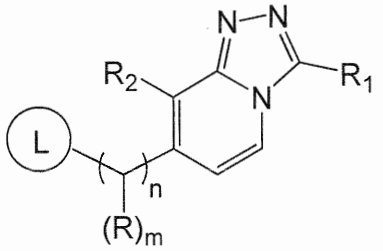
involving mGluR2, which would use a combination of a positive allosteric modulator of mGluR2 together with an orthosteric agonist of mGluR2.

WO 2007/104783, WO 2008/107479 and WO 2009/033704 (Addex & Janssen Pharmaceutica) describe pyridinone derivatives as mGluR2 positive allosteric modulators. WO 2009/062676 (Addex & Janssen) published on 22 May 2009 discloses imidazopyridine derivatives as mGluR2 positive allosteric modulators. The present triazolopyridine derivatives are centrally active, potent compounds providing alternative mGluR2 positive allosteric modulators with improved solubility and salt forming properties.

Summary

In a first aspect, there is provided a compound of formula (I)



(I)

or a stereochemically isomeric form thereof

wherein

n is selected from the group consisting of 0, 1 and 2;

m is selected from the group consisting of 0, 1, and 2;

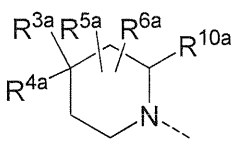
R is selected from methyl or trifluoromethyl;

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 phenyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, 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 C_{1-3}alkyl substituted

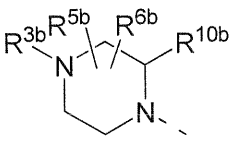
with one or more independently selected halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; 4-(2,3,4,5-tetrahydro-benzo[f][1,4]oxazepine)methyl; Het^1; Het^1C_{1-3}alkyl; Het^2; and Het^2C_{1-3}alkyl;

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;

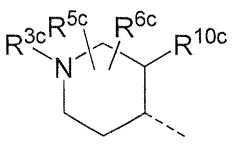
(L) is an *N*-containing heterocycle selected from the group consisting of (L-a), (L-b), (L-c), (L-d), (L-e), (L-f), (L-g) and (L-h) below



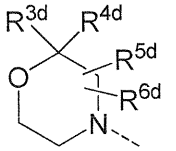
(L-a)



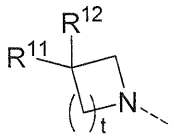
(L-b)



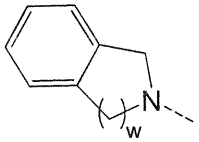
(L-c)



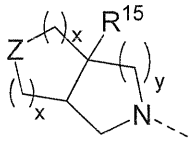
(L-d)



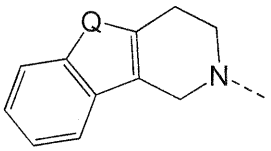
(L-e)



(L-f)



(L-g)



(L-h)

wherein

R^{3a} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents or hydroxyl; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxy-C_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and

morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl and (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; unsubstituted phenyloxy; phenyloxy substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxy(C_{1-3}alkyl)oxy; unsubstituted (phenylC_{1-3}alkyl)oxy; phenyl(C_{1-3}alkyl)oxy wherein the phenyl part of the substituent is substituted with 1, 2, or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenyloxyC_{1-3}alkyl; (phenyloxy)C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; unsubstituted phenylamino; phenylamino substituted with 1 or 2 independently selected halo substituents; (phenylC_{1-3}alkyl)amino; (phenylamino)(C_{1-3}alkyl); (C_{3-7}cycloalkyl)C_{1-3}alkyl; [phenyl(C_{3-7}cycloalkyl)]C_{1-3}alkyl; Het^1; Het^2; Het^2oxy; Het^2methyloxy; Het^3; and phenyl with two vicinal substituents which taken together form a bivalent radical of formula

-N=CH-NH- (a),

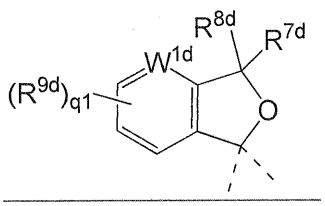
-CH=CH-NH- (b), or

-O-CH_2-CH_2-NH- (c);

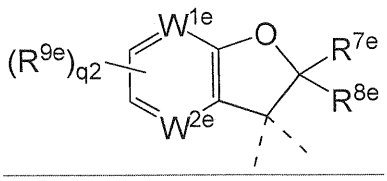
R^{4a} is selected from the group consisting of hydrogen; halogen; trifluoromethyl; trifluoromethoxy; hydroxyl; C_{1-3}alkyl; C_{1-3}alkyloxy; hydroxyC_{1-3}alkyl; hydroxyl-C_{1-3}alkyloxy; fluoroC_{1-3}alkyl; fluoroC_{1-3}alkyloxy; cyano; unsubstituted phenyl; and phenyl substituted with 1 or 2 substituents independently selected from the group

consisting of halo, C_{1-3}alkyloxy, hydroxyC_{1-3}alkyl, trifluoromethyl and trifluoromethoxy;

