

(2010) Quantitative comparison of phosphodiesterase mRNA distribution in human brain and peripheral tissues. *Neuropharmacol.* 59, 367-374).

Additionally, PDE2 inhibitors have been shown to be beneficial in the reduction of oxidative stress-induced anxiety, supporting their use in the treatment of anxiety in
 5 neuropsychiatric and neurodegenerative disorders that involve oxidative stress, such as Alzheimer's disease, Parkinson's disease and multiple sclerosis.

PDE2 inhibitors have been shown to enhance long term potentiation of synaptic transmission and to improve memory acquisition and consolidation in the object
 10 recognition and in the social recognition tests in rats. Furthermore, PDE2 inhibitors have been shown to reverse the MK-801 induced working memory deficit in the T-maze in mice. PDE2 inhibitors have also been shown to display activity in forced swim test and light/dark box models; and to show anxiolytic-like effects in elevated plus-maze, hole-board and open-field tests and to prevent stress-induced changes in
 15 apoptosis and behaviour.

Thus, PDE2 inhibitors may be useful in the treatment of memory deficiency, cognitive disorders, anxiety, bipolar disorder and depression.

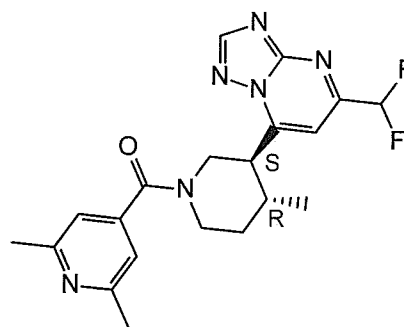
20 WO2015/164508 (Dart Neuroscience, LLC) discloses substituted [1,2,4]triazolo[1,5-a]pyrimidin-yl compounds as PDE2 inhibitors. WO2017/076900 (Janssen Pharmaceutica NV) discloses [(3S,4R)-3-[5-(difluoromethyl)-[1,2,4]triazolo[1,5-a]pyrimidin-7-yl]-4-methyl-1-piperidyl]-(2,6-dimethyl-4-pyridyl)methanone.

25 There is still a need for PDE2 inhibitor compounds with an advantageous balance of properties, for example with improved potency, better selectivity against PDE3 and/or PDE10, and/or better chemical or metabolic stability.

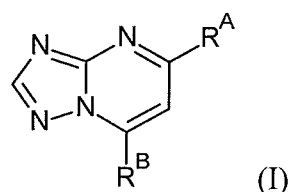
SUMMARY

30 It is the object of the present disclosure to provide novel inhibitors of PDE2 that may be potentially useful in the treatment of diseases related to PDE2 enzyme activity.

Thus, the present disclosure is directed to compounds of Formula (I)



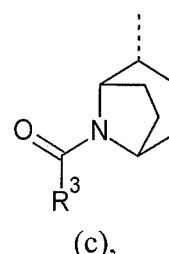
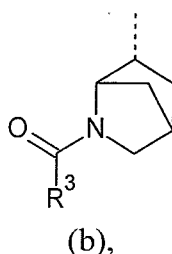
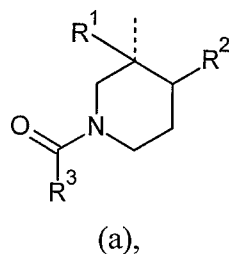
with the proviso that the compound is not ;
 and the N-oxides, and the pharmaceutically acceptable salts and the solvates thereof.
 According to one aspect, there is provided a compound having the formula (I),



5 or a stereoisomeric form thereof, wherein

R^A is selected from the group consisting of H, CH_3 , CN, and CHF_2 ;

R^B is a radical selected from the group consisting of (a), (b) and (c):



10 wherein

R^1 is H, F or CH_3 ;

R^2 is H or C_{1-4} alkyl, in particular methyl or n-butyl; with the proviso that when R^2 is H, then R^1 is F or CH_3 ;

