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产品名称：EVP-6124 (hydrochloride)
产品别名：Encenicline hydrochloride

生物活性：

Description	Encenicline hydrochloride (EVP-6124 hydrochloride) is a novel partial agonist of α7 neuronal nicotinic acetylcholine receptors (nAChRs).
IC_{50} & Target	α 7 nAChR[1]
In Vitro	Encenicline (EVP-6124) displaces [^{3}H]-MLA (Methyllycaconitine) (K_i=9.98 nM, pIC_{50}=7.65±0.06, n=3) and [^{125}I]-α-bungarotoxin (K_i=4.33 nM, pIC_{50}=8.07±0.04, n=3). Encenicline (EVP-6124) is approximately 300 fold more potent than the natural agonist ACh (K_i=3 μM), measured in binding assays using [^{3}H]-MLA. Encenicline hydrochloride inhibits the 5-HT_3 receptor by 51% at 10 nM, the lowest concentration tested. Evaluation of the human 5-HT_{2B}receptor expressed in CHO cells demonstrates displacement of [^{3}H]-mesulergine (K_i=14 nM) and only antagonist activity in the rat gastric fundus assay at an IC_{50} of 16 μM. In binding and functional experiments, Encenicline (EVP-6124) shows selectivity for α7 nAChRs and does not activate or inhibit heteromeric α4β2 nAChRs[1].
In Vivo	Encenicline hydrochloride has good brain penetration and an adequate exposure time. Encenicline hydrochloride (0.3 mg/kg, p.o.) significantly restores memory function in scopolamine-treated rats (0.1 mg/kg, i.p.) in an object recognition task (ORT). Although donepezil at 0.1 mg/kg, p.o. or Encenicline hydrochloride at 0.03 mg/kg, p.o. did not improve memory in this task, co-administration of these sub-efficacious doses fully restored memory. In a natural forgetting test, an ORT with a 24 h retention time, Encenicline hydrochloride improved memory at 0.3 mg/kg, p.o. This improvement is blocked by the selective α7 nAChR antagonist methyllycaconitine (0.3 mg/kg, i.p. or 10 μg, i.c.v.). Encenicline hydrochloride is found to bind moderately to rat plasma proteins with a mean fu of 0.11±0.01 (mean±SD) or 11%. Over a range of 0.1-30 mg/kg, p.o., Encenicline hydrochloride demonstrates proportional dose escalation. T_{max} is at 4 h in plasma and 2 h brain, although the brain concentrations remained similar between 2 and 8 h. The B:P ratios are 1.7-5.1 between 1 and 8 h[1]. Pharmacokinetic studies have shown that Encenicline hydrochloride (0.4 mg/kg, i.p.) reaches peak brain concentration 2 hr after administration and remains at effective concentrations for at least 4 hr. Encenicline hydrochloride is administered to WT mice at ZT0 (0.4 mg/kg i.p single dose) and significantly increases the saturation index of NMDARs in slices obtained 4 hr later without causing prolonged wakefulness or enhanced locomotor activity [2].

In Vitro:

DMSO： ≥ 50 mg/mL (139.94 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.7988 mL	13.9938 mL	27.9877 mL
5 mM	0.5598 mL	2.7988 mL	5.5975 mL
10 mM	0.2799 mL	1.3994 mL	2.7988 mL

*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

Solvent&Solubility	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 (7.00 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.00 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% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (7.00 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.00 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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (7.00 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.00 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]. Prickaerts J, et al. EVP-6124, a novel and selective α7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of α7 nicotinic acetylcholine receptors. Neuropharmacology. 2012 Feb;62(2):109 [2]. Thomas Papouin, et al. Septal Cholinergic Neuromodulation Tunes the Astrocyte-Dependent Gating of Hippocampal NMDA Receptors to Wakefulness. Neuron. 2017 May 17;94:1-15. [3]. Papouin T, et al. Septal Cholinergic Neuromodulation Tunes the Astrocyte-Dependent Gating of Hippocampal NMDA Receptors to Wakefulness. Neuron. 2017 May 17;94(4):840-854.e7. [4]. Maehara S, et al. Pharmacological characterization of a novel potent, selective, and orally active phosphodiesterase 2A inhibitor, PDM-631. Eur J Pharmacol. 2017 Sep 15;811:110-116.

实验参考：

	Rats[1] Twenty-four 2.5-month-old male Wistar rats (average body weight: 329 g) are used. Before testing EVP-6124, the effects of scopolamine alone at 0.03, 0.1, or 0.3 mg/kg, i.p. in the ORT are determined (n=8 per treatment). Scopolamine (0.1 mg/kg, i.p.) injected 30 min before T1 resulted in a robust deficit at T2 when a 1 h interval is used. The d2 index is not significantly different from the chance level of performance; and there are no changes in exploratory behavior for 0.1 mg/kg, i.p. of

Animal Administration	scopolamine compared with saline. Subsequently, the ability of Encenicline (EVP-6124) to reverse the memory impairment induced by 0.1 mg/kg of scopolamine is tested. First, scopolamine and then Encenicline (EVP-6124) (0.03, 0.1, 0.3, and 1.0 mg/kg, p.o.) are administered 30 min before T1. For the control treatments, animals received either deionized water (p.o.) plus saline (i.p.) or deionized water (p.o.) plus 0.1 mg/kg scopolamine (i.p.). Mice[2] Adult male mice (3-6 months old) are used throughout this study. Encenicline (EVP-6124) is injected i.p. (0.4 mg/kg) at Zeitgeber time (ZT0) in awake mice (9 mice total for this experiment), in the animal facility. Mice are then immediately returned to their home cage with their siblings and left undisturbed for 4 hr (ZT4). During this time, they are closely monitored to check for possible behavioral effects of Encenicline (EVP-6124) injection. All of the 9 injected mice nested and are immobile in the hour following the injection.
References	[1]. Prickaerts J, et al. EVP-6124, a novel and selective α7 nicotinic acetylcholine receptor partial agonist, improves memory performance by potentiating the acetylcholine response of α7 nicotinic acetylcholine receptors. Neuropharmacology. 2012 Feb;62(2):109 [2]. Thomas Papouin, et al. Septal Cholinergic Neuromodulation Tunes the Astrocyte-Dependent Gating of Hippocampal NMDA Receptors to Wakefulness. Neuron. 2017 May 17;94:1-15. [3]. Papouin T, et al. Septal Cholinergic Neuromodulation Tunes the Astrocyte-Dependent Gating of Hippocampal NMDA Receptors to Wakefulness. Neuron. 2017 May 17;94(4):840-854.e7. [4]. Maehara S, et al. Pharmacological characterization of a novel potent, selective, and orally active phosphodiesterase 2A inhibitor, PDM-631. Eur J Pharmacol. 2017 Sep 15;811:110-116.