

Papaverine, a relatively specific PDE10A inhibitor, and PDE10A-knockout mice have been used to explore the physiology of this enzyme and the possible therapeutic utility of PDE10A inhibition. Inhibition of this enzyme pharmacologically or through gene disruption causes a reduction in activity and a reduced response to psychomotor stimulants. Inhibition also
5 reduces the conditioned avoidance response, a behavioural response that is predictive of clinical antipsychotic activity (Siuciak, J.A.; et al., *Neuropharmacology* 2006, 51 (2), 386-396; Siuciak, J.A.; et al., *Neuropharmacology* 2006, 51 (2), 374-385).

In addition PDE10A inhibition bears the potential to improve the negative and cognitive symptoms associated to schizophrenia. Indeed papaverine have been shown to attenuate the defi-
10 cits in the extra-dimensional shift learning induced in rats by sub-chronic treatment with PCP, an animal paradigm of NMDA receptor hypofunction (Rodefer, J.S., et al., *Eur. J. Neuroscience* 2005, 2,; 1070-1076). In addition increased social interaction in PDE10A2-deficient mice have been observed (Sano, H. *J. Neurochem.* 2008, 105, 546-556).

Diseases that can be treated with PDE10A inhibitors include, but are not limited to, dis-
15 eases thought to be mediated in part by dysfunction of the basal ganglia, of other parts of the central nervous system and of other PDE10A expressing tissues. In particular, diseases can be treated, where inhibition of PDE10A can have therapeutic effects.

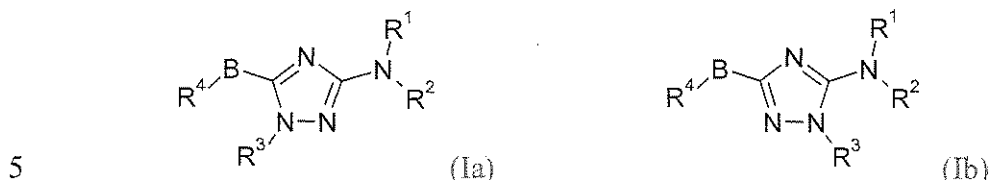
These diseases include, but are not limited to, certain psychotic disorders such as schizo-
phrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional
20 disorder or substance-induced psychotic disorder, anxiety disorders such as panic disorder, ob-
sessive-compulsive disorder, acute stress disorder or generalized anxiety disorder, obses-
sive/compulsive disorders, drug addictions, movement disorders such as Parkinson's disease or
restless leg syndrome, cognition deficiency disorders such as Alzheimer's disease or multi-
infarct dementia, mood disorders such as depression or bipolar disorders, or neuropsychiatric
25 conditions such as psychosis, attention-deficit/hyperactivity disorder (ADHD) or related atten-
tional disorders.

The compounds of the present ~~invention~~ disclosure are also suitable for the treatment of diabetes and related disorders such as obesity by regulating the cAMP signaling system.

PDE10A inhibitors might also be useful in preventing neurons from undergoing apopto-
30 sis by raising cAMP and cGMP levels and, thus, might possess anti-inflammatory properties. Neurodegenerative disorders treatable with PDE10A inhibitors include, but are not limited to, as Alzheimer's disease, Huntington's disease, Parkinson's disease, multiple sclerosis, stroke or spinal cord injury.

The growth of cancer cells is inhibited by cAMP and cGMP. Thus by raising cAMP and cGMP, PDE10A inhibitors can also be used for the treatment of different solid tumors and hematological malignancies such as renal cell carcinoma or breast cancer.

In a first aspect, there is provided a compound of formula (Ia) or (Ib)



wherein

B is C₁-C₄-alkylene, C₂-C₄-alkenylene, C₂-C₄-alkynylene, C₃-C₅-cycloalkyl,

10 R¹ and R², are independently selected from hydrogen, C₁-C₇-alkyl optionally substituted by C₃-C₅-cycloalkyl; C₁-C₇-hydroxyalkyl, C₁-C₇-alkoxyalkyl, C₁-C₇-haloalkyl, C₃-C₅-cycloalkyl, R¹ and R² together with the nitrogen atom to which they are attached, form a azaspirocycloalkyl, a bicyclic ring or heterocycloalkyl which can be substituted by 1 to 3 substituents independently selected from the group consisting of halogen, C₁-C₇-alkyl, C₁-C₇ alkoxyalkyl; C₁-C₇-hydroxyalkyl, C₁-C₇ alkoxy, C₁-C₇-haloalkyl, hydroxyl, -NR⁹R¹⁰ and oxo;