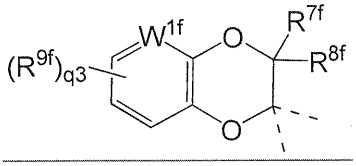
or $CR^{3a}R^{4a}$ forms a radical of formula (d), (e), (f), (g) or (h);



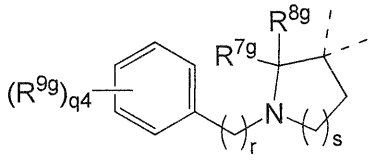
(d)



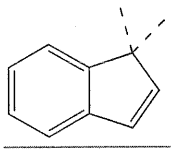
(e)



(f)



(g)



(h)

wherein

each W^{1d}, W^{1e}, W^{2e} and W^{1f} is independently selected from CH and N;

each R^{7d}, R^{7e}, R^{7f}, R^{7g}, R^{8d}, R^{8e}, R^{8f}, R^{8g} is independently selected from hydrogen, methyl and fluoro; or each $CR^{7d}R^{8d}$, $CR^{7e}R^{8e}$, $CR^{7f}R^{8f}$, $CR^{7g}R^{8g}$ form a carbonyl group;

each R^{9d}, R^{9e}, R^{9f}, and R^{9g} is fluoro;

each q1, q2, q3 or q4 is independently selected from 0, 1 and 2;

r is 0 or 1;

s is 0 or 1;

each R^{3b} and R^{3c} is selected from the group consisting of C_{1-3}alkyl; C_{1-3}alkyl substituted with one or more independently selected halo substituents; unsubstituted phenyl; phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- and di(C_{1-3}alkyl)amino, and morpholinyl; unsubstituted (phenyl)C_{1-3}alkyl; (phenyl)-C_{1-3}alkyl wherein the phenyl and the C_{1-3}alkyl part of the substituent may each be

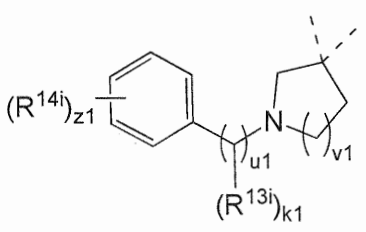
independently substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, hydroxyC_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, cyano, hydroxyl, amino, carboxyl, C_{1-3}alkyloxyC_{1-3}alkyl, C_{1-3}alkyloxy, C_{1-3}alkyloxy substituted with one or more independently selected halo substituents, C_{1-3}alkylcarbonyl, mono- or di(C_{1-3}alkyl)amino, morpholinyl, C_{3-7}cycloalkyl, (C_{3-7}cycloalkyl)C_{1-3}alkyl, and (C_{3-7}cycloalkyl)-C_{1-3}alkyloxy; unsubstituted (phenyloxy)C_{1-3}alkyl; (phenyloxy)-C_{1-3}alkyl substituted with 1 or 2 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, C_{1-3}alkyloxy, and C_{1-3}alkyloxy substituted with one or more independently selected halo substituents; (phenylamino)(C_{1-3}alkyl); phenyl with two vicinal substituents which taken together form a bivalent radical of formula (a), (b) or (c) as previously defined; Het^1; Het^2; Het^3; unsubstituted C_{3-7}cycloalkyl; C_{3-7}cycloalkyl substituted with 1 or 2 substituents independently selected from C_{1-3}alkyl, C_{1-3}alkyl substituted with one or more independently selected halo substituents, or hydroxyl; (C_{3-7}cycloalkyl)C_{1-3}alkyl; and [phenyl-(C_{3-7}cycloalkyl)]C_{1-3}alkyl;

R^{3d} and R^{4d} are each independently selected from the group consisting of hydrogen and C_{1-3}alkyl;

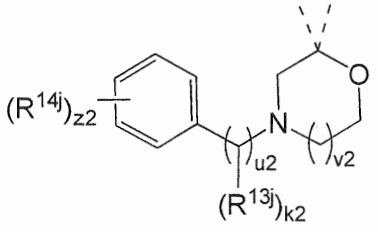
each R^{5a}, R^{5b}, R^{5c}, R^{5d}, R^{6a}, R^{6b}, R^{6c} and R^{6d} is independently selected from the group consisting of hydrogen and C_{1-3}alkyl; or each pair $R^{5a}R^{6a}$, $R^{5b}R^{6b}$, $R^{5c}R^{6c}$, $R^{5d}R^{6d}$ are substituents on the same carbon atom and each $CR^{5a}R^{6a}$, $CR^{5b}R^{6b}$, $CR^{5c}R^{6c}$, $CR^{5d}R^{6d}$ together form a (C=O) or a C_{3-7}cycloalkylidene radical;

each R^{10a}, R^{10b} and R^{10c} is selected from H, C_{1-3}alkyl and C_{1-3}alkyloxy;

wherein, in (L-e),
when t is 1 or 2, R^{11} is hydrogen and R^{12} is selected from a substituent selected from the group consisting of phenyl, phenyloxy and phenylamino, each of which may be optionally substituted with 1 or 2 halo substituents; or
when t is 1 or 3, then $CR^{11}R^{12}$ form a radical of formula (i) or formula (j)



