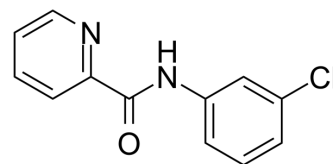


VU0364770

Cat. No.:	HY-100588		
CAS No.:	61350-00-3		
Molecular Formula:	C ₁₂ H ₉ ClN ₂ O		
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	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (429.79 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		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

- 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
- 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. VU0364770 exhibits EC₅₀s 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

Rat mGlu ₄ 290 nM (EC ₅₀)	Human mGlu ₄ 1.1 μM (EC ₅₀)	mGlu ₆ 6.8 μM (EC ₅₀)	mGlu ₅ 17.9 μM (EC ₅₀)
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In Vitro

VU0364770 is a selective positive allosteric modulator of mGlu₄ in recombinant systems. VU0364770 is a potent PAM of

multiple signaling pathways that enhances the response of the rat and human mGlu₄ receptors to the endogenous agonist glutamate. VU0364770 produces a concentration-dependent potentiation of the response to an EC₂₀ concentration of glutamate with EC₅₀ 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 IC₅₀ 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 mGlu₄ at 10 μM). When further evaluated in a full concentration-response curve format, VU0364770 exhibits antagonist activity at mGlu₅ with a potency of 17.9±5.5 μM and PAM activity at mGlu₆ with a potency of 6.8±1.7 μM (compare with the potency of VU0364770 on the rat mGlu₄ 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 cleared 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 mGlu₄ 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 EC₈₀ 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. Rats 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 are 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.* 2012 Feb;340(2):404-21.

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

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