

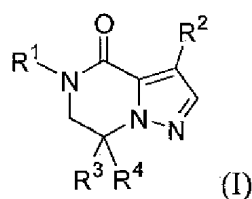
Clinical trials are, for example, underway with mGluR2/3 antagonist RO4995819 (F. Hoffmann-La Roche Ltd.) in adjunctive therapy in patients with Major Depressive Disorder having inadequate response to ongoing antidepressant treatment (ClinicalTrials.gov Identifier NCT01457677, retrieved 19 February 2014).

- 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 mediating synaptic plasticity, this mechanism is likely to contribute to both antidepressant and procognitive properties of these compounds. Inhibition of
25 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.

Summary

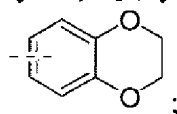
- 30 The present disclosure, in one aspect, is directed to 6,7-dihydropyrazolo[1,5-a]pyrazin-4(5H)-one derivatives of Formula (I)



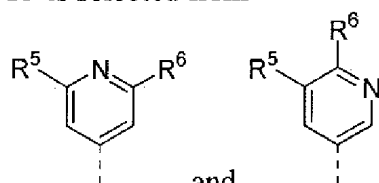
and stereoisomeric forms thereof,

wherein

R¹ is phenyl or 2-pyridinyl, each optionally substituted with one or more substituents each independently selected from the group of halo, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, -O-C₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyloxy, -C₁₋₄alkyl-OH, C₁₋₄alkylthio, mono- or poly-haloC₁₋₄alkylthio, cyano, C₃₋₇cycloalkyl optionally substituted with trifluoromethyl, and -SF₅; or is



R² is selected from



wherein R⁵ and R⁶ are each independently selected from the group of hydrogen, halo, cyano, C₁₋₄alkyl, -C₁₋₄alkyl-OH, C₃₋₇cycloalkyl, mono- or poly-haloC₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, -O-C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyloxy, 1-acetylazetidin-3-yl, and NR'R'';

wherein R' is selected from hydrogen and C₁₋₄alkyl;

R'' is selected from hydrogen and C₁₋₄alkyl; or

R' and R'' together with the Nitrogen atom to which they are attached form a

heterocyclic group selected from the group of 1-azetidinyl, 1-pyrrolidinyl,

1-piperidinyl, 1-piperazinyl, and 4-morpholinyl; wherein each of the heterocyclic

groups may be optionally substituted with a substituent selected from halo, hydroxyl, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, and -(CO)C₁₋₄alkyl;

R³ is selected from hydrogen and C₁₋₄alkyl;

R⁴ is selected from the group of hydrogen, C₁₋₄alkyl, mono- or poly-haloC₁₋₄alkyl, -C₁₋₄alkyl-O-C₁₋₄alkyl, and -C₁₋₄alkyl-OH;

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

The present disclosure, in another aspect, also 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 disclosure, in another aspect, relates to a compound of Formula (I) or a pharmaceutical composition as defined above for use as a medicament. The disclosure, in another aspect, relates to a compound of Formula (I) or a pharmaceutical composition as defined above 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.

The disclosure, in another aspect, relates to a compound of Formula (I) or a pharmaceutical composition as defined above for use in the treatment or prevention of central nervous system disorders or conditions 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 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; schizophrenia and other psychotic disorders; somatoform disorders; and hypersomnic sleep disorder.

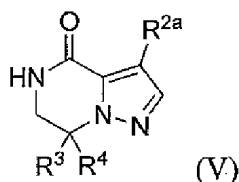
Furthermore, the disclosure relates to a process for preparing a pharmaceutical composition according to the disclosure, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound of Formula (I).

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 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, in another aspect, 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, 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.

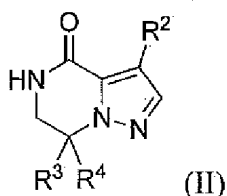
The disclosure, in another aspect, also relates to a product comprising a compound of Formula (I) and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from 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, in another aspect, relates to compound of Formula (V)



wherein R^{2a} is halo, and R³ and R⁴ are as defined above.