15

R^3 is Ar, Het, or Ar-C_{2-4} alkenyl; wherein

Ar represents phenyl or naphthyl, each optionally substituted with 1, 2 or 3 substituents, each independently selected from the group consisting of halo; CN;

20 $\text{NR}^{2A}\text{R}^{2B}$ wherein R^{2A} and R^{2B} are each independently selected from H and CH_3 ; OH; C_{1-6} alkyl optionally substituted with 1, 2 or 3 independently selected halo substituents;

C₁₋₆alkyl substituted with CN; C₃₋₆cycloalkyl; C₁₋₆alkyloxy optionally substituted with 1, 2 or 3 independently selected halo substituents; and pyrazolyl;

Het represents

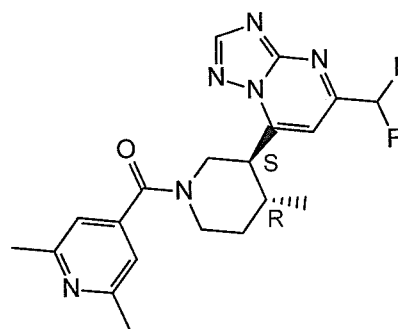
- 5 (i) a 5-membered heteroaryl selected from the group consisting of 1H-pyrrolyl; thienyl; furanyl; 1H-pyrazolyl; 1H-imidazolyl; 1,2-oxazolyl; 1,3-oxazolyl; and thiazolyl; each of which may be optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of halo; C₁₋₄alkyl optionally substituted with 1, 2, or 3 independently selected halo substituents; NR^{3A}R^{3B} wherein R^{3A} and R^{3B} are each
10 independently selected from H and CH₃; and furan-2-yl; or

- (ii) a 6-membered heteroaryl selected from the group consisting of pyridyl, pyrimidinyl, pyrazinyl, and pyridazinyl; each of which may be optionally substituted with 1, 2 or 3 substituents each independently selected from the group consisting of
15 halo; OH; CN; NR^{4A}R^{4B} wherein R^{4A} and R^{4B} are each independently selected from H and CH₃; C₁₋₄alkyl optionally substituted with 1, 2 or 3 independently selected halo substituents; C₁₋₄alkyl substituted with OH; C₃₋₆cycloalkyl; C₃₋₆cycloalkyloxy; C₁₋₄alkyloxy optionally substituted with 1, 2 or 3 independently selected halo substituents; and C₁₋₄alkyloxyC₁₋₄alkyl; or

- 20 (iii) a 8- to 10-membered bicyclic partially unsaturated heterocyclyl selected from the group consisting of 2,3-dihydro-1-benzofuranyl; 2H-chromenyl; 3,4-dihydro-2H-chromenyl; 2,3-dihydro-1H-indolyl optionally substituted at the 1-position with C₁₋₄alkyl, methylsulfonyl, 1-acetyl, or fluoroacetyl; 2,2-difluoro-1,3-benzodioxolyl;
25 1,3-benzodioxolyl optionally substituted with a methyl substituent; 3,4-dihydro-2H-1,4-benzoxazinyl optionally substituted with C₁₋₄alkyl; 5,6,7,8-tetrahydroimidazo[1,2-a]pyridinyl; 5,6,7,8-tetrahydroquinolinyl optionally substituted with a halo substituent; and 2,3-dihydropyrazolo[5,1-b][1,3]oxazolyl; or

