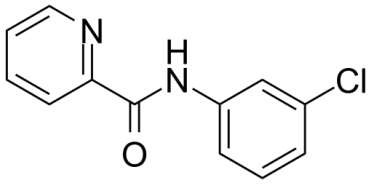
Data Sheet

Product Name:	VU0364770
Cat. No.:	CS-6072
CAS No.:	61350-00-3
Molecular Formula:	C12H9ClN2O
Molecular Weight:	232.67
Target:	mGluR
Pathway:	GPCR/G Protein; Neuronal Signaling
Solubility:	DMSO : ≥ 100 mg/mL (429.79 mM)



BIOLOGICAL ACTIVITY:

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]. IC50 & Target: EC50: 1.1±0.2 μM ($mGlu_4$)[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **Animal Administration:** VU0364770 is suspended in an aqueous solution of

10% Tween 80[1].[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.

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. 2012 Feb;340(2):404-21.

CAIndexNames:

2-Pyridinecarboxamide, N-(3-chlorophenyl)-

SMILES:

O=C(C1=NC=CC=C1)NC2=CC=CC(Cl)=C2

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