The disclosure, in another aspect, relates to a compound of Formula (II)

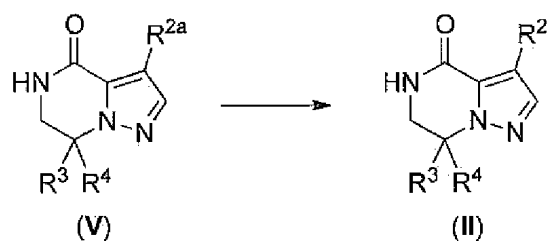


wherein R², R³ and R⁴ are as defined above.

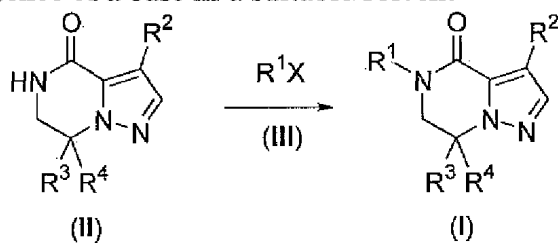
The disclosure, in another aspect, relates to a process for the preparation of a compound

according to Formula (I) as defined herein, comprising steps a) and b)

a) reacting a compound of Formula (V), wherein R^{2a} is halo, with a suitable boron species, in the presence of a palladium catalyst and a suitable base and solvent, to form a compound of Formula (II)



- b) reacting the compound of Formula (II) obtained in step a) with a compound of Formula (III) where X is halo, in the presence of a suitable coupling agent or a catalyst and ligand, in the presence of a base in a suitable solvent

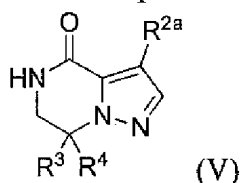


8. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use as a medicament.
9. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use in the treatment or in the prevention of central nervous system conditions or a 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.
10. A compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7 for use in the treatment or prevention of central nervous system disorders or conditions 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.
11. The compound or the pharmaceutical composition for use according to claim 9 or 10, wherein the central nervous system conditions or diseases are selected from dementia or neurocognitive disorder, major depressive disorder, depression, treatment resistant depression, attention-deficit/hyperactivity disorder and schizophrenia.
12. A process for preparing the pharmaceutical composition according to claim 7, 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 6.

13. A product comprising a compound according to any one of claims 1 to 6 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.

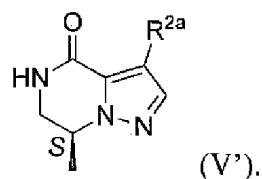
14. A product comprising a compound according to any one of claims 1 to 6 and an additional pharmaceutical agent, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of central nervous system conditions or diseases selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

15. A compound of Formula (V)

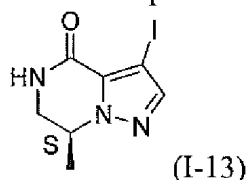
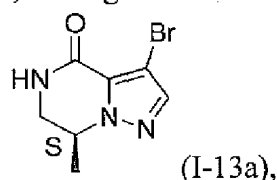


wherein R^{2a} is halo, and R^3 and R^4 are as defined in any one of claims 1 to 6.

16. A compound according to claim 15, having the Formula (V')

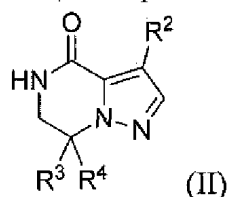


17. A compound according to claim 15 or 16, having the Formula (I-13) or (I-13a)



5 or a salt thereof.

