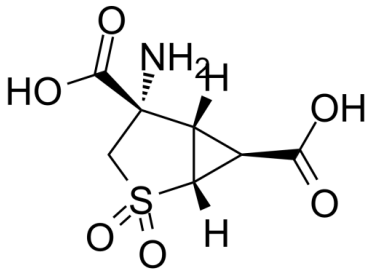
Data Sheet

Product Name:	LY404039
Cat. No.:	CS-1345
CAS No.:	635318-11-5
Molecular Formula:	$C_7H_9NO_6S$
Molecular Weight:	235.21
Target:	mGluR
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : 3.84 mg/mL (16.33 mM; Need ultrasonic and warming); H2O : 5.2 mg/mL (22.11 mM; ultrasonic and adjust pH to 6 with NaOH)



BIOLOGICAL ACTIVITY:

LY404039 is a potent, selective and orally active **mGluR2** and **mGluR3** agonist with **K_i**s of 149 nM and 92 nM for **recombinant human mGluR2** and **mGluR3**, respectively. LY404039 shows >100-fold selectivity for mGluR2/3 over other receptors/transproters. LY404039 has antipsychotic and anxiolytic effects[1]. **In Vitro:** LY404039 is a nanomolar potent agonist in rat neurons expressing native mGlu2/3 receptors (K_i = 88 nM)[1].

Functionally, LY404039 potently inhibits Forskolin-stimulated cAMP formation in cells expressing human mGlu2 (EC_{50} = 23 nM) and mGlu3 receptors (EC_{50} = 48 nM)[1].

Electrophysiological studies indicate that LY404039 suppresses electrically evoked excitatory activity in the striatum, and serotonin-induced L-glutamate release in the prefrontal cortex. LY404039 suppresses the frequency of 5-HT-induced excitatory postsynaptic currents (EPSCs) with an EC_{50} of 82.3 nM and with a near maximal suppression of 85.6% at 1 μM[1].

LY404039 inhibits the binding of the D2-specific antagonist, [3H]domperidone, to the human cloned D2 receptor with dissociation constants of 8.2 nM at D2High and 1640 nM at D2Low. Using rat striatal tissue, LY404039 has dissociation constants of 12.6 nM at D2High and 2100 nM at D2Low[2]. **In Vivo:** LY404039 attenuates amphetamine- and phencyclidine-induced hyperlocomotion (3-30 and 10 mg/kg, respectively). LY404039 (3-10 mg/kg) inhibits conditioned avoidance responding. LY404039 also reduces fear-potentiated startle in rats (3-30 μg/kg) and marble burying in mice (3-10 mg/kg), indicating anxiolytic-like effects. LY404039 (10 mg/kg) also increases dopamine and serotonin release/turnover in the prefrontal cortex[3].

Following oral administration of LY404039 to fasted rats at doses of 1, 3, or 10 mg/kg, exposure increased proportionally with dose. LY404039 (10 mg/kg; p.o.) treatment shows the C_{max} is 1528.5 ng/mL and T_{max} is 2 hours in rats[1].

References:

[1]. Linda M Rorick-Kehn, et al. Pharmacological and pharmacokinetic properties of a structurally novel, potent, and selective metabotropic glutamate 2/3 receptor agonist: in vitro characterization of agonist (-)-(1R,4S,5S,6S)-4-amino-2-sulfonylbicyclo[3.1.0]-hexane-4,6-dicarboxylic acid (LY404039). J Pharmacol Exp Ther. 2007 Apr;321(1):308-17.

[2]. Seeman P. An agonist at glutamate and dopamine D2 receptors, LY404039. Neuropharmacology. 2013 Mar;66:87-8.

[3]. Rorick-Kehn LM, et al. In vivo pharmacological characterization of the structurally novel, potent, selective mGlu2/3 receptor agonistLY404039 in animal models of psychiatric disorders. Psychopharmacology (Berl). 2007 Jul;193(1):121-36.

CAIndexNames:

2-Thiabicyclo[3.1.0]hexane-4,6-dicarboxylic acid, 4-amino-, 2,2-dioxide, (1R,4S,5S,6S)-

SMILES:

O=C([C@]1(N)CS([C@@]2([H])[C@H](C(O)=O)[C@@]12[H])(=O)=O)O

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