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产品名称：Cebranopadol
产品别名：GRT6005

生物活性：

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 Ki 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 Ki 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].
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 ED50 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. Development of analgesic tolerance in the chronic constriction injury model is clearly delayed compared with that from an equianalgesic dose of morphine (complete tolerance on day 26 versus day 11, respectively). Unlike morphine, cebranopadol did not disrupt motor coordination and respiration at doses within and exceeding the analgesic dose range. Cebranopadol, by its combination of agonism at NOP and opioid receptors, affords highly potent and efficacious analgesia in various pain models with a favorable side effect profile[1].

In Vitro:

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

H_2O : < 0.1 mg/mL (insoluble)

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

*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

Solvent&Solubility	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: 0.67 mg/mL (1.77 mM); Suspended solution; Need ultrasonic 此方案可获得 0.67 mg/mL (1.77 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 6.7000003 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: 0.67 mg/mL (1.77 mM); Suspended solution; Need ultrasonic 此方案可获得 0.67 mg/mL (1.77 mM)的均匀悬浊液，悬浊液可用于口服和腹腔注射。 以 1 mL 工作液为例，取 100 μL 6.7000003 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: ≥ 0.67 mg/mL (1.77 mM); Clear solution 此方案可获得 ≥ 0.67 mg/mL (1.77 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 6.7000003 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Animal Administration	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.

Kinase Assay	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].
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.