

amphetamine- (Galici et al. J Pharm Exp Ther 2005, 315(3), 1181-1187) induced hyperlocomotion, and in reversal of amphetamine-induced disruption of prepulse inhibition of the acoustic startle effect (Galici et al. 2005) models of schizophrenia.

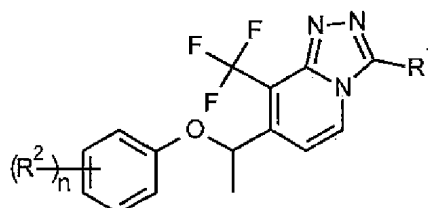
JNJ-40411813/ADX71149, an mGlu2 PAM (which in rat also displays 5-HT_{2A} antagonism activity due to a rat-specific metabolite) has undergone clinical trials for the treatment of schizophrenia, and anxiety-depression (see for instance www.Clinicaltrials.gov). Non-clinical data in the lactate-induced panic model in rodents suggests that it could have potential in the treatment of further anxiety disorders such as panic disorder and phobias, such as agoraphobia (Shekhar et al. Neuropsychopharmacology 2013, 38, S435-S593 (W220)). JNJ-40411813 was also observed to reduce craving and improve smoking cessation-induced deficits in attention and episodic memory versus placebo (Salih et al. Journal of Psychopharmacology, submitted) and showed an efficacy signal in S-ketamine-induced negative symptoms in healthy volunteers and patients with predominant negative symptoms of schizophrenia (De Boer et al. Society of Biological Psychiatry 68th Annual Scientific Convention of Society of Biological Psychiatry, May 16-18, 2013, Hilton Union Square, San Francisco, California, Abstract 2013-P-1060-SOBP).

Positive allosteric modulators enable potentiation of the glutamate response, but they have also been shown to potentiate the response to orthosteric mGluR2 agonists 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.

Various compounds have been described as mGluR2 positive allosteric modulators. WO2010/130424, WO2010/130423, WO2010/130422, and WO2012/062750, WO2012/062751, and WO2012/062759, published on 18 November 2010 and 18 May 2012, respectively, disclose 1,2,4-triazolo[4,3-a]pyridine derivatives as mGluR2 positive allosteric modulators.

SUMMARY

In one aspect, there is provided a compound of Formula (I)



or a stereochemically isomeric form thereof, wherein

R¹ is selected from the group consisting of C₁₋₆alkyl, (C₃₋₈cycloalkyl)C₁₋₃alkyl, and (C₁₋₃alkyloxy)C₁₋₃alkyl;

5 each R² is independently selected from F, Cl, C₁₋₃alkyl, C₁₋₃alkyloxy, mono- or polyhaloC₁₋₃alkyl, and mono- or polyhaloC₁₋₃alkyloxy;

n is an integer selected from 1, 2, and 3;

or a pharmaceutically acceptable salt or solvate thereof.

10 In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound as defined herein and a pharmaceutically acceptable carrier or excipient.

In another aspect, there is provided a compound as defined herein or a pharmaceutical composition as defined herein, for use as a medicament.

15 In another aspect, there is provided a compound as defined herein or a pharmaceutical composition as defined herein for use in the treatment or prevention of a central nervous system disorder selected from the group of anxiety disorders, psychotic disorders selected from the group consisting of schizophrenia, schizoaffective disorder and schizophreniform disorder, personality disorders, substance-related disorders, eating disorders, mood disorders, migraine, epilepsy or convulsive disorders, childhood disorders, cognitive disorders, neurodegeneration, autistic disorders, neurotoxicity and
20 ischemia.

In another aspect, there is provided a product comprising (a) a compound as defined herein; 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 schizophrenia (in particular,
25 negative symptoms or residual symptoms thereof), generalized anxiety disorder, bipolar disorder (I or II), migraine, behavioral and psychological symptoms of dementia, epilepsy or convulsive disorders, panic disorder, mixed anxiety and depression, and agoraphobia.

30 DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to potent mGluR2 PAM compounds with an advantageous balance of properties. Thus, the present invention is directed to 1,2,4-triazolo[4,3-a]pyridine derivatives of Formula (I)

11. A product comprising
- (a) a compound as defined in any one of claims 1 to 4; and
 - (b) an mGluR2 orthosteric agonist,
- 5 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 schizophrenia (in particular, negative symptoms or residual symptoms thereof), generalized anxiety disorder, bipolar disorder (I or II), migraine, behavioral and psychological symptoms of dementia, epilepsy or convulsive disorders, panic disorder,
- 10 mixed anxiety and depression, and agoraphobia.