- 30 (iv) a 9- to 10-membered bicyclic heteroaryl selected from the group consisting of 1-benzofuranyl; 1-benzothiophenyl; 1H-indolyl; 1,3-benzoxazolyl; 1,3-benzothiazolyl; indolizinyl; 1H-benzimidazolyl; imidazo[1,2-a]pyridinyl; pyrazolo[1,5-a]pyridinyl; 1H-thieno[2,3-c]pyrazolyl; imidazo[2,1-b]thiazolyl; pyrrolo[2,3-c]pyridinyl; thieno[3,2-b]pyridinyl; quinolinyl; isoquinolinyl; quinoxalinyl; 1,8-naphthyridinyl; and
35 1,6-naphthyridinyl; each of which may be optionally substituted with 1 or 2 substituents each independently selected from the group consisting of halo; OH; NR^{5A}R^{5B} wherein R^{5A} and R^{5B} are each independently selected from H and CH₃;

C₁₋₄alkyl optionally substituted with 1, 2 or 3 independently selected halo substituents;
and C₁₋₄alkyloxy optionally substituted with 1, 2 or 3 independently selected halo
substituents;



5 with the proviso that the compound is not ;
or an N-oxide, or a pharmaceutically acceptable salt or a solvate thereof.

Illustrative of the disclosure is a pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a compound of Formula (I) as described
10 herein, or a pharmaceutically acceptable salt or a solvate thereof. An illustration of the
disclosure is a pharmaceutical composition made by mixing a compound of Formula (I)
as described herein, or a pharmaceutically acceptable salt or a solvate thereof, and a
pharmaceutically acceptable carrier. Illustrating the disclosure is a process for making a
pharmaceutical composition comprising mixing a compound of Formula (I) as
15 described herein, or a pharmaceutically acceptable salt or a solvate thereof, and a
pharmaceutically acceptable carrier. According to another aspect, there is provided a
pharmaceutical composition comprising a therapeutically effective amount of a
compound as defined herein and a pharmaceutically acceptable carrier. According to
another aspect, there is provided a process for preparing a pharmaceutical composition
20 as defined herein, characterized in that a pharmaceutically acceptable carrier is
intimately mixed with a therapeutically effective amount of a compound as defined
herein.

Further illustrative of the disclosure are methods to enhance neuronal plasticity
comprising administering to a subject in need thereof a therapeutically effective amount
25 of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt
or a solvate thereof, or pharmaceutical compositions described herein.

Exemplifying the disclosure are methods of treating a disorder mediated by the
PDE2 enzyme, comprising administering to a subject in need thereof a

therapeutically effective amount of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt or a solvate thereof, or pharmaceutical compositions described herein.

5 Further exemplifying the disclosure are methods of inhibiting the PDE2 enzyme, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt or a solvate thereof, or pharmaceutical compositions described herein.

10 An example of the disclosure is a method of treating a disorder selected from the group consisting of neurological and psychiatric disorders, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula

(I) as described herein, or a pharmaceutically acceptable salt or a solvate thereof, or pharmaceutical compositions described herein.

An example of the disclosure is a method of treating a disorder selected from the group of neurological and psychiatric disorders selected from psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; stroke; and autistic disorders, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) as described herein, or a pharmaceutically acceptable salt or a solvate thereof, or a pharmaceutically acceptable salt or a solvate thereof or pharmaceutical compositions described herein. According to another aspect, there is provided a compound as defined herein or a pharmaceutical composition as defined herein for use in treating or preventing a central nervous system disorder selected from the group of psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; disorders related to memory acquisition and consolidation; stroke; and autistic disorder.

An example of the disclosure is a method of treating a disorder selected from the group consisting of neurological and psychiatric disorders comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) as described herein or a pharmaceutically acceptable salt or a solvate thereof, or pharmaceutical compositions described herein.

An example of the disclosure is a method of treating a disorder selected from the group of neurological and psychiatric disorders selected from psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; disorders related to memory acquisition and consolidation; stroke; and autistic disorders, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) or a salt or a solvate thereof, or pharmaceutical compositions described herein. According to another aspect, there is provided use of a therapeutically effective amount of a compound as defined herein or a therapeutic amount of a pharmaceutical composition as defined herein in the manufacture of a medicament for treating a disorder selected from the group of psychotic disorders and conditions; anxiety

disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; disorders related to memory acquisition and consolidation; stroke; and autistic disorder.

