

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 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 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. 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.

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



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;

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

According to another aspect of the present 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.

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According to another aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient for use as a medicament. According to another aspect of the present

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disclosure, there is provided a compound of Formula (I) or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient 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 psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

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According to another aspect of the present disclosure, there is provided a compound of Formula (I) or a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient for 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 symptom and related disorders; and hypersomnolence disorder.

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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, dementia, amnestic and other cognitive disorders; disorders usually first diagnosed in infancy, childhood or adolescence; substance-related disorders;

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schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

5 According to another aspect of the present disclosure there is provided a process for preparing a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) and a pharmaceutically acceptable carrier or excipient, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

10 The disclosure also relates to a method of treating or preventing a central nervous system disorder 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 psychotic disorders; somatoform disorders; and hypersomnic sleep disorder, comprising administering to a
15 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.

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 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 present disclosure, there is provided a product comprising a 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 symptom and related disorders; and hypersomnolence disorder.

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

Description of the figures

Figure 1 shows the effect of Co. No. 8 (mg/kg p.o., 4 h prior to test) on exploration times of the new vs. the familiar arm in the V-maze by rats in the absence or presence of PCP (0 (= veh) or 0.75 mg/kg s.c., 0.5 h prior to test). Data are reported as Mean $\pm$ SEM, n = 12/group; ANOVA with LSD-post hoc, p vs. familiar arm: *** p<0.001, *<0.05. In Figure 1, veh means vehicle and CPD means Co. No. 8.

Detailed description of the invention

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

R¹ is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents 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 C₁₋₄alkyl; C₃₋₇cycloalkyl; Het¹; Aryl; Het²; and C₁₋₄alkyl substituted with one or more substituents each independently selected from the group consisting of halo, C₃₋₇cycloalkyl, Aryl, Het¹ and Het²; wherein

- 5 Aryl is phenyl optionally substituted with one or more substituents each independently selected from the group consisting of halo, C₁₋₄alkyl, -C₁₋₄alkyl-OH, monohalo-C₁₋₄alkyl, polyhalo-C₁₋₄alkyl, -CN, -O-C₁₋₄alkyl, -OH, -C₁₋₄alkyl-O-C₁₋₄alkyl, -NR'R'', -NHC(O)C₁₋₄alkyl, -C(O)NR'R'', -C(O)NH[C(O)C₁₋₄alkyl], -S(O)₂NR'R'', -S(O)₂NH[C(O)C₁₋₄alkyl] and -SO₂-C₁₋₄alkyl;

13. A process for preparing the pharmaceutical composition according to claim 8, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound according to any one of claims 1 to 7.

14. A product comprising a compound according to any one of claims 1 to 7 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 symptom and related disorders; and hypersomnolence disorder.