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Lieferung & Zahlungsart

siehe unsere Liefer- und Versandbedingungen

Zuschläge

- Mindermengenzuschlag
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Edelinontrine

Cat. No.: HY-15441

CAS No.: 1082744-20-4

Molecular Formula: $C_{20}H_{25}N_7O_2$

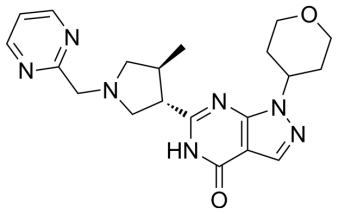
Molecular Weight: 395.46

Target: Phosphodiesterase (PDE)

Pathway: Metabolic Enzyme/Protease

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 : ≥ 54.6 mg/mL (138.07 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5287 mL	12.6435 mL	25.2870 mL
	5 mM	0.5057 mL	2.5287 mL	5.0574 mL
	10 mM	0.2529 mL	1.2644 mL	2.5287 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: ≥ 2.5 mg/mL (6.32 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.32 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.32 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Edelinontrine (PF-04447943) is a potent inhibitor of human recombinant PDE9A (IC_{50}=12 nM) with >78-fold selectivity, respectively, over other PDE family members (IC_{50}>1000 nM).

IC_{50} & Target

PDE9

In Vitro

Using recombinant human, rhesus, and rat PDE9A2 in a cell free assay Edelinontrine is shown to have a K_i of 2.8±0.26,

	4.5±0.13, and 18.1±1.9 nM (n=4, 11 and 9 respectively). Edelinontrine is found to be highly selective over other PDE enzymes (PDE1, K_i=8600±2121 nM, n = 5; PDE2A3, K_i>99,000 nM; PDE3A, K_i>50,000 nM; PDE4A, K_i>29,000 nM; PDE5A, K_i=14,980±5025 nM, n=5; PDE6C, K_i=5324±2612 nM, n=4; PDE7A2, K_i>75,000 nM; PDE8A, K_i>50,000 nM; PDE10, K_i>51,250±20,056 nM, n=4; PDE11, K_i>80,000 nM) and no other significant activity at ~60 other receptors/enzymes. In HEK whole cells expressing rhesus PDE9A2, Edelinontrine inhibits ANP (0.3 μM) stimulated cGMP with an IC_{50} of 375±36.9 nM (n=16)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Based on i.v. and p.o. dosing, pharmacokinetic studies with Edelinontrine in the rat indicates a T_{max} of 0.3 h, $T_{1/2}$ of 4.9 h, Cl of 21.7 mL/min/kg and an oral bioavailability of 47%. Thirty minutes following oral administration in rats (1-30 mg/kg), Edelinontrine concentrations dose-dependently increase in blood, brain and cerebrospinal fluid (CSF). The brain:plasma exposure ratios 30 min after dosing range from 0.13 at the 1 mg/kg dose to 0.33 at the 30 mg/kg dose. CSF levels are approximately 50% of brain levels. In mice, Edelinontrine (3, 10, 30 mg/kg p.o.) dose-dependently increases plasma and brain concentrations of Edelinontrine while the brain to plasma ratio ranged from 0.26 to 0.7 although this is not entirely dose dependent. CSF cGMP levels increase in a dose-dependent manner from a basal level of 3 pmol/mL to 13.3 pmol/mL (3.5-fold) at the 30 mg/kg dose. CSF cGMP levels also increase in a dose-dependent manner from a basal level of 3 pmol/mL in vehicle treated animals to 13.3 pmol/mL (3.5-fold) at the 30 mg/kg dose. CSF cGMP levels are elevated at all doses tested with a maximal effect of 3.5 fold increase above controls at 30 mg/kg[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The rhesus PDE9A2 construct is subcloned into a pcDNA3.3 TOPO vector and HEK 293 cells, stably transfected to constitutively express rhesus PDE9A2 and hNPR1, are incubated with PF-04447943 (30 μM to 1.5 nM) in assay media at a density of 10,000 cells/well, for 30 min at 37°C. Cyclic GMP formation is stimulated by incubation with 0.3 μM ANP (Atrial Natriuretic Peptide) for another 30 min at 37°C. Following incubation, cells are lysed with Antibody/Lysis buffer and ED Reagent for 1 h at room temperature. After a subsequent incubation with EA Reagent for 30 min at room temperature, followed by incubation with Substrate Reagent for 1 h at room temperature, cGMP concentrations are determined by measuring luminescence on the Envision Microplate Luminometer. The maximal inhibition (100% activity) in the cell based assay is determined using 30 μM PF-04447943 and 0% activity is defined by the DMSO control. PF-04447943 is titrated in quadruplicate, in a 10 point titration. Percentage inhibition is calculated using the maximal inhibition value and IC_{50} values are calculated from concentration response curves using Prism software[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice and Rats[2] For the mouse studies, male C57Bl/6J mice are administered PF-04447943 (3, 10, 30 mg/kg p.o.). For the rat studies rats (strain, weight range and supplier as described in the novel object recognition study below) are administered PF-04447943 10 mg/kg i.v. and p.o.. At various times after administration the animals are anesthetized with isoflurane; blood samples are withdrawn via cardiac puncture and placed in EDTA tubes on ice. Plasma is separated and frozen at -70°C until assayed for drug concentration. PF-04447943 and the internal standard are monitored in the positive ion mode at the transition from m/z 396.2 to 203.1 and m/z 477.3 to 266.2, respectively. Quantification is performed using Analyst 1.4 based on duplicate standard curves. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharmacol Sin. 2017 Sep;38(9):1257-1268.
- Neurochem Int. 2020 Feb;133:104630.
- Patent. US20230111925A1.

- bioRxiv. 2021 Feb 02.

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REFERENCES

[1]. Kleiman RJ, et al. Phosphodiesterase 9A regulates central cGMP and modulates responses to cholinergic and monoaminergic perturbation in vivo. J Pharmacol Exp Ther. 2012 May;341(2):396-409.

[2]. Hutson, P. H, et al. The selective phosphodiesterase 9 (PDE9) inhibitor PF-04447943 (6-[(3S,4S)-4-methyl-1-(pyrimidin-2-ylmethyl)pyrrolidin-3-yl]-1-(tetrahydro-2H-pyran-4-yl)-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one) enhances synaptic plasticity and

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