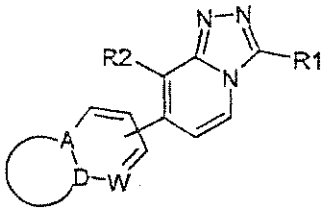
involving mGluR2, which would use a combination of a positive allosteric modulator of mGluR2 together with an orthosteric agonist of mGluR2.

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



(I)

or a stereochemically isomeric form thereof, wherein

the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

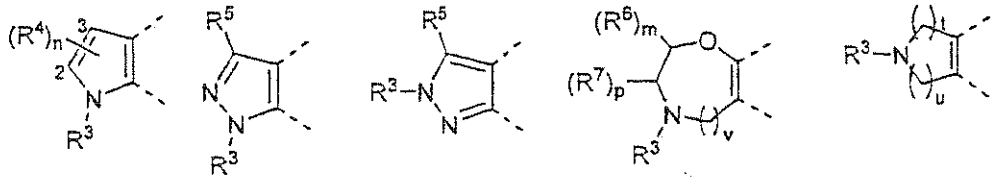
R^1 is selected from the group consisting of hydrogen; C_{1-6}alkyl; (C_{1-3}alkyloxy)-C_{1-3}alkyl; [(C_{1-3}alkyloxy)-C_{1-3}alkyloxy]C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted benzyl; benzyl substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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 one or more independently selected C_{1-3}alkyl substituted with one or more independently selected halo substituents; (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 substituted with one or more independently selected halo substituents; C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; C_{1-3}alkyl; C_{3-7}cycloalkyl; and

(C_{3-7}cycloalkyl)C_{1-3}alkyl;



forms a radical selected from (a), (b), (c), (d) and (e):



(a) (b) (c) (d) (e)

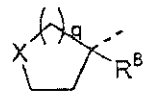
wherein

the bond drawn into (a) indicates that R^4 may be attached to any of carbon ring atoms 2 and 3;

each R^3 is independently selected from the group consisting of hydrogen; unsubstituted C_{1-6}alkyl; C_{1-6}alkyl substituted with one or more substituents independently selected from the group consisting of halo, hydroxy, C_{1-3}alkoxy and trifluoromethyl; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxy, C_{1-3}alkoxy and trifluoromethyl; C_{3-7}cycloalkylC_{1-3}alkyl; unsubstituted phenyl; phenyl substituted with one or more substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; Het^3; and Het^3C_{1-3}alkyl;

or

each R^3 is independently selected from a cyclic radical of formula (f)



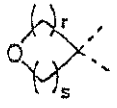
(f)

wherein R^8 is selected from hydrogen, C_{1-3}alkyl, C_{1-3}alkyloxy and hydroxyC_{1-3}alkyl;

q is 1 or 2 ;

X is selected from O, CH_2 and $CR^9(OH)$, wherein R^9 is selected from hydrogen, C_{1-3}alkyl and C_{3-7}cycloalkyl; or

X is a cyclic radical of formula (g)



(g)

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

each R^4, R^6 and R^7 are each independently selected from C_{1-3}alkyl and C_{1-3}alkyl substituted with one or more independently selected halo substituents;
each R^5 is independently selected from the group consisting of hydrogen, C_{1-3}alkyl, and C_{1-3}alkyl substituted with one or more independently selected halo substituents;
n, m and p are each independently selected from 0, 1 and 2;
v is 0 or 1;
t and u are each independently selected from 1 and 2;
W is selected from N and CR^{10};
wherein R^{10} is selected from hydrogen, halo and trifluoromethyl;

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with one or more each independently selected from the group consisting of C_{1-6}alkyl; mono-, di- and tri-haloC_{1-3}alkyl; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy;
each Het^2 is pyridyl or pyrimidinyl; and
each Het^3 is a heterocycle selected from the group consisting of tetrahydropyran, pyridyl; and pyrimidinyl; each of them being optionally substituted with one or more substituents each independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkoxy and trifluoromethyl; and
halo is selected from fluoro, chloro, bromo and iodo;
or a pharmaceutically acceptable salt or a solvate thereof.

In the 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.

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

In the fourth aspect, the present invention refers to a compound as defined above or a pharmaceutical composition as defined above for use in 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.

In the fifth aspect, the present invention refers to a 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, behavioral 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 the sixth aspect, the present invention refers to a compound as defined above in combination with an orthosteric agonist of mGluR2 for use in treating or preventing a disorder as cited in 4th and 5th aspect.

In the 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 the eighth aspect, the present invention refers to a product comprising

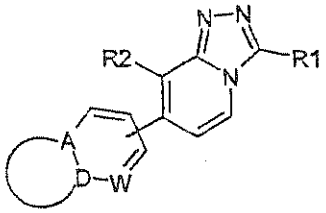
(a) a compound as defined above; and

(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

the bond drawn into the ring indicates that the bond may be attached to any carbon ring atom;

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}alkyl, (C_{1-3}alkyloxy)C_{1-3}alkyl, C_{1-3}alkyloxy, 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 one or more independently selected C_{1-3}alkyl substituted with one or more independently selected halo substituents; (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 substituted with one or more independently selected halo substituents; C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; C_{1-3}alkyl; C_{3-7}cycloalkyl; and

mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, neurotoxicity and ischemia.

10. A compound according to claim 9, for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety, schizophrenia, migraine, depression, epilepsy, behavioral 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 treating or preventing 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 admistering 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.~~