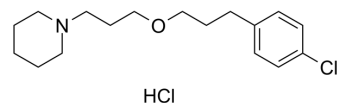


Pitolisant hydrochloride

Cat. No.:	HY-12199B
CAS No.:	903576-44-3
Molecular Formula:	C ₁₇ H ₂₇ Cl ₂ NO
Molecular Weight:	332.31
Target:	Histamine Receptor
Pathway:	GPCR/G Protein; Immunology/Inflammation; Neuronal Signaling
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

H₂O : 100 mg/mL (300.92 mM; Need ultrasonic)
 DMSO : ≥ 43 mg/mL (129.40 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		1 mg	5 mg	10 mg
	1 mM	3.0092 mL	15.0462 mL	30.0924 mL
	5 mM	0.6018 mL	3.0092 mL	6.0185 mL
	10 mM	0.3009 mL	1.5046 mL	3.0092 mL

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

In Vivo

- Add each solvent one by one: PBS
Solubility: 50 mg/mL (150.46 mM); Clear solution; Need ultrasonic
- Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
Solubility: ≥ 2.5 mg/mL (7.52 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
Solubility: ≥ 2.5 mg/mL (7.52 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pitolisant hydrochloride is a potent and selective nonimidazole inverse agonist at the recombinant human histamine H3 receptor (K_i=0.16 nM).

IC₅₀ & Target

K_i: 0.16 nM (H3 receptor)^[1]
 EC₅₀: 1.5 nM (H3 receptor)^[1]

In Vitro

On the stimulation of guanosine 5'-O-(3-[³⁵S]thio)triphosphate binding to this receptor, Pitolisant (BF2.649) behaves as a

competitive antagonist with a K_i value of 0.16 nM and as an inverse agonist with an EC_{50} value of 1.5 nM and an intrinsic activity ~50% higher than that of ciproxifan. Pitolisant displaces [125 I]iodoproxyfan binding from mouse brain cortical membranes with an IC_{50} value of 26.4±4.5 nM. Taking into account the K_D value of the radioligand (161±9 pM), the deduced K_i value for Pitolisant is 14±1 nM. Pitolisant displaces [125 I]iodoproxyfan binding from membranes of rat glioma C6 cells stably expressing the human H_3 receptor with an IC_{50} value of 4.2±0.2 nM. Taking into account the K_D value of the radioligand (50±4 pM), the deduced K_i value for Pitolisant is 2.7±0.5 nM. Pitolisant progressively reverses this response with a Hill coefficient close to unity and an IC_{50} value of 330±68 nM, leading to a K_i value of 17±4 nM. Pitolisant elicits a dose-dependent decrease of the basal-specific [35 S]GTP γ S binding to membranes with a maximal effect corresponding to 75±1% of the basal-specific binding and an EC_{50} value of 1.5±0.1 nM^[1].

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

In Vivo

The administration of Pitolisant at a single dose of 10 mg/kg 30 min before a single dose of LY170053 (2 mg/kg b.w.) also significantly affects immobility time in the FST. Subsequent administration of the aforementioned drug sequence in mice statistically significantly increases the duration of immobility in comparison to the time determined in the control group in the FST. It decreased locomotor activity as well. In contrast, the results obtained in subchronic treatment after fifteen administrations of both drugs (Pitolisant 10 mg/kg b.w., and after 30 min LY170053 2 mg/kg b.w., and again after 4 h LY170053 2 mg/kg b.w.) show that the administration of Pitolisant followed by that of LY170053 equalized the locomotor activity in mice; in comparison to the level of motility in the control group, to which only Pitolisant is administered. More importantly, this combination of drugs significantly reduces immobility time to the level obtained in the control group in the forced swim test in mice [one-way ANOVA; $F_{(3,20)}=4.226, P=0.0181$]^[2]. Rats given Pitolisant (10 mg/kg) during the conditioning phase stayed 502±94 s on the paired texture, a value not statistically different from that of controls, indicating that Pitolisant did not support place preference^[3].