15 R³ is selected from hydrogen, C₃-C₅-cycloalkyl, C₁-C₇-alkoxyalkyl, C₁-C₇-haloalkyl, heterocycloalkyl, -(CH₂)_{0,1,2} - aryl optionally substituted by C₁-C₇ alkoxy and C₁-C₇-alkyl optionally substituted by C₃-C₅-cycloalkyl;

20 R⁴ is selected from heteroaryl optionally substituted by 1 to 3 substituents selected from halogen, C₁-C₇-alkyl, C₁-C₇-hydroxyalkyl, C₁-C₇-haloalkoxy, C₁-C₇-haloalkyl, C₃-C₅-cycloalkyl, cyano, amino, nitro, -O-R⁶-C(O)-R⁷, -SO₂R⁸, C₁-C₂-alkoxy optionally substituted by C₁-C₂-alkoxy, heterocycloalkyl,

R⁶ and R⁸ are selected from C₁-C₇-alkyl,

R⁷ is selected from heterocycloalkyl,

R⁹ and R¹⁰ are independently selected from hydrogen, C₁-C₇-alkyl, -C(O)-O- C₁-C₇-alkyl.

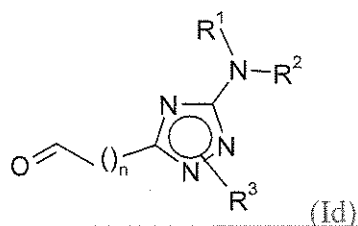
25 In a second aspect, there is provided use of a compound as defined herein for the preparation of a medicament for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive

disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

In a third aspect, there is provided a compound as defined herein for the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer.

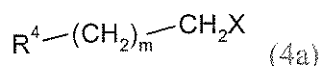
In a fourth aspect, there is provided a process for the manufacture of compounds of formula I as defined herein, which process comprises

a) reacting a compound of formula (Id)

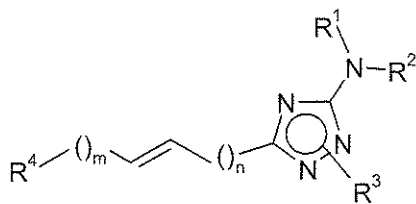


with

b) a compound of formula (4a)



to a compound of formula (Ie)



wherein n and m are 0 or 1, R¹, R², R³, R⁴ and X are as defined herein.

Unless otherwise indicated, the following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

5 The terms “compound(s) of the formula (Ia) and(Ib)”, “compound(s) of formula (Ia) and(Ib)”, “compound(s) of this invention” or “compound(s) of the present invention” refer to any compound selected from the genus of compounds as defined by the formula (Ia) and(Ib) including stereoisomers, tautomers, solvates, and salts (e.g. pharmaceutically acceptable salts) thereof.

10 It must be noted that, as used in the specification and the claims, the singular forms "a", "an" and "the" include plural referents unless the context clearly dictates otherwise.

When indicating the number of substituents, the term "one or more" means from one substituent to the highest possible number of substitution, i.e. replacement of one hydrogen up to replacement of all hydrogens by substituents.

15 The term “optional” or “optionally” denotes that a subsequently described event or circumstance may but need not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not.

The term “substituent” denotes an atom or a group of atoms replacing a hydrogen atom on the parent molecule.

20 The term “halogen” refers to fluorine, chlorine, bromine and iodine, more superficially fluorine, chlorine and bromine.

 The term “alkyl” denotes a monovalent linear or branched saturated hydrocarbon group of 1 to 12 carbon atoms. In particular embodiments, alkyl has 1 to 7 carbon atoms, and in more particular embodiments 1 to 4 carbon atoms. Examples of alkyl include methyl, ethyl, propyl,
25 isopropyl, n-butyl, iso-butyl, sec-butyl, or tert-butyl.