5 Also exemplifying the disclosure is a compound of Formula (I) or a salt or a solvate thereof, or a pharmaceutical composition described herein, for use as a medicament. According to another aspect, there is provided a compound as defined herein, of a pharmaceutical composition as defined herein, for use as a medicament.

10 Further exemplifying the disclosure is a compound of Formula (I) or a salt or a solvate thereof, or a pharmaceutical composition according to the disclosure for use in the treatment, prevention, amelioration, control or reduction of the risk of various neurological and psychiatric disorders associated with phosphodiesterase 2 dysfunction in a mammal, including a human, the treatment or prevention of which is affected or facilitated by the inhibition of phosphodiesterase 2.

15 An example of the disclosure is a compound of Formula (I) or a pharmaceutically acceptable salt or a solvate thereof according to the present disclosure.

or a pharmaceutical composition according to the disclosure for use in the treatment, prevention, amelioration, control or reduction of the risk of various disorders selected from psychotic disorders and conditions; anxiety disorders; movement disorders; drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions

5 comprising as a symptom a deficiency in attention and/or cognition; disorders related to memory acquisition and consolidation; stroke; and autistic disorder.

An example of the disclosure is a method of treating a disorder selected from the group consisting of Alzheimer's disease, mild cognitive impairment, senility, dementia, dementia with Lewy bodies, Down's syndrome, dementia associated with

10 stroke, dementia associated with Parkinson's disease and dementia associated with beta-amyloid, preferably Alzheimer's disease, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt or a solvate thereof, or pharmaceutical compositions described herein. According to another aspect, there is provided a compound as defined

15 herein in combination with an additional pharmaceutical agent for use in the treatment or prevention of a condition as cited in any one as defined herein. According to another aspect, there is provided a product comprising

(a) a compound as defined herein; and

(b) an additional pharmaceutical agent,

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

Another example of the disclosure is a compound of Formula (I) or a pharmaceutically acceptable salt or a solvate thereof described herein for use in treating: (a) Alzheimer's Disease, (b) mild cognitive impairment, (c) senility,

25 (d) dementia, (e) dementia with Lewy bodies, (f) Down's syndrome, (g) dementia associated with stroke, (h) dementia associated with Parkinson's disease, (i) dementia associated with beta-amyloid, (j) depressive disorders and (k) anxiety disorders, in a subject in need thereof.

30 DESCRIPTION OF THE FIGURES

Figure 1 shows the effect of compound 110 on weak HFS-induction of long term potentiation (LTP) at the mossy fiber synapse.

Figure 2 shows the experimental design for theta-burst stimulation.

Figure 3 shows the effect of compound 70 on weak HFS-induction of long term potentiation (LTP) at the mossy fiber synapse.

Figure 4 shows the effect of compound 25a on weak HFS-induction of long term potentiation (LTP) at the mossy fiber synapse.

- 5 Figure 5 shows the effect of compound 220 on weak HFS-induction of long term potentiation (LTP) at the mossy fiber synapse.

13. A compound according to any one of claims 1 to 7 in combination with an additional pharmaceutical agent for use in the treatment or prevention of a condition as cited in any one of claims 10 to 11.

5 **14.** A product comprising

 (a) a compound as defined in any one of claims 1 to 7; 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 cited in any one of claims 10 to 11.

10

15. Use of a therapeutically effective amount of a compound according to any one of claims 1 to 7 or a therapeutic amount of a pharmaceutical composition according to claim 8 in the manufacture of a medicament for treating a disorder selected from the group of psychotic disorders and conditions; anxiety disorders; movement disorders;

15 drug abuse; mood disorders; neurodegenerative disorders; disorders or conditions comprising as a symptom a deficiency in attention and/or cognition; disorders related to memory acquisition and consolidation; stroke; and autistic disorder.