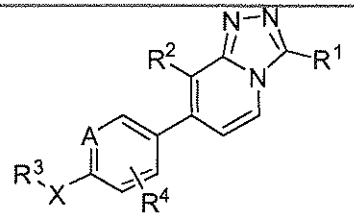
such as LY379268 or DCG-IV. These data provide evidence for yet another novel therapeutic approach to treat the above mentioned neurological and psychiatric diseases involving mGluR2, which would use a combination of a positive allosteric modulator of mGluR2 together with an orthosteric agonist of mGluR2.

The present triazolopyridine derivatives are centrally active, potent compounds providing alternative mGluR2 positive allosteric modulators with improved solubility and salt forming properties.

Summary of Invention

In a first aspect, the present invention refers to a compound having the formula (I)



(I)

or a stereochemically isomeric form thereof, wherein

A is CH or N;

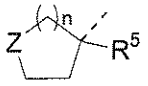
R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di-(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;

R^2 is selected from the group consisting of cyano; halo; C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkoxy substituted with one or more halo substituents; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or more substituents each independently selected from the group consisting of hydroxyl, halo, C_{1-3}alkyl, tri-haloC_{1-3}alkyl and C_{3-7}cycloalkyl; unsubstituted phenyl; phenyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy; Het^3; unsubstituted pyridyl; pyridyl substituted with

one or more substituents each independently selected from C_{1-3}alkyl, C_{1-3}alkyloxy, C_{3-7}cycloalkyl, and halo; trihaloC_{1-3}alkyl; and hydroxyC_{1-3}alkyl; or

R^3 is a cyclic radical of formula (a)



(a)

wherein

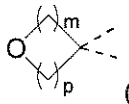
R^5 is selected from the group consisting of hydrogen; C_{1-3}alkyl; C_{1-3}alkyloxy; and hydroxyC_{1-3}alkyl;

n is 1 or 2 ;

Z is selected from CH_2 or $CR^6(OH)$ wherein R^6 is selected from the group consisting of hydrogen, C_{1-3}alkyl and trifluoromethyl;

or R^5 and R^6 together form a radical CH_2-CH_2; or

Z is a cyclic radical of formula (b)



(b)

wherein m and p are independently selected from 0, 1 and 2, provided that $m + p \geq 2$;

R^4 is selected from the group consisting of hydrogen; halo; and C_{1-3}alkyl substituted with one or more halo substituents; and

X is selected from the group consisting of a covalent bond, C_{1-3}alkanediyl, O, NH, S, SO, SO_2, $C(OH)(CH_3)$, CH_2-O, O-CH_2, CH_2-NH, NH-CH_2, CHF, and CF_2;

each Het^1 is a saturated heterocyclic radical selected from the group consisting of pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with one or more substituents each independently selected from the group consisting of C_{1-6}alkyl, C_{1-3}alkyl substituted with one or more halo substituents, unsubstituted phenyl and phenyl substituted with one or more substituents each independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;

each Het^2 is unsubstituted pyridyl or pyrimidinyl; and

each Het^3 is a saturated heterocyclic radical selected from the group consisting of pyrrolidinyl; piperidinyl; piperazinyl; tetrahydropyranyl; and morpholinyl; each of which may be optionally substituted with one or more substituents independently selected from the group consisting of C_{1-6}alkyl, halo, hydroxyl, C_{1-3}alkyl substituted with one or more halo substituents, unsubstituted phenyl, and phenyl substituted with one or more substituents each independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;

or a pharmaceutically acceptable salt or a solvate thereof.

In a second aspect, the present invention refers to a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined above and a pharmaceutically acceptable carrier or excipient.

In a third aspect, the present invention refers to a compound as defined above for use as a medicament.

In a fourth aspect, the present invention refers to a compound as defined above or a pharmaceutical composition as defined above for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

In a fifth aspect, the present invention refers to the compound as defined above, for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety, schizophrenia, migraine, depression, epilepsy, behavioural and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, generalized anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse, and mixed anxiety and depression.

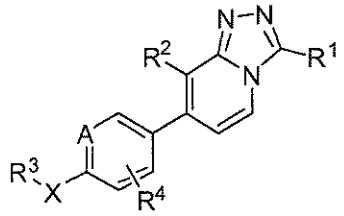
In a sixth aspect, the present invention refers to a compound as defined above in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of a disorder as cited above.

In a seventh aspect, the present invention refers to a process for preparing a pharmaceutical composition as defined above, characterized in that a pharmaceutically acceptable carrier is intimately mixed with a therapeutically effective amount of a compound as defined above.

In an eighth aspect, the present invention refers to a product comprising (a) a compound as defined above; and (b) a mGluR2 orthosteric agonist, as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators is beneficial.

Detailed description of the Invention

The present invention relates to compounds having metabotropic glutamate receptor 2 modulator activity, said compounds having the Formula (I)



(I)

and the stereochemically isomeric forms thereof, wherein

A is CH or N;

R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkoxy, C_{1-3}alkyl, C_{1-3}alkyloxyC_{1-3}alkyl, hydroxyC_{1-3}alkyl, cyano, hydroxyl, amino, C(=O)R', C(=O)OR', C(=O)NR'R'', mono- or di-(C_{1-3}alkyl)amino, morpholinyl, (C_{3-7}cycloalkyl)C_{1-3}alkyloxy, trifluoromethyl and trifluoromethoxy, wherein R' and R'' are independently selected from hydrogen and C_{1-6}alkyl; (benzyloxy)C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with trihaloC_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2 and Het^2C_{1-3}alkyl;

R^2 is selected from the group consisting of cyano; halo; C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more halo substituents; C_{1-3}alkoxy substituted with one or more halo substituents; C_{3-7}cycloalkyl; and (C_{3-7}cycloalkyl)C_{1-3}alkyl;

R^3 is selected from the group consisting of hydrogen; C_{1-3}alkyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or more substituents each independently selected from the group consisting of hydroxyl, halo, C_{1-3}alkyl, tri-

schizophrenia, migraine, depression, epilepsy, behavioural and psychological symptoms of dementia, major depressive disorder, treatment resistant depression, bipolar depression, generalized anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse, and mixed anxiety and depression.

11. A compound according to any one of claims 1 to 6 in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of a disorder as cited in claim 9 or 10.

12. A process for preparing a pharmaceutical composition as defined in claim 7, 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 6.

13. A product comprising

(a) a compound as defined in any one of claims 1 to 6; and

(b) a mGluR2 orthosteric agonist,

as a combined preparation for simultaneous, separate or sequential use in the treatment or prevention of a condition in neuromodulatory effect of mGluR2 allosteric modulators, in particular positive mGluR2 allosteric modulators is beneficial.

~~14. A method of treating or preventing a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia comprising administering to a subject in need thereof a compound according to any one of claims 1 to 6 or a pharmaceutical composition according to claim 7.~~