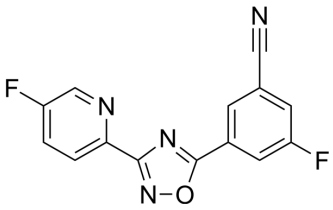
AZD 9272

Cat. No.:	HY-110254
CAS No.:	327056-26-8
Molecular Formula:	$C_{14}H_6F_2N_4O$
Molecular Weight:	284.22
Target:	mGluR
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	AZD 9272 is a brain penetrant mGluR5 antagonist.
IC_{50} & Target	mGluR5
In Vitro	AZD 9272 causes a concentration dependent decrease in the magnitude of the intracellular Ca^{2+} response to 1.5 μM of the mGluR group I selective agonist DHPG in both the human and the rat mGluR5 expressing cell lines. The maximal inhibition is 100%. The mean IC_{50} (±SD) value at the human mGluR5 is 7.6±1.1 nM (n=13) for AZD9272. The mean IC_{50} value at the rat mGluR5 is 2.6±0.3 nM (n=3) for AZD9272. In contrast, 10 μM of AZD9272 does not diminish the response to 10 μM ATP in the background GHEK cells. Increasing concentrations of AZD9272 causes a decrease in the potency and the maximal response of DHPG. AZD9272 completely reverses the glutamate-stimulated (EC_{80}, 80 μM) phosphatidyl inositol hydrolysis in human mGluR5-GHEK cells in a concentration-dependent manner, with IC_{50} of 26±3 nM (n=21)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The clearance of AZD 9272 is low following a single intravenous dose at 3 μmol/kg and AZD 9272 is eliminated from plasma with terminal half-lives between 2 and 6 h. The terminal half-lives following oral dosing are similar to the half-lives following intravenous dosing. The volume of distribution at steady state is intermediate for AZD9272[1]. AZD9272 causes no cocaine-appropriate responding and causes a non-dose-dependent reduction in response rates at higher doses. AZD9272 at 2.84 mg/kg causes greater than 80% and typically more than 99% MTEP-appropriate responding up to 20 hours after dose, with a decline to approximately 20% at 24 hours after dose, yielding a $t_{1/2}$ of 21.93 hours, and causes no systematic effects on response rates. The first time point at which AZD9272 causes >90% MTEP-appropriate responding is at 30 minutes after dose [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Saturable binding and competition binding studies utilize incubations of 1 hour at 22°C. For saturation studies, membranes from mGluR5-GHEK cells are incubated with increasing concentrations (0.1 to 30 nM) of [^{3}H]AZD9272, in the presence or absence of 10 μM MPEP. In a variation of these studies, saturable [^{3}H]AZD9272 binding is determined in the presence of low concentrations (10 and 20 nM) of MPEP. Consistency of the B_{max} in the presence or absence of MPEP supports the interaction of these ligands with a unitary binding site[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]	hmGluR5-GHEK cells are seeded onto 96 well plates at 50,000 cells/well in media containing 10 µCi/mL [^{3}H]myo-inositol. Cells are incubated overnight (16 h), then washed three times and incubated for 1 hour at 37°C in HEPES buffered saline supplemented with 1 unit/mL glutamate pyruvate transaminase and 2 mM pyruvate. Cells are washed once in HEPES buffered saline and pre-incubated for 10 minutes in HEPES buffered saline containing 10 mM LiCl. Antagonist activity is determined by pre-incubating cells with AZD9272 for 10 minutes, then incubating for 30 minutes at 37°C in the presence of glutamate (EC_{80}, 80 µM). AZD9272 is tested at 10 concentrations between 1 nM and 30 µM, in duplicate. The reaction is terminated by the addition of 0.1 mL perchloric acid (5%) on ice, with incubation at 4°C for at least 30 minutes[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Approximately 48 male Wistar rats weighing 240 to 250 g at the beginning of the experiments are housed in pairs, or group housed up to 8 rats per cage, in a colony room with water accessible at all times and lights on between 6:00 AM and 6:00 PM; by restricting access to food, animals are kept at approximately 80% of free feeding weight. All animals are divided into different groups and trained to discriminate cocaine (3.4 mg/kg i.p., 15 minutes), PCP (1.6 mg/kg i.p., 30 minutes), MTEP (2 mg/kg i.p., 30 minutes), or AZD9272 (1.6 mg/kg p.o., 60 minutes) from no drug[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Swedberg MD, et al. AZD9272 and AZD2066: selective and highly central nervous system penetrant mGluR5 antagonists characterized by their discriminative effects. J Pharmacol Exp Ther. 2014 Aug;350(2):212-22.

[2]. Raboisson P, et al. Discovery and characterization of AZD9272 and AZD6538-Two novel mGluR5 negative allosteric modulators selected for clinical development. Bioorg Med Chem Lett. 2012 Nov 15;22(22):6974-9.

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