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Novel bicyclo[3.1.0]hexane analogs as antagonists of metabotropic glutamate 2/3 receptors for the treatment of depression

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ABSTRACT

Negative modulators of metabotropic glutamate 2 & 3 receptors demonstrate antidepressant-like activity in animal models and hold promise as novel therapeutic agents for the treatment of major depressive disorder. Herein we describe our efforts to prepare and optimize a series of conformationally constrained 3,4-disubstituted bicyclo[3.1.0]hexane glutamic acid analogs as orthosteric (glutamate site) $mGlu_{2/3}$ receptor antagonists. This work led to the discovery of a highly potent and efficacious tool compound **18** ($hmGlu_2$ IC_{50} 46 ± 14.2 nM, $hmGlu_3$ IC_{50} = 46.1 ± 36.2 nM). Compound **18** showed activity in the mouse forced swim test with a minimal effective dose (MED) of 1 mg/kg ip. While in rat EEG studies it exhibited wake promoting effects at 3 and 10 mg/kg ip without any significant effects on locomotor activity. Compound **18** thus represents a novel tool molecule for studying the impact of blocking $mGlu_{2/3}$ receptors both *in vitro* and *in vivo*.

Metabotropic glutamate (mGlu) receptors belong to the class C GPCR family and consist of eight known subtypes which have been historically divided into three groups (Group I: $mGlu_1$ &$_5$; Group II: $mGlu_2$ &$_3$; Group III: $mGlu_{4,\ 6,\ 7}$ &$_8$) The Group II mGlu receptors are highly expressed in prefrontal cortex, striatum, thalamus, hippocampus, and amygdala, where they act to regulate neuronal excitability via presynaptic, postsynaptic and glial mechanisms. Activation of $mGlu_{2/3}$ receptors is known to inhibit the synaptic release of glutamate, leading to a reduction of synaptic transmission. Accordingly, $mGlu_{2/3}$ agonists (e.g. (1*S*,2*S*,5*R*,6*S*)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (LY354740), (1*R*,4*S*,5*S*,6*S*)-4-amino-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid 2,2-dioxide (LY404039), Fig. 1) produce beneficial effects in rodent models (anxiety, psychosis, pain) thought to be driven by excessive glutamate neurotransmission, and oral prodrugs of these agents ((1*S*,2*S*,5*R*,6*S*)-2-(L-Alanylamino)bicyclo[3.1.0]hexane-2,6-di carboxylic acid (LY544344), (1*R*,4*S*,5*S*,6*S*)-4-(L-methionyl amino)-2-thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid 2,2-dioxide (LY2140023)) have demonstrated efficacy in generalized anxiety disorder [1] and schizophrenia patients [2], respectively.

Conversely, $mGlu_{2/3}$ receptor antagonists facilitate the presynaptic release of glutamate and thereby enhance synaptic AMPA- and NMDA-receptor activation and neurotransmission under conditions where $mGlu_{2/3}$ receptors are tonically activated. Consistent with this, preclinical studies have demonstrated that $mGlu_{2/3}$ antagonists such as (1*S*,2*S*)-2-[(1*S*)-1-amino-1-carboxy-2-(9H-xanthen-9-yl)ethyl]cyclopropanecarboxylic acid (LY341495) and (1*R*,2*R*,3*R*,5*R*,6*R*)-2-amino-3-[(3,4-dichlorobenzyl)oxy]-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid (MGS0039) (Fig. 1) elicit glutamate-driven AMPA receptor-dependent antidepressant [3] and wake-promoting [4] responses in rodents.

