Huntington's disease, addiction, and depression. PDE10 inhibitors may be also useful in other conditions such as obesity, non-insulin dependent diabetes, bipolar disorder, obsessive compulsive disorder and pain.

The efficacy of PDE10A inhibition in models of cognition and against negative symptoms of schizophrenia has also been suggested by recent in vivo studies in which this mechanism has been associated with increased sociality in the Social Approach/Social Avoidance assay, reversed effect of chronic MK-801 treatment in a forced swim test, enhancement of social odor recognition in mice and improved novel object recognition in rats.

Background art

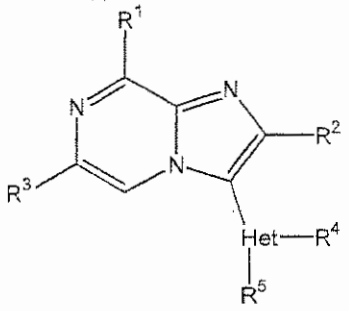
WO 2009/146358 discloses substituted 2-phenyl and 2-pyridinyl-imidazo[1,2-*a*]pyrazine-8-carboxamide derivatives as sirtuin-modulating compounds.

Bioorg. Med. Chem. Lett. 17 (2007) 486-490 discloses [8-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyrazin-2-yl][4-(pyridin-2-yl)-1,4-diazepan-1-yl]methanone; [8-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyrazin-2-yl](3-phenylpiperidin-1-yl)methanone; [8-(4-methylpiperazin-1-yl)imidazo[1,2-*a*]pyrazin-2-yl][4-(6-methylpyridin-2-yl)-1,4-diazepan-1-yl]methanone; 8-(4-methylpiperazin-1-yl)-*N*-(2-phenylpropyl)imidazo[1,2-*a*]pyrazine-2-carboxamide as mGluR1 antagonists (K_i between 407-1204 nM).

Description of the ~~Invention~~Disclosure

We have now found novel compounds that are PDE10 inhibitors. As already indicated above, compounds having this type of action are likely to be useful in the treatment of neurological, psychiatric (and metabolic) disorders. In particular, the present compounds are likely to be useful in antipsychotic therapy, providing extended therapeutic profile, low EPS liability and less off-target effects than observed with the current antipsychotics. The present compounds are centrally active, potent compounds which display efficacy in preclinical behavior challenge models in which known clinical useful antipsychotics display similar positive responses, such as in the reversal of apomorphine-induced stereotypy and phencyclidine (PCP)-induced hyperlocomotion in rodents. Additionally, representative compounds reverse the hypolocomotion effects exerted by SCH23390, a D1 receptor antagonist, and the behavioural effects exerted by depletion of monoamines in rodents, such as the sedation observed after administration of reserpine and the sedation and catalepsy induced by Ro-4-1248. Thus, the present compounds may act as dopamine modulating agents, inhibiting states of dopaminergic (D_2) hyperactivity and reversing states of dopaminergic (D_1) hypoactivity.

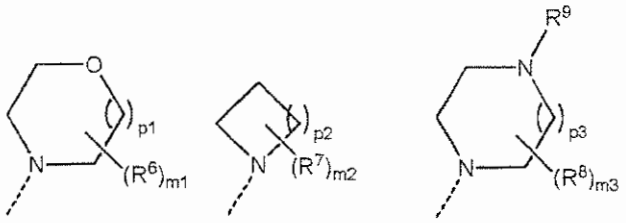
The present ~~invention~~disclosure, in a first aspect, relates to compounds having PDE10 inhibitory activity, said compounds having Formula (I)



(I)

and the stereoisomeric forms thereof, wherein

R^1 is selected from the group consisting of a radical of formula (a-1), (a-2) and (a-3);



(a-1) (a-2) (a-3);

wherein

each R^6, R^7, and R^8 independently is selected from the group consisting of fluoro; C_{1-4}alkyl; C_{1-4}alkyloxy; and C_{1-4}alkyl substituted with 1, 2 or 3 fluoro atoms;

R^9 is hydrogen or C_{1-4}alkyl;

each m_1, m_2, and m_3 is independently selected from 0, 1, 2, 3 and 4;

p_2 is selected from 1, 2, 3 and 4;

each p_1 and p_3 is independently selected from 1 and 2;

or R^1 is selected from the group consisting of unsubstituted pyridinyl; pyridinyl substituted with 1 or 2 substituents selected from the group consisting of halogen, C_{1-4}alkyl, trifluoromethyl and C_{1-4}alkyloxy; and unsubstituted tetrahydropyranyl;

R^2 is selected from the group consisting of hydrogen; C_{1-4}alkyl; trifluoromethyl; C_{3-8}cycloalkyl; C_{1-4}alkyloxy; and cyano;

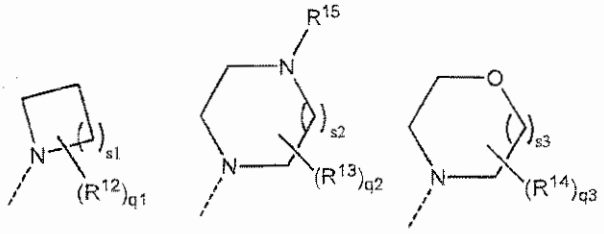
R^3 is selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{3-8}cycloalkyl; and C_{1-4}alkyl substituted with 1, 2 or 3 fluoro atoms;

