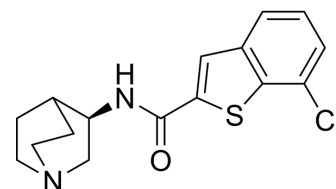


Encenicline

Cat. No.:	HY-15430
CAS No.:	550999-75-2
Molecular Formula:	C ₁₆ H ₁₇ ClN ₂ OS
Molecular Weight:	320.84
Target:	nAChR
Pathway:	Membrane Transporter/Ion Channel; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Encenicline (EVP-6124) is a novel partial agonist of $\alpha 7$ neuronal nicotinic acetylcholine receptors (nAChRs).
IC₅₀ & Target	$\alpha 7$ nAChR ^[1]
In Vitro	<p>Encenicline (EVP-6124) displaces [³H]-MLA (Methyllycaconitine) ($K_i=9.98$ nM, $pIC_{50}=7.65\pm 0.06$, $n=3$) and [¹²⁵I]-α-bungarotoxin ($K_i=4.33$ nM, $pIC_{50}=8.07\pm 0.04$, $n=3$). Encenicline (EVP-6124) is approximately 300 fold more potent than the natural agonist ACh ($K_i=3$ μM), measured in binding assays using [³H]-MLA. Encenicline inhibits the 5-HT₃ 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 [³H]-mesulergine ($K_i=14$ nM) and only antagonist activity in the rat gastric fundus assay at an IC₅₀ of 16 μM. In binding and functional experiments, Encenicline shows selectivity for $\alpha 7$ nAChRs and does not activate or inhibit heteromeric $\alpha 4\beta 2$ nAChRs^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Encenicline (EVP-6124) has good brain penetration and an adequate exposure time. Encenicline (EVP-6124) (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 at 0.03 mg/kg, p.o. did not improve memory in this task, co-administration of these sub-effficacious doses fully restored memory. In a natural forgetting test, an ORT with a 24 h retention time, Encenicline improved memory at 0.3 mg/kg, p.o. This improvement is blocked by the selective $\alpha 7$ nAChR antagonist methyllycaconitine (0.3 mg/kg, i.p. or 10 μg, i.c.v.). Encenicline (EVP-6124) is found to bind moderately to rat plasma proteins with a mean fu of 0.11 ± 0.01 (mean\pmSD) or 11%. Over a range of 0.1-30 mg/kg, p.o., Encenicline (EVP-6124) 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 (EVP-6124) (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 (EVP-6124) 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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Kinase Assay^[1]	Binding or activity of EVP-6124 is measured at 10 μ M in a selectivity panel according to standard validated protocols under
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conditions defined by the contractor. For the 5-HT_{2A} receptor binding assay, membranes are prepared from HEK293 cells expressing the human recombinant 5-HT_{2A} receptor. For 5-HT_{2B} and 5-HT_{2C} receptor binding assays, membranes are prepared from CHO cells expressing the human recombinant 5-HT_{2B} or 5-HT_{2C} receptor. Affinity is determined by incubating different concentrations of EVP-6124 in binding buffer for 1 h. For 5-HT_{2A} binding, the incubation is at 22°C in the presence of 0.5 nM [³H]-ketanserin; for 5-HT_{2B}, at 22°C in the presence of 2 nM [³H]-mesulergine; and for 5-HT_{2C}, at 37°C in the presence of 1 nM [³H]-mesulergine. Nonspecific binding is determined in the presence of 1 μM ketanserin, 10 μM mesulergine, or 10 μM RS-102221 for 5-HT_{2A}, 5-HT_{2B}, or 5-HT_{2C}, respectively. All measurements are performed in triplicate. EVP-6124 is also tested in the 5-HT_{2B} rat gastric fundus tissue response assay. Briefly, inhibition of α-methyl serotonin-induced contraction is isometrically measured. All measurements are performed in duplicate^[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration ^{[1][2]}

Rats^[1]

Twenty-four 2.5-month-old male Wistar rats (average body weight: 329 g) are used. Before testing Encenicline, 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 scopolamine compared with saline. Subsequently, the ability of Encenicline to reverse the memory impairment induced by 0.1 mg/kg of scopolamine is tested. First, scopolamine and then Encenicline (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 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 injection. All of the 9 injected mice nested and are immobile in the hour following the injection.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Neuron. 2017 May 17;94(4):840-854.e7.
- Eur J Pharmacol. 2017 Sep 15;811:110-116.
- Psychopharmacology (Berl). 2019 Apr;236(4):1245-1253.
- Faculty of Health Sciences. 2020 Oct.

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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.

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