As part of our ongoing research efforts targeting these receptors, we explored the effect of structural modifications at the C3- and C4-positions of LY354740 on functional $mGlu_{2/3}$-mediated activity. Literature data [18] as well as our own in-house structure

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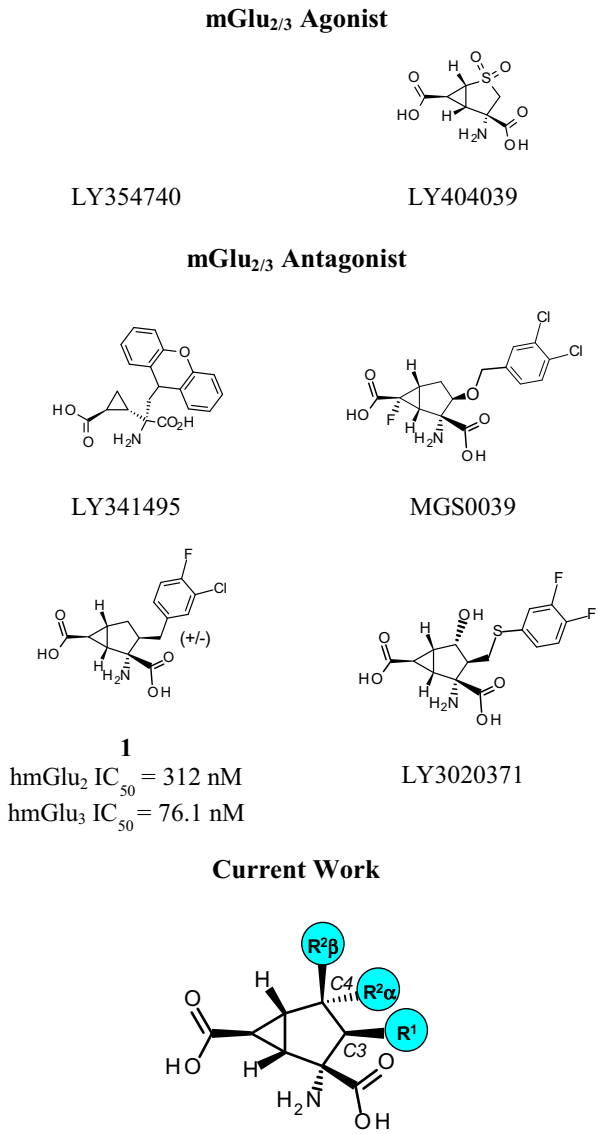
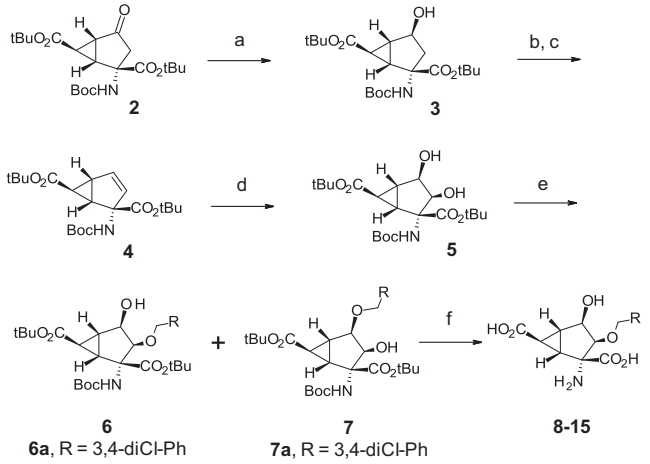


Fig. 1. Literature and in-house $mGlu_{2/3}$ receptor ligands.

activity relationship (SAR) data as exemplified by compound (+/−)-**1** [5], showed that substitution at the C3- position of LY354740 produced compounds that are functional antagonists. Conversely, we have published an extensive SAR of analogs of LY354740 with a range of C4-postion substituents that exhibit agonist activity [6,7]. In order to further understand the effects of substituents at these two positions on functional activity we set out to develop synthetic methodologies that would enable their dual functionalization. This work has led to the identification of a number of novel potent and selective $mGlu_{2/3}$ receptor antagonists.