 The term “alkylene” denotes a linear saturated divalent hydrocarbon group of 1 to 7 carbon atoms or a divalent branched saturated divalent hydrocarbon group of 3 to 7 carbon atoms. Examples of alkylene groups include methylene, ethylene, propylene, 2-methylpropylene, butylene, 2-ethylbutylene, pentylene, hexylene.

9 ~~—— The use of a compound of claims 1 – 8 for the treatment or prophylaxis of psy-~~
~~chotic disorders, schizophrenia, positive, negative and/or cognitive symptoms associated with~~
~~schizophrenia, delusional disorder, substance-induced psychotic disorder, anxiety disorders, pan-~~
~~ic disorder, obsessive/compulsive disorders, acute stress disorder, generalized anxiety disorder,~~
5 ~~drug addictions, movement disorders, Parkinson's disease, restless leg syndrome, cognition defi-~~
~~ciency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipo-~~
~~lar disorders, neuropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, at-~~
~~tentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative~~
~~disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, he-~~
10 ~~matological malignancies, renal cell carcinoma or breast cancer.~~

109. The use of a compound of claims 1 – 8 for the preparation of a medicament for
the treatment or prophylaxis of psychotic disorders, schizophrenia, positive, negative and/or
cognitive symptoms associated with schizophrenia, delusional disorder, substance-induced psy-
chotic disorder, anxiety disorders, panic disorder, obsessive/compulsive disorders, acute stress
15 disorder, generalized anxiety disorder, drug addictions, movement disorders, Parkinson's disease,
restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dement-
tia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, atten-
tion-deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2
diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke,
20 spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast can-
cer.

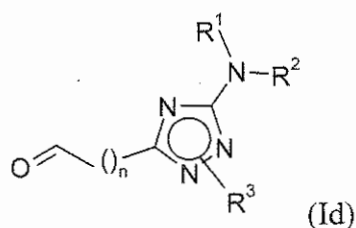
110. A compound of claims 1 - 8 for the treatment or prophylaxis of psychotic disor-
ders, schizophrenia, positive, negative and/or cognitive symptoms associated with schizophrenia,
delusional disorder, substance-induced psychotic disorder, anxiety disorders, panic disorder, ob-
25 sessive/compulsive disorders, acute stress disorder, generalized anxiety disorder, drug addictions,
movement disorders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders,
Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neu-
ropsychiatric conditions, psychosis, attention-deficit/hyperactivity disorder, attentional disorders,
diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Hunting-
30 ton's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malig-
nancies, renal cell carcinoma or breast cancer.

12. ~~—— A method for the treatment or prophylaxis of psychotic disorders, schizophrenia,~~
~~positive, negative and/or cognitive symptoms associated with schizophrenia, delusional disorder,~~
~~substance-induced psychotic disorder, anxiety disorders, panic disorder, obsessive/compulsive~~
35 ~~disorders, acute stress disorder, generalized anxiety disorder, drug addictions, movement disor~~

ders, Parkinson's disease, restless leg syndrome, cognition deficiency disorders, Alzheimer's disease, multi-infarct dementia, mood disorders, depression, bipolar disorders, neuropsychiatric conditions, psychosis, attention deficit/hyperactivity disorder, attentional disorders, diabetes and related disorders, type 2 diabetes mellitus, neurodegenerative disorders, Huntington's disease, multiple sclerosis, stroke, spinal cord injury, solid tumors, hematological malignancies, renal cell carcinoma or breast cancer, which method comprises administering an effective amount of a compound as defined in claims 1-8.

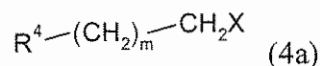
1311. A process for the manufacture of compounds of formula I as defined in claims 1-8, which process comprises

a) reacting a compound of formula (Id)

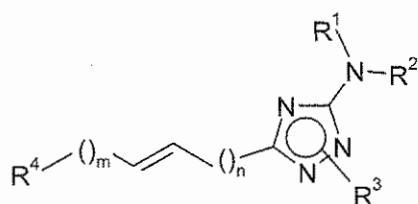


with

b) a compound of formula (4a)



to a compound of formula (Ie)



wherein n and m are 0 or 1, R^1 , R^2 , R^3 , R^4 and X are as defined in the previous claims.

1412. The process of claim 1311, wherein n = 0 and m = 0.