Het is a 5- or 6- membered heterocyclic ring, selected from the group consisting of pyridinyl; pyrimidinyl; pyridazinyl; pyrazinyl; pyrrolyl; oxazolyl; thiazolyl; imidazolyl; pyrazolyl; isothiazolyl; isoxazolyl; oxadiazolyl and triazolyl;

R^4 is selected from the group consisting of hydrogen; C_{1-4}alkyl; C_{1-4}alkyl substituted with 1, 2 or 3 fluoro atoms; (difluorocyclopropyl)methyl; (cyclopropyl)difluoromethyl; hydroxyC_{1-4}alkyl; C_{3-8}cycloalkyl; (C_{3-8}cycloalkyl)-C_{1-4}alkyl; C_{1-4}alkyloxyC_{1-6}alkyl; C_{1-4}alkyloxy; C_{1-4}alkyloxy substituted with 1, 2 or 3 fluoro atoms; (C_{3-8}cycloalkyl)C_{1-4}alkyloxy; (C_{1-4}alkyloxyC_{1-4}alkyl)oxy; (C_{1-4}alkyl)-carbonyl; (C_{1-4}alkyl)carbonylC_{1-4}alkyl; (C_{3-8}cycloalkyl)carbonyl; (C_{3-8}cycloalkyl)-carbonylC_{1-4}alkyl; unsubstituted phenyl; phenyl substituted with 1 or 2 substituents selected from the group consisting of halogen, C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, cyano and C_{1-4}alkyloxy; unsubstituted benzyl; benzyl substituted with 1 or 2 substituents selected from the group consisting of halogen, C_{1-4}alkyl, trifluoromethyl, trifluoromethoxy, cyano and C_{1-4}alkyloxy; unsubstituted tetrahydrofuranyl; tetrahydrofuranylmethyl; unsubstituted tetrahydropyranyl; tetrahydropyranylmethyl; pyridinylmethyl; quinolinylmethyl; ($NR^{10}R^{11}$)C_{1-4}alkyl; and $NR^{10}R^{11}$;

R^5 is hydrogen or fluoro;

R^{10} and R^{11} are independently selected from hydrogen and C_{1-4}alkyl, or taken together with the ring nitrogen atom may form a radical of Formula (b-1), (b-2) or (b-3)



(b-1) (b-2) (b-3);

wherein each R^{12}, R^{13} and R^{14} independently is C_{1-4}alkyl or C_{1-4}alkyloxy;

R^{15} is hydrogen or C_{1-4}alkyl;

each q_1, q_2 and q_3 is independently selected from 0, 1, 2, 3 and 4;

s_1 is selected from 1, 2, 3 and 4;

each s_2 and s_3 is independently selected from 1 and 2;

and the pharmaceutically acceptable salts and the solvates thereof.

The present ~~invention also~~disclosure, in a second aspect, relates to a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient.

Additionally, the ~~invention~~disclosure, in a third aspect, relates to a compound of Formula (I) for use as a medicament~~,~~. The disclosure also relates ~~and~~ to a compound of Formula (I) for use in the treatment or in the prevention of neurological, psychiatric or metabolic disorders and diseases.

The disclosure, in a fourth aspect, relates to a compound as defined above or a pharmaceutical composition as defined above for use in the treatment or in the prevention of neurological, psychiatric or metabolic disorders and diseases.

The disclosure, in a fifth aspect, relates to a compound or a pharmaceutical composition as defined above for use in the treatment or in the prevention of a disorder selected from the group of psychotic disorders; anxiety disorders; movement disorders; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; drug addiction disorders; pain and metabolic disorders.

Additionally, the ~~invention~~disclosure relates to the use of a compound of Formula (I) in combination with an additional pharmaceutical agent for use in the treatment or prevention of neurological, psychiatric or metabolic disorders and diseases.

The disclosure, in a sixth aspect, relates to a compound as defined above in combination with an additional pharmaceutical agent for use in the treatment or prevention of a condition as defined above.

Furthermore, the ~~invention~~disclosure, in a seventh aspect, relates to a process for preparing a pharmaceutical composition according to the invention, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

The ~~invention~~disclosure also relates to a product comprising a compound of Formula (I) and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of neurological, psychiatric or metabolic disorders and diseases.

The disclosure, in an eighth aspect, relates to a product comprising

(a) a compound as defined above; and

(b) an additional pharmaceutical agent,

as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition as defined above.

Detailed Description of the Invention

The chemical names of the compounds of the present invention were generated according to the nomenclature rules agreed upon by the Chemical Abstracts Service (CAS) using Advanced Chemical Development, Inc., software (ACD/Name product version 10.01; Build 15494, 1 Dec 2006). In case of tautomeric forms, the name of the depicted tautomeric form of the structure was generated. However it should be clear that the other non-depicted tautomeric form is also included within the scope of the present invention.

Definitions

The term "halogen" or "halo" as used herein alone or as part of another group refers to fluoro, chloro, bromo or iodo, with fluoro or chloro being preferred.

The term "C_{1-4}alkyl" or"C_{1-6}alkyl" as employed herein alone or as part of another group, unless otherwise stated, refers to a saturated straight or branched hydrocarbon radical, having unless otherwise stated, from 1 to 4 or 1 to 6 carbon atoms, which is attached to the rest of the molecule by a single bond, such as methyl, ethyl, propyl, butyl, 1-pentyl, 1-methylethyl, 1,1-dimethylethyl, 2-methylpropyl, and 3-methylbutyl.

The term "C_{3-8}cycloalkyl" as employed herein alone or as part of another group