We began our work employing the previously reported enantiomerically pure ketone **2** [6] which can be synthesized on multi-kilogram scale (Scheme 1). Ketone **2** was reduced to give the $C4_{\beta}$-alcohol **3** in high yield and with excellent diastereoselectivity using L-Selectride®. The alcohol was converted to the corresponding mesylate using methyl sulfonyl chloride (MsCl) and triethyl amine (TEA) and then subjected to tetrabutylammonium fluoride (TBAF) to cleanly give the elimination product **4** in good yield along with unreacted alcohol **3** which could be recovered by normal phase chromatography. Alkene **4** was oxidized using catalytic osmium tetroxide (OsO4) and *N*-methylmorpholine-*N*-oxide (NMO) as a co-oxidant to give the expected *cis* $C3_{\beta}$,$C4_{\beta}$-diol

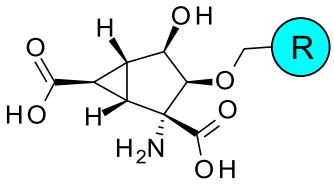


Scheme 1. Reagents and Conditions: (a) L-Selectride® (1 M in THF, 1.5 eq.), THF, 0 °C then 30% H_2O_2, $NaHCO_3$ (quantitative); (b) MsCl, TEA; (c) TBAF, THF, reflux (76% 2 steps); (d) OsO_4 (0.05 eq.), NMO (2.5 eq.), acetone, water [>50:1dr] (91%); (e) RCH_2Br (1.5 eq.), Ag_2O (1.5 eq.), TBAI (1 eq.), DMF [generally 3:1 regioselectivity for **6** vs **7**] (R = 3,4-diCl-Ph, 94%); (f) Acetic acid, water, 140 °C, microwave (20–84%).

5 in high diastereoselective (>50:1) and synthetic yield through oxidant approach from the less sterically hindered face of the bicyclo[3.1.0]hexane ring system. Regioselective alkylation of the C3 carbinol was achieved using silver oxide (Ag_2O) and tetrabutyl ammonium iodine (TBAI) and a benzyl halide to give a mixture of the mono C3 and C4 benzyl ethers **6** and **7** that were separated by normal phase chromatography. In this way, the diol **5** was selectively alkylated with 3,4-dichlorobenyl bromide to give a 3:1 mixture of the 3,4-dichlorobenzyl ether intermediates **6a** and **7a** that were readily separated by normal phase column chromatography to give pure intermediate **6a** in 72% yield. Structural confirmation of **6a** was established by proton NMR [8]. Exhaustive deprotection of intermediate **6a** in glacial acetic acid and water using our previously reported procedure [6] at elevated temperatures in a microwave provided the $C4_{\beta}$-hydroxyl-$C3_{\beta}$-3,4-dichlorobenzyl ether **11** as a white solid in 74% yield and in high chemical purity (as determined by proton NMR and LCMS) following concentration of the reaction mixture and trituration of the recovered solid with water and ether. Using a similar process a series of $C4_{\beta}$-hydroxyl-$C4_{\beta}$-benzyl ethers **8**–**15** were prepared and their functional $hmGlu_2$ and $hmGlu_3$ activity was evaluated.

Based on our initial biochemical results of the $C4_{\beta}$-hydroxyl-$C4_{\beta}$-benzyl ethers **8**–**15** (Table 1), further investigation of the C4

Table 1
cAMP $hmGlu_2$ and $hmGlu_3$ receptor functional activity for $C4_{\beta}$-hydroxyl-$C3_{\beta}$-benzyl ethers.



Compds.	R	$hmGlu_2$ IC_{50} (nM) ± SEM [19]	$hmGlu_3$ IC_{50} (nM) ± SEM [19]
8	Ph	306 ± 36.3	239 ± 139
9	3-Cl-Ph	280 ± 142	178 ± 136
10	4-Cl-Ph	210 ± 22.7	145 ± 18.4
11	3,4-diCl-Ph	169 ± 56	153 ± 130
12	2,5-diCl-Ph	387 ± 94.3	185 ± 68.7
13	2,3-diCl-Ph	149 ± 31.4	83.2 ± 80.2
14	3-F-4-Cl-Ph	225 ± 56.9	127 ± 84.8
15	3-Me-4-F-Ph	215 ± 65.4	85.0 ± 16.9