Cebranopadol

Cat. No.: HY-15536

CAS No.: 863513-91-1

Molecular Formula: $C_{24}H_{27}FN_2O$

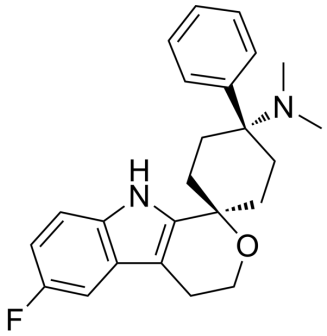
Molecular Weight: 378.48

Target: Opioid Receptor

Pathway: GPCR/G Protein; Neuronal Signaling

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 6.67 mg/mL (17.62 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6421 mL	13.2107 mL	26.4215 mL
	5 mM	0.5284 mL	2.6421 mL	5.2843 mL
	10 mM	0.2642 mL	1.3211 mL	2.6421 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 0.67 mg/mL (1.77 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 0.67 mg/mL (1.77 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.67 mg/mL (1.77 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cebranopadol is an analgesic NOP and opioid receptor agonist with K_is/EC_{50}s of 0.9 nM/13 nM, 0.7 nM/1.2 nM, 2.6 nM/17 nM, 18 nM/110 nM for human NOP, MOP, KOP and delta-opioid peptide (DOP) receptor, respectively.

IC_{50} & Target

EC50: 13±2 nM (hNOP receptor), 1.2±0.4 nM (hMOP receptor), 17±5 nM (hKOP receptor), 110±28 nM (hDOP receptor)[1]

In Vitro

Cebranopadol binds with high affinity (subnanomolar to nanomolar range) to nociceptin/orphanin FQ peptide (NOP) and opioid receptors, with K_i of 1±0.5 nM, 2.4±1.2 nM, and 64±11 nM for rat NOP, mu-opioid peptide (MOP) receptor, and kappa-

	opioid peptide (KOP) receptor, and with K_i of 0.9±0.2 nM, 0.7±0.3 nM, and 2.6±1.4 nM for Rat NOP, MOP, and KOP receptor[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Cebranopadol exhibits highly potent and efficacious antinociceptive and antihypersensitive effects in several rat models of acute and chronic pain (tail-flick, rheumatoid arthritis, bone cancer, spinal nerve ligation, diabetic neuropathy) with ED_{50} values of 0.5-5.6 μg/kg after intravenous and 25.1 μg/kg after oral administration. In comparison with selective MOP receptor agonists, cebranopadol is more potent in models of chronic neuropathic than acute nociceptive pain. Cebranopadol's duration of action is long (up to 7 hours after intravenous 12 μg/kg; >9 hours after oral 55 μg/kg in the rat tail-flick test). The antihypersensitive activity of cebranopadol in the spinal nerve ligation model is partially reversed by pretreatment with the selective NOP receptor antagonist J-113397 or the opioid receptor antagonist naloxone, indicating that both NOP and opioid receptor agonism are involved in this activity[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Human MOP, DOP, KOP, and NOP receptor binding assays are run in microtiter plates with wheat germ agglutinin-coated scintillation proximity assay beads. [N-allyl-2,3-^{3}H]naloxone and [tyrosyl-3,5-^{3}H]deltorphin II, [^{3}H]Ci-977, and [leucyl-^{3}H]nociceptin are used as ligands for the MOP, DOP, KOP, and NOP receptor binding studies, respectively. The K_D values of the radioligands used for the calculation of K_i values are provided as supplemental information. The assay buffer used for the MOP, DOP, and KOP receptor binding studies is 50 mM Tris-HCl (pH 7.4) supplemented with 0.052 mg/mL bovine serum albumin. For the NOP receptor binding studies, the assay buffer used is 50 mM HEPES, 10 mM $MgCl_2$, 1 mM EDTA (pH 7.4). The final assay volume of 250 μL/well included 1 nM [^{3}H]naloxone, 1 nM [^{3}H]deltorphin II, 1 nM [^{3}H]Ci-977, or 0.5 nM [^{3}H]nociceptin as a ligand and cebranopadol in dilution series. Cebranopadol is diluted with 25% DMSO in water to yield a final 0.5% DMSO concentration, which also served as a respective vehicle control. Assays are started by the addition of beads (1 mg beads/well), which had been preloaded for 15 minutes at room temperature with 23.4 μg of human MOP membranes, 12.5 μg of human DOP membrane, 45 μg of human KOP membranes, or 25.4 μg of human NOP membranes per 250 μL of final assay volume. After short mixing, the assays are run for 90 minutes at room temperature. The microtiter plates are then centrifuged for 20 minutes at 500 rpm, and the signal rate is measured by means of a 1450 MicroBeta Trilux. IC_{50} values reflecting 50% displacement of [^{3}H]naloxone-, [^{3}H]deltorphin II-, [^{3}H]Ci-977-, or [^{3}H]nociceptin-specific receptor binding are calculated by nonlinear regression analysis. Individual experiments are run in duplicate and are repeated three times in independent experiments[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats[1] The pharmacokinetic properties of cebranopadol in rats are investigated after a single intravenous dose of 160 μg/kg cebranopadol. The intravenous dose is administered as a bolus in a volume of 2 mL/kg with a catheter in the vena femoralis. Blood samples (200 μL/sample) are withdrawn via an implanted arterial catheter (arteria carotis) by an automated blood sampling system at the following sampling times: 0 (predose), 5, 15, 30, 60, 180, 360, 720, and 1440 minutes after administration. Blood samples are centrifuged, and plasma is separated. Plasma concentrations of cebranopadol are determined using a validated liquid chromatography-tandem mass spectrometry method. The lower limit of quantification for cebranopadol in this method is 0.05 ng/mL using a sample volume of 50 μL of plasma. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Anesthesiology. 2021 Jun.
- Sci Signal. 2019 Mar 26;12(574). pii: eaau8072.
- Inflammopharmacology. 2018 Apr;26(2):361-374.

- Molecules. 2023 Nov 30, 28(23), 7862.
- Sci Rep. 2022 May 3;12(1):7154.

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REFERENCES

[1]. Linz K, et al. Cebranopadol: a novel potent analgesic nociceptin/orphanin FQ peptide and opioid receptor agonist. J Pharmacol Exp Ther. 2014 Jun;349(3):535-48.

[2]. de Guglielmo G, et al. Cebranopadol Blocks the Escalation of Cocaine Intake and Conditioned Reinstatement of Cocaine Seeking in Rats. J Pharmacol Exp Ther. 2017 Sep;362(3):378-384.

[3]. Satat K, et al. Evaluation of cebranopadol, a dually acting nociceptin/orphanin FQ and opioid receptor agonist in mouse models of acute, tonic, and chemotherapy-induced neuropathic pain. Inflammopharmacology. 2017 Oct 25.

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