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PROTOCOL

Kinase Assay ^[1]

[35 S]GTP γ S binding assays are performed. CHO-K1 cells stably expressing the human H_3 receptor (~400 fmol/mg protein) are homogenized in ice-cold buffer (50 mM Tris/HCl, pH 7.4). Homogenates are centrifuged twice (20,000g for 10 min at 4°C), and the final pellet is resuspended in 50 volumes of buffer. Membranes (550 μ g of protein) are pretreated with adenosine deaminase (1 U/mL) and incubated for 60 min at 25°C with 0.1 nM [35 S]GTP γ S and the drugs to be tested in a final volume of 1 mL of assay buffer (50 mM Tris/HCl, 50 mM NaCl, 5 mM MgCl₂, 10 μ M GDP, and 0.02% bovine serum albumin, pH 7.4). The nonspecific binding is determined using 10 μ M nonradioactive GTP γ S. Incubations are stopped by rapid filtration under vacuum through GF/B glass fiber filters. After washing with ice-cold water, the radioactivity trapped on filters is counted by liquid scintillation spectrometry. A similar assay is used to assess competitive antagonism. In brief, membranes (10 μ g of protein) of HEK-293 cells stably expressing the human H_3 receptor (~600 fmol/mg protein) are preincubated in presence of Pitolisant in the buffer (50 mM Tris/HCl, pH 7.4, 10 mM MgCl₂, 100 mM NaCl, and 10 μ M GDP) in a 96-well microplate under gentle agitation at room temperature (19-20°C) for 30 min before the addition of 0.1 nM [35 S]GTP γ S (final volume 200 μ L). The nonspecific binding is determined using a 10 μ M concentration of nonradioactive GTP γ S. After 30 min, incubations performed in triplicate are stopped by rapid filtration under vacuum on a Multiscreen MAFCOB50 microplate. Radioactivity trapped on filters is counted by liquid scintillation spectrometry^[1].

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Animal Administration ^{[2][3]}

Mice^[2]

Adult female Albino Swiss mice weighing 20-22 g are used in the study. LY170053 or Pitolisant are suspended in 1% Tween 80. The compounds or vehicle are administered intraperitoneally (i.p.) 30 min prior to the acute experiment. In the Pitolisant+LY170053 group, Pitolisant is administered 15 min before LY170053. Subchronic treatment is done at about 9:00 am (0.2 mL Tween to control group, Pitolisant-10 mg/kg b.w. to Pitolisant group, LY170053-2 mg/kg b.w. to LY170053 group, Pitolisant-10 mg/kg b.w. and LY170053 after 15 min-2 mg/kg b.w. to Pitolisant+LY170053 group) and at about 1:00 pm (LY170053 group and Pitolisant+LY170053 group).

Rats^[3]

Male Wistar rats (220-300 g) receive vehicle (methylcellulose 1%, p.o.), and Pitolisant (10 mg/kg, p.o.). Ninety minutes later, they are killed by decapitation and nucleus accumbens are dissected out, weighed, frozen in liquid nitrogen and stored at -

80°C. Tissues are homogenized in 1 mL of a 0.4 N perchloric acid/2.7 mM EDTA solution. After centrifugation (8000 rpm, 20 min, 4°C), supernatants are analysed by HPLC coupled to electrochemical detection.
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Brain Res. 2020 Aug 1;1740:146873.

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REFERENCES

- [1]. Ligneau X, et al. BF2.649 [1-{3-[3-(4-Chlorophenyl)propoxy]propyl}piperidine, hydrochloride], a nonimidazole inverse agonist/antagonist at the human histamine H3 receptor: Preclinical pharmacology. J Pharmacol Exp Ther. 2007 Jan;320(1):365-75.
- [2]. Dudek M, et al. H3 histamine receptor antagonist pitolisant reverses some subchronic disturbances induced by LY170053 in mice. Metab Brain Dis. 2016 Oct;31(5):1023-9.
- [3]. Uguen M, et al. Preclinical evaluation of the abuse potential of Pitolisant, a histamine H₃ receptor inverse agonist/antagonist compared with CRL 40476. Br J Pharmacol. 2013 Jun;169(3):632-44.
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