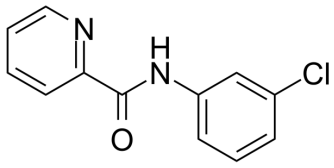
VU0364770

Cat. No.:	HY-100588
CAS No.:	61350-00-3
Molecular Formula:	$C_{12}H_9ClN_2O$
Molecular Weight:	232.67
Target:	mGluR
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (429.79 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	4.2979 mL	21.4897 mL	42.9793 mL
5 mM	0.8596 mL	4.2979 mL	8.5959 mL
10 mM	0.4298 mL	2.1490 mL	4.2979 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (10.74 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (10.74 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

VU0364770 is a selective and potent positive allosteric modulator (PAM) of mGlu4. VU0346770 exhibits EC_{50}s of 290 nM and 1.1 μM at rat mGlu4 and human mGlu4 receptor, respectively. VU0364770 exhibits antagonist activity at mGlu5 with a potency of 17.9 μM and PAM activity at mGlu6 with a potency of 6.8 μM. VU0364770 also possesses activity at MAO with K_i values of 8.5 and 0.72 μM for human MAO-A and human MAO-B, respectively[1].

IC_{50} & Target	Rat $mGlu_4$	Human $mGlu_4$	$mGlu_6$	$mGlu_5$
	290 nM (EC50)	1.1 μM (EC50)	6.8 μM (EC50)	17.9 μM (EC50)

In Vitro

VU0364770 is a selective positive allosteric modulator of $mGlu_4$ in recombinant systems. VU0364770 is a potent PAM of

	multiple signaling pathways that enhances the response of the rat and human $mGlu_4$ receptors to the endogenous agonist glutamate. VU0364770 produces a concentration-dependent potentiation of the response to an EC_{20} concentration of glutamate with EC_{50} of 1.1±0.2 μM and increases the maximal response to glutamate from 100 to 227±17%. Because of concerns that this chemical scaffold might possess activity at MAO, full IC_{50} determinations is performed for VU0364770 at the MAO-A and MAO-B isoforms; these studies result in K_is of 8.5 and 0.72 μM for human MAO-A and human MAO-B, respectively. When tested at a 10 μM concentration at each mGlu receptor, VU0364770 exhibits weak PAM activity (4.3-fold left shift of the glutamate CRC) at mGlu6 and antagonist activity (3.3-fold right shift of the glutamate CRC) at mGlu5 (compare to the 16.5-fold left shift of the glutamate concentration-response for $mGlu_4$ at 10 μM). When further evaluated in a full concentration-response curve format, VU0364770 exhibits antagonist activity at $mGlu_5$ with a potency of 17.9±5.5 μM and PAM activity at $mGlu_6$ with a potency of 6.8±1.7 μM (compare with the potency of VU0364770 on the rat $mGlu_4$ receptor of 290±80 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	VU0364770 exhibits suitable pharmacokinetic properties for systemic dosing in animal models. After intravenous administration, VU0364770 is rapidly clears from the systemic circulation (165 ml/min/kg) and exhibits a volume of distribution of 2.92 L/kg. VU0364770 is a highly protein-bound ligand displaying free fractions of 2.7 and 1.8% in human and rat plasma, respectively. VU0364770 also shows an improved pharmacokinetic profile relative to previously reported $mGlu_4$ PAMs with enhanced central penetration and a total brain-to-plasma ratio of more than 1 after systemic administration of a 10 mg/kg dose. VU0364770 produces a dose-dependent reversal of haloperidol-induced catalepsy. VU0364770 dose-dependently reverses haloperidol (0.75 mg/kg)-induced catalepsy in rats, significant at doses of 10 to 56.6 mg/kg, after subcutaneous dosing ($F_{6,69}$=8.04; p<0.001)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The effects of VU0364770 on rat mGlu1 and mGlu5 are assessed by using calcium mobilization and measuring the glutamate concentration-response relationship in the presence and absence of 10 μM VU0364770. Using a double-addition protocol, VU0364770 is added to the cells, followed 2.5 min later by a full concentration-response of glutamate. Shifts of the concentration-response relationship are used to assess potential potentiator (left shift of more than 2-fold) or antagonist (right shift of more than 2-fold or depression of the maximum response by at least 75%) activity of VU0364770. Compounds are further assessed for mGlu5 antagonist activity by performing a full concentration-response curve, starting at 30 μM and serially diluted it by using 1:3 dilutions, in the presence of an EC_{80} concentration of glutamate[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats[1] Adult male Sprague-Dawley rats, weighing 250 to 300 g, are used. Rat are examined for catalepsy 30 min after the administration of either VU0364770 (1-56.6 mg/kg s.c.), VU0364772 (1-56.6 mg/kg s.c.), A2A antagonist (56.6 mg/kg p.o.), Preladenant (0.03-30 mg/kg p.o.), or vehicle. In the interaction studies rats ate administered VU0364770 (10 or 30 mg/kg) + vehicle, VU0364770 (10 or 30 mg/kg)+Preladenant (0.1-1 mg/kg), or vehicle+Preladenant (0.1-1 mg/kg) 30 min before testing. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Jones CK, et al. The metabotropic glutamate receptor 4-positive allosteric modulator VU0364770 produces efficacy alone and in combination with L-DOPA or an adenosine 2A antagonist in preclinical rodent models of Parkinson's disease. J Pharmacol Exp Ther.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA