioxy, difluoromethylenedioxy and ethylenedioxy; wherein -L- is a linker selected from -
20 CH₂-CH₂- and -CH=CH-; wherein HET is selected from the group consisting of:



wherein one or more of the carbon-bound hydrogen in the HET optionally may be substituted with up to three substituents R7, R8 and R9 individually selected from C₁-C₆ alkyl; halogen; cyano, halo(C₁-C₆)alkyl; aryl, alkoxy and C₁-C₆ hydroxyalkyl;

5 and wherein * denotes the attachment point; and tautomers and pharmaceutically acceptable salts thereof, and polymorphic forms thereof.

10 In one aspect, there is provided a compound selected from the group of 7-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline, and 6-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl)-[1,3]dioxolo[4,5-g]quinoline.

In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of the compound as disclosed herein and a pharmaceutically acceptable carrier, diluent or excipient.

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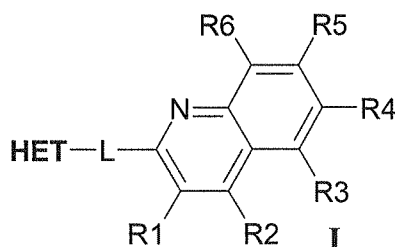
In yet another aspect, there is provided a use of the compound as disclosed herein or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of a neurodegenerative or psychiatric disorder.

20 Further objectives of the invention disclosure will become apparent upon reading the present specification.

Detailed description of the invention

Embodiments of the invention

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

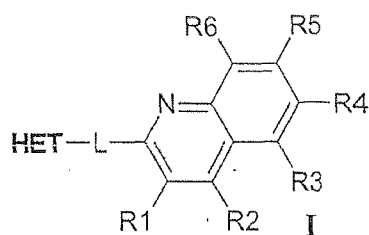


30 wherein R1, R2, R3, R4, R5 and R6 are individually selected from the group consisting of hydrogen, hydroxyl, cyano, C₁-C₆ alkyl; C₁-C₆ alkoxy, halogen, methylenedioxy, difluoromethylenedioxy and ethylenedioxy

wherein -L- is a linker selected from -CH₂-CH₂- and -CH=CH-

What is claimed:

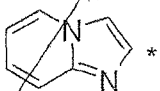
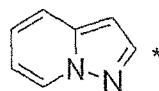
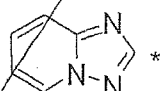
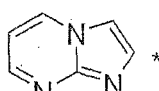
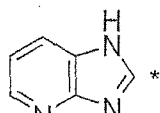
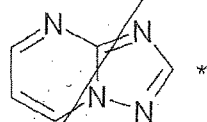
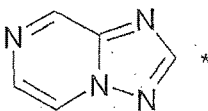
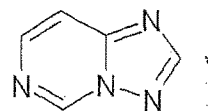
1. A compound having the structure of formula I:



wherein R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are individually selected from the group consisting of hydrogen, hydroxyl, cyano, C_1 - C_6 alkyl; C_1 - C_6 alkoxy, halogen, methylenedioxy, difluoromethylenedioxy and ethylenedioxy

wherein -L- is a linker selected from $-CH_2-CH_2-$ and $-CH=CH-$

wherein HET is selected from the group consisting of

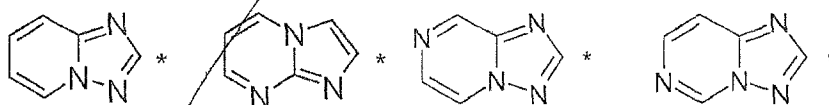


wherein one or more of the carbon-bound hydrogen in the HET optionally may be substituted with up to three substituents R_7 , R_8 and R_9 individually selected from C_1 - C_6 alkyl; halogen; cyano, halo(C_1 - C_6)alkyl; aryl, alkoxy and C_1 - C_6 hydroxyalkyl

and wherein * denotes the attachment point,

and tautomers and pharmaceutically acceptable salts thereof, and polymorphic forms thereof.

- 5 2. The compound of claim 1 wherein one or more of R1 to R6 is selected from the group consisting of C₁-C₃ alkyl substituted with one or more F and unsubstituted C₁-C₃ alkyl.
- 10 3. The compound of claim 1 wherein one or more of R1-R6 is selected from the group consisting of methoxy, difluoromethoxy and trifluoromethoxy.
4. The compound of claim 1 wherein one or more of R1-R6 is selected from the group consisting of fluorine and chlorine.
- 15 5. The compound of claim 1 wherein -L- is -CH₂-CH₂-
6. The compound of claim 1 wherein -L- is -CH=CH-
- 20 7. The compound of any of claims 1 to 6 wherein HET is selected from the group consisting of



wherein * denotes the attachment point.

- 25 8. The compound of claim 1 wherein HET is substituted with one substituent R7 selected from the group consisting of C₁-C₆ alkyl, such as methyl; halogen, such as chlorine or bromine; cyano; halo(C₁-C₆)alkyl, such as trifluoromethyl; aryl such as phenyl; and C₁-C₆ hydroxyalkyl such as CH₂CH₂OH.
- 30 9. The compound of claim 1 or 8 wherein HET is substituted with two substituents R7 and R8 individually selected from the group consisting of C₁-C₆ alkyl, such as methyl; halogen, such as chlorine or bromine; cyano;

halo(C₁-C₆)alkyl, such as trifluoromethyl; aryl such as phenyl; and C₁-C₆ hydroxyalkyl such as CH₂CH₂OH.

- 5 10. The compound of claim 1 or 8 wherein HET is substituted with three substituents R7, R8 and R9 individually selected from the group consisting of C₁-C₆ alkyl, such as methyl; halogen, such as chlorine or bromine; cyano; halo(C₁-C₆)alkyl, such as trifluoromethyl; aryl such as phenyl; and C₁-C₆ hydroxyalkyl such as CH₂CH₂OH.
- 10 11. The compound of claim 1 or 8 wherein HET is unsubstituted.
12. The compound of claim 1 wherein HET is selected from the group consisting of (5,7-Dimethyl-imidazo[1,2-a]pyrimidin-2-yl), 5,7-Dimethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl), (5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl), (8-Methoxy-5-methyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl) and 15 5,8-Dimethyl-[1,2,4]triazolo[1,5-a]pyridin-2-yl).
13. The compound of any of claim 1 to 12, or a pharmaceutically acceptable salt thereof, for use as a medicament.
- 20 14. A pharmaceutical composition comprising a therapeutically effective amount of the compound of any of claims 1-12 and a pharmaceutically acceptable carrier, diluent or excipient.
- 25 15. The use of the compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder.

Claims:

1. A compound selected from the group of 7-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl)-2,3-dihydro-[1,4]dioxino[2,3-g]quinoline, and 6-(2-(5,8-dimethyl-[1,2,4]triazolo[1,5-a]pyrazin-2-yl)-ethyl)-[1,3]dioxolo[4,5-g]quinoline.
2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, for use as a medicament.
3. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claim 1 and a pharmaceutically acceptable carrier, diluent or excipient.
4. The use of the compound of claim 1, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder.