

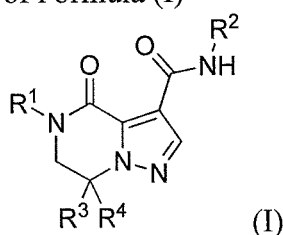
Clinical trials are, for example, underway with mGluR2/3 antagonist decoglurant RO4995819 (F. Hoffmann-La Roche Ltd.) in adjunctive therapy in patients with Major Depressive Disorder having inadequate response to ongoing antidepressant treatment (ClinicalTrials.gov Identifier NCT01457677, retrieved 19 February 2014).

- 5 WO 2013066736 (Merck Sharp & Dohme Corp.) describes quinoline carboxamide and quinoline carbonitrile compounds as mGluR2 NAMs. WO2013174822 (Domain Therapeutics) describes 4H-pyrazolo[1,5-a]quinazolin-5-ones and 4H-pyrrolo [1,2-a]quinazolin-5-ones and in vitro mGluR2 NAM activity thereof. WO 2014064028 (F. Hoffman-La Roche AG) discloses a selection of mGlu2/3 negative allosteric
10 modulators and their potential use in the treatment of Autistic Spectrum Disorders (ASD).

- The group-II receptors are mainly located on presynaptic nerve terminals where they exert a negative feedback loop to the release of glutamate into the synapse (Kelmendi
15 et al, Primary Psychiatry 13:80-86, 2006). Functional inhibition of these receptors by antagonists or negative allosteric modulators therefore lifts the brake on glutamate release, resulting in enhanced glutamatergic signaling. This effect is believed to underlie the antidepressant-like and procognitive effects observed in preclinical species with inhibitors of the Group-II receptor. In addition, treatment of mice with group-II
20 orthosteric antagonists has been shown to enhance signaling by growth factors such as brain derived neurotrophic factor (BDNF) (Koike et al, Behavioural Brain Research 238:48-52, 2013). Since BDNF and other growth factors have been shown to be critically involved in mediating synaptic plasticity, this mechanism is likely to contribute to both antidepressant and procognitive properties of these compounds.
- 25 Inhibition of mGluRs of the group-II receptor family is therefore considered to represent a potential therapeutic mechanism for neurological disorders, including depression and cognitive or memory dysfunction.

DESCRIPTION

- 30 According to an aspect of the disclosure there is provided 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one derivatives of Formula (I)



and stereoisomeric forms thereof, wherein

R⁴ is selected from the group consisting of hydrogen, C₁₋₄alkyl, monohalo-C₁₋₄alkyl, polyhalo-C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -C₁₋₄alkyl-OH;

and the N-oxides and the pharmaceutically acceptable salts and the solvates thereof.

- 5 According to another aspect of the disclosure there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient.

10 According to another aspect of the disclosure there is provided a compound of Formula (I) for use as a medicament. According to another aspect of the disclosure there is provided a compound of Formula (I) for use in the treatment or in the prevention of central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other
15 psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

The disclosure also 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 central nervous system conditions or diseases selected from mood disorders; delirium,
20 dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

25 According to another aspect of the disclosure there is provided a compound as defined herein for use in the treatment or prevention of central nervous system conditions or diseases selected from the group consisting of depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

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According to another aspect of the disclosure there is provided a process for preparing a pharmaceutical composition as defined herein, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

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The disclosure also relates to a method of treating or preventing a central nervous system disorder selected from mood disorders; delirium, dementia, amnesic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder, comprising administering to a subject in need thereof, a therapeutically effective amount of a compound of Formula (I) or a therapeutically effective amount of a pharmaceutical composition according to the disclosure.

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The 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 central nervous system conditions or diseases selected from mood disorders; delirium, dementia, amnestic and other
5 cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

According to another aspect of the disclosure there is provided a product comprising a
10 compound as defined herein and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic
15 symptom and related disorders; and hypersomnolence disorder.

The disclosure also relates to 6,7-dihydropyrazolo[1,5-a]pyrazine-4(5H)-one derivatives designed to bind irreversibly to the mGluR2 receptor.

20 DETAILED DESCRIPTION OF THE INVENTION

The present invention relates in particular to compounds of Formula (I) as defined hereinabove, and stereoisomeric forms thereof, wherein

R¹ is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents
25 each independently selected from the group consisting of halo, C₁₋₄alkyl, monohalo-C₁₋₄alkyl, polyhalo-C₁₋₄alkyl, -C₁₋₄alkyl-OH, -CN, -C₁₋₄alkyl-O-C₁₋₄alkyl, C₃₋₇cycloalkyl, -O-C₁₋₄alkyl, monohalo-C₁₋₄alkyloxy, polyhalo-C₁₋₄alkyloxy, SF₅, C₁₋₄alkylthio, monohalo-C₁₋₄alkylthio and polyhalo-C₁₋₄alkylthio;

R² is selected from the group consisting of hydrogen; C₁₋₄alkyl; C₃₋₇cycloalkyl; Het¹;
30 Aryl; -C(O)R⁵; -C(O)Het²; Het²; and C₁₋₄alkyl substituted with one or more substituents each independently selected from the group consisting of C₃₋₇cycloalkyl, Aryl, Het¹ and Het²; wherein

R⁵ is selected from the group consisting of hydrogen, C₁₋₄alkyl and C₃₋₇cycloalkyl;

Aryl is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, -O-C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl and -SO₂-C₁₋₄alkyl;

5 Het¹ is selected from the group consisting of oxetanyl, tetrahydrofuranyl and tetrahydropyranyl;

Het² is (a) a 6-membered aromatic heterocyclyl substituent selected from the group consisting of pyridinyl, pyrimidinyl, pyrazinyl and pyridazinyl, each of which may be optionally substituted with one or more substituents each independently selected from

11. A process for preparing the pharmaceutical composition according to claim 6, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined in any one of claims 1 to 5.

- 5 **12.** A product comprising a compound as defined in any one of claims 1 to 5 and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia
10 spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.