产品名称：**VU 0364770**
产品别名：**VU0364770**

生物活性：

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 Ki values of 8.5 and 0.72 μM for human MAO-A and human MAO-B, respectively[1].

IC_{50} & Target [1]

Rat $mGlu_4$	Human $mGlu_4$	$mGlu_6$	$mGlu_5$
290 nM (EC_{50})	1.1 μM (EC_{50})	6.8 μM (EC_{50})	17.9 μM (EC_{50})

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].

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

Solvent&Solubility	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。 储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。 -80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。 ***In Vivo:*** 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.5 mg/mL (10.74 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (10.74 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。 2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (10.74 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (10.74 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Animal Administration	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.
Kinase Assay	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].
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

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