(i)



(j)

wherein

each R^{13i} and R^{13j} is independently selected from methyl and trifluoromethyl;

each R^{14i} or R^{14j} is fluoro;

each u1 and u2 is independently 0, 1 or 2;

v1 is selected from the group of 0, 1 and 2;

v2 is selected from the group of 1 and 2;

each z1 and z2 is independently selected from the group of 0, 1 and 2;

each k1 and k2 is independently selected from the group of 0, 1 and 2;

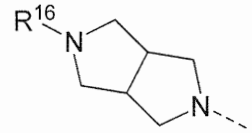
wherein, in (L-f) w is 1 or 2;

wherein in (L-g)

Z is $CR^{16}R^{17}$ and R^{15} is hydrogen when each x is 0 and y is 1; or

Z is $CR^{16}R^{17}$ and R^{15} is selected from the group consisting of hydrogen, methyl and phenyl when each x is 0 and y is 2; or

(L-g) is (L-g") when Z is NR^{16}



(L-g");

wherein R^{16} and R^{17} are each independently selected from the group consisting of hydrogen; unsubstituted phenyl; and phenyl substituted with 1, 2 or 3 halo substituents;

wherein in (L-h),

Q is O or N-R^{18}, wherein R^{18} is selected from hydrogen and C_{1-3}alkyl;

wherein

each Het^1 is a saturated heterocyclic radical selected from pyrrolidinyl; piperidinyl; piperazinyl; and morpholinyl; each of which may be optionally substituted with 1 or 2 substituents independently selected from the group consisting of C_{1-6}alkyl,

halo, C_{1-3}alkyl substituted with one or more independently selected halo substituents, unsubstituted phenyl or phenyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, trifluoromethyl, and trifluoromethoxy; and

each Het^2 is an aromatic heterocyclic radical selected from pyridinyl and pyrimidinyl; each of which is unsubstituted or substituted with 1 or 2 substituents selected from the group consisting of halo; C_{1-3}alkyl; C_{1-3}alkyloxy; and C_{1-3}alkyl substituted with one or more independently selected halo substituents;

each Het^3 is a heterocyclic radical selected from 1,3-thiazolyl optionally substituted with C_{1-3}alkyl; unsubstituted benzofuranyl; unsubstituted 3,4-dihydro-*2H*-chromenyl; and unsubstituted *1H*-indolyl;

each halo is selected from the group consisting of fluoro, chloro, bromo and iodo;
or a pharmaceutically acceptable salt or a solvate thereof.

In a second aspect, there is provided 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, there is provided a compound as defined above for use as a medicament.

In a fourth aspect, there is provided 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, there is provided 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, generalised anxiety disorder, post-traumatic stress disorder, bipolar mania, substance abuse and mixed anxiety and depression.

In a sixth aspect, there is provided a compound as defined above in combination with an orthosteric agonist of mGluR2 for use in the treatment or prevention of a disorder as defined above.

In a seventh aspect, there is provided 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, there is provided a product comprising

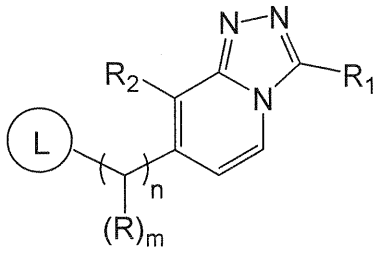
(a) a compound as defined above; and

(b) an mGluR2 orthosteric agonist,

as a combined preparation for simultaneous, separate or sequential 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.

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

n is selected from the group consisting of 0, 1 and 2;
m is selected from the group consisting of 0, 1, and 2;
R is selected from methyl or trifluoromethyl;
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 phenyl; unsubstituted benzyl; benzyl substituted with 1, 2 or 3 substituents independently selected from the group consisting of halo, C_{1-3}alkyl, C_{1-3}alkyloxy, 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 C_{1-3}alkyl substituted with one or more independently selected halo substituents; (C_{3-7}cycloalkyl)C_{1-3}alkyl; [(C_{3-7}cycloalkyl)C_{1-3}alkyloxy]C_{1-3}alkyl; (C_{3-7}cycloalkyl)C_{1-3}alkyloxy; 4-(2,3,4,5-