18. A compound of Formula (II)



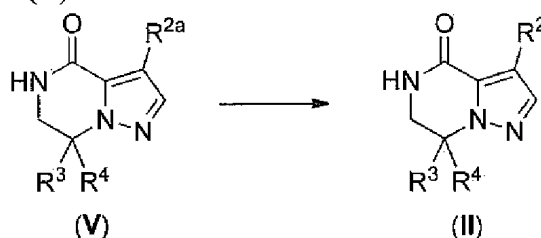
wherein R^2 , R^3 and R^4 are as defined in any one of claims 1 to 6.

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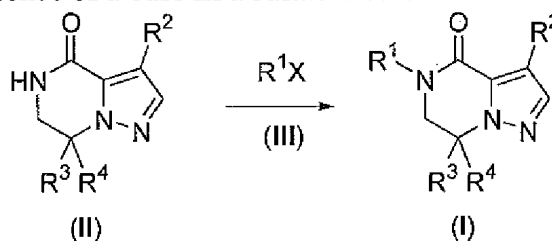
19. A process for the preparation of a compound according to Formula (I) as defined in any one of claims 1 to 6, comprising steps a) and b)

a) reacting a compound of Formula (V), wherein R^{2a} is halo, with a suitable boron species, in the presence of a palladium catalyst and a suitable base and solvent, to form a compound of Formula (II)

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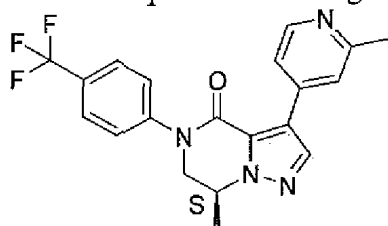


b) reacting the compound of Formula (II) obtained in step a) with a compound of Formula (III) where X is halo, in the presence of a suitable coupling agent or a catalyst and ligand, in the presence of a base in a suitable solvent



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20. A compound according to claim 1 or 2, wherein the compound is

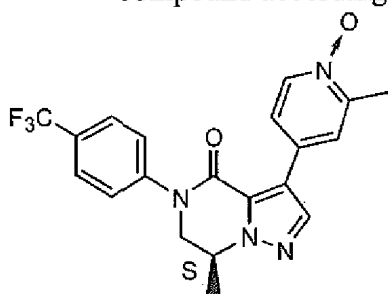


or a N-oxide, or a pharmaceutically acceptable salt

thereof.

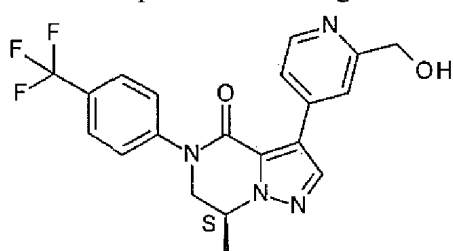
21. The compound according to claim 20, wherein the compound is the free base, the hydrochloride salt, the sulfate salt, the methane sulfonate salt or the maleate salt.

22. The compound according to claim 20, wherein the compound is



or a pharmaceutically acceptable salt thereof.

23. A compound according to claim 1 or 2, wherein the compound is



or a pharmaceutically acceptable salt thereof.

24. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any one of claims 20 to 23 and a pharmaceutically acceptable carrier or excipient.

25. A compound according to any one of claims 20 to 23 or a pharmaceutical composition according to claim 24 for use as a medicament.

26. A compound according to any one of claims 20 to 23 or a pharmaceutical composition according to claim 24 for use in the treatment or in the prevention of

central nervous system conditions or a 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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27. A compound according to any one of claims 20 to 23 or a pharmaceutical composition according to claim 24 for use in the treatment or prevention of central nervous system disorders or conditions selected from depressive disorders; neurocognitive disorders; neurodevelopmental disorders; substance-related and
10 addictive disorders; schizophrenia spectrum and other psychotic disorders; somatic symptom and related disorders; and hypersomnolence disorder.

28. The compound or the pharmaceutical composition for use according to claim 26 or 27, wherein the central nervous system conditions or diseases are selected from
15 dementia or neurocognitive disorder, major depressive disorder, depression, treatment resistant depression, attention-deficit/hyperactivity disorder and schizophrenia.