of phosphodiesterase, especially type 2 in the therapeutic field.

Pyrrolodihydroisoquinolines and variants thereof are disclosed as inhibitors of PDE10 in WO 05/03129 and WO 05/02579. Piperidinyl-substituted quinazolines and isoquinolines that serve as PDE10 inhibitors are disclosed in WO 05/82883. WO 06/11040 discloses substituted quinazoline and isoquinoline compounds that serve as inhibitors of PDE10. US 20050182079 discloses substituted tetrahydroisoquinolinyl derivatives of quinazoline and isoquinoline that serve as effective phosphodiesterase (PDE) inhibitors. In particular, US 20050182079 relates to said compounds, which are selective inhibitors of PDE10. Analogously, US 20060019975 discloses piperidine derivatives of quinazoline and isoquinoline that serve as effective phosphodiesterase (PDE) inhibitors. US 20060019975 also relates to compounds that are selective inhibitors of PDE10. WO 06/028957 discloses cinnoline derivatives as inhibitors of phosphodiesterase type 10 for the treatment of psychiatric and neurological syndromes.

However, these disclosures do not pertain to the compounds of the invention, which are structurally unrelated to any of the known PDE10 inhibitors (Kehler, J. *et al. Expert Opin. Ther. Patents* **2007**, *17*, 147-158 and Kehler, J. *et al. Expert Opin. Ther. Patents* **2009**, *19*, 1715-1725), and which have now been found by the inventors to be highly active and selective PDE10A enzyme inhibitors.

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**

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

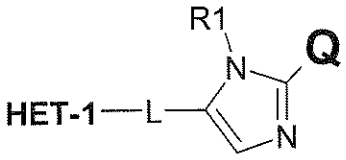
A further objective ~~of the present invention~~ is to provide compounds which

have such activity, and which have improved solubility, metabolic stability and/or bioavailability compared to prior art compounds.

Another objective ~~of the 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.

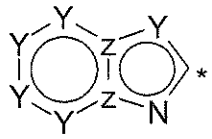
Further objectives ~~of the invention~~ will become apparent upon reading the present specification.

Accordingly, in one ~~aspect~~embodiment the present ~~invention~~disclosure relates to compounds of formula **I**:




**I**

wherein **HET-1** is a heteroaromatic group of formula **II** containing from 2 to 4 nitrogen atoms:

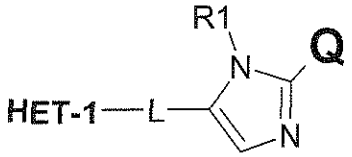



**II**

wherein Y can be N or CH, Z can be N or C, and wherein **HET-1** may optionally be substituted with up to three substituents R7, R8 and R9 individually selected from H; $C_1$-$C_6$ alkyl such as Me; halogen such as chlorine and bromine; cyano; halo($C_1$-$C_6$)alkyl such as trifluoromethyl; aryl such as phenyl; alkoxy, such as methoxy, dimethoxy, ethoxy, methoxy-ethoxy and ethoxy-methoxy, and $C_1$-$C_6$ hydroxyalkyl such as $CH_2CH_2OH$, and wherein *

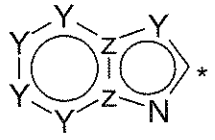
and tautomers and pharmaceutically acceptable salts thereof, and polymorphic forms thereof.

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




**I**

wherein **HET-1** is a heteroaromatic group of formula **II** containing from 2 to 4 nitrogen atoms:




**II**

wherein Y can be N or CH, Z can be N or C, and wherein **HET-1** may optionally be substituted with up to three substituents R2-R4 individually selected from hydrogen, $C_1$-$C_6$ alkyl; halogen; cyano, halo($C_1$-$C_6$)alkyl; aryl, alkoxy and $C_1$-$C_6$ hydroxyalkyl, and wherein * denotes the attachment point,

**Q** is a is phenyl, optionally substituted with one to five substituents, or a monocyclic 5-membered or 6-membered heteroaromatic group containing 1 or 2 heteroatoms

-L- is a linker selected from -S-$CH_2$- , -$CH_2$-S- , -$CH_2$-$CH_2$-, -CH=CH-, and $-C\equiv C-$

$R_1$ is selected from H, $C_1$-$C_6$ alkyl; $C_1$-$C_6$ alkyl($C_3$-$C_8$)cycloalkyl; $C_1$-$C_6$ hydroxyalkyl, $CH_2CN$, $CH_2C(O)NH_2$, $C_1$-$C_6$ arylalkyl, and $C_1$-$C_6$ alkyl-heterocycloalkyl,

and tautomers and pharmaceutically acceptable salts thereof, and polymorphic forms thereof, provided that the compound is not 2-(5-phenyl-1H-imidazol-2-ylmethylsulfanyl)-1H-benzoimidazole or 2-(5-phenyl-1H-imidazol-2-yl-sulfanyl-methyl)-1H-benzoimidazole.

In separate embodiments ~~of the invention~~, the compound of formula I is selected among the specific compounds disclosed in the Experimental Section herein.

The invention further provides a compound of formula I as disclosed herein, or a pharmaceutically acceptable salt thereof, for use as a medicament.

In another aspect, the present invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula I as disclosed herein and a pharmaceutically acceptable carrier, diluent or excipient.

The invention further provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder.

Furthermore, in yet another ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of treating a subject suffering from a neurodegenerative disorder, comprising administering to the subject a therapeutically effective amount of a compound of formula I. In a still further ~~aspect~~embodiment, the present ~~invention~~disclosure provides a method of treating a subject suffering from a psychiatric disorder, comprising administering to the subject a therapeutically effective amount of a compound of formula I. In another embodiment, the present ~~invention~~disclosure provides a method of treating a subject suffering from a drug addiction, such as an alcohol, amphetamine, cocaine, or opiate addiction.

Another aspect relates to the use of a compound as defined above, for the preparation of a medicament in the treatment of a drug addiction in a mammal, including a human, such as an alcohol, amphetamine, cocaine, or opiate addiction.

Yet another aspect relates to the use of a compound as defined above, for the preparation of a medicament for the treatment of a neurodegenerative or psychiatric disorder, wherein the neurodegenerative disorder is selected from the group consisting of Alzheimer's disease, multi-infarct dementia, alcoholic dementia or other drug-related dementia, dementia associated with intracranial tumors or cerebral trauma, dementia associated with Huntington's disease or Parkinson's disease, or AIDS-related dementia; delirium; amnestic disorder; post-traumatic stress disorder; mental retardation; a learning disorder, for example reading disorder, mathematics disorder, or a disorder of written expression; attention-deficit/hyperactivity disorder; and age-related cognitive decline, and the psychiatric disorder is selected from the group consisting of schizophrenia, for example of the paranoid, disorganized, catatonic, undifferentiated, or residual type; schizophreniform disorder; schizoaffective disorder, for example of the delusional type or the depressive type; delusional disorder; substance-induced psychotic disorder, for example psychosis induced by alcohol, amphetamine, cannabis, cocaine, hallucinogens, inhalants, opioids, or phencyclidine; personality disorder of the paranoid type; and personality disorder of the schizoid type.

## Detailed Description of the Invention

### Definition of Substitutents

As used in the context of the present invention, the terms “halo” and “halogen” are used interchangeably and refer to fluorine, chlorine, bromine or iodine.