Product Data Sheet

Product Name: Pitolisant oxalate
Cat. No.: GC36932

Chemical Properties

Cas. No.	362665-57-4		
SMILES	ClC1=CC=C(CCCOCCCN2CCCCC2)C=C1.O=C(O)C(O)=O		
Formula	$C_{19}H_{28}ClNO_5$	M.Wt	385.88
Solubility	DMSO: 50 mg/mL (129.57 mM)	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	Pitolisant oxalate		

Protocol

[35S]GTPγS binding assays are performed. CHO-K1 cells stably expressing the human H3 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 µg of protein) are pretreated with adenosine deaminase (1 U/mL) and incubated for 60 min at 25°C with 0.1 nM [35S]GTPγS 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 µM GDP, and 0.02% bovine serum albumin, pH 7.4). The nonspecific binding is determined using 10 µM nonradioactive

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Kinase experiment:

GTPγS. 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 μg of protein) of HEK-293 cells stably expressing the human H3 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 μM 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 [35S]GTPγS (final volume 200 μL). The nonspecific binding is determined using a 10 μM concentration of nonradioactive GTPγS. 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 experiment:

Mice[2] Adult female Albino Swiss mice weighing 20-22 g are used in the study. Olanzapine 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+Olanzapine group, Pitolisant is administered 15 min before Olanzapine. 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, Olanzapine-2 mg/kg b.w. to Olanzapine group, Pitolisant-10 mg/kg b.w. and Olanzapine after 15 min-2 mg/kg b.w. to Pitolisant+Olanzapine group) and at about 1:00 pm (Olanzapine group and Pitolisant+Olanzapine group).Rats[3] Male Wistar rats (220-300 g) receive vehicle (methylcellulose 1%, p.o.), Pitolisant (10 mg/kg, p.o.) or D-amphetamine (2.5 mg/kg, i.p. in saline). 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. Tissue concentrations of dopamine (DA), dihydroxyphenyl acetic acid (DOPAC) and homovanillic acid (HVA) are determined and the corresponding ratios (DOPAC/DA, HVA/DA) are calculated.

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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 olanzapine 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 H receptor inverse agonist/antagonist compared with Modafinil. Br J Pharmacol. 2013 Jun;169(3):632-44.

Background

Pitolisant is a nonimidazole histamine H_3 receptor antagonist (K_i = 0.16 nM) and inverse agonist (EC_{50} = 1.5 nM).[1] It increases the levels of *tele*-methylhistamine in mouse brain, indicating histaminergic neuron activity, with an ED_{50} value of 1.6 mg/kg. Pitolisant also increases dopamine and acetylcholine levels in the rat prefrontal cortex when administered at a dose of 10 mg/kg. It decreases the time spent in slow wave sleep and increases the time spent awake in cats. Pitolisant (2.5 and 5 mg/kg), when administered post-training, facilitates contextual fear memory consolidation and reverses dizocilpine-induced amnesia in mice.[2] When administered following reactivation, it reverses dizocilpine-induced reconsolidation deficits.

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1.Ligneau, X., Perrin, D., Landais, L., 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 pharmacologyJ. Pharmacol. Exp. Ther.320(1)365-375(2007) 2.Brabant, C., Charlier, Y., and Tirelli, E.The histamine H?-receptor inverse agonist pitolisant improves fear memory in miceBehav. Brain Res.243199-204(2013)

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