Irdabisant hydrochloride

Cat. No.: HY-109968A

CAS No.: 1005398-61-7

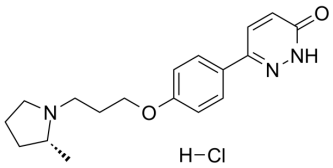
Molecular Formula: $C_{18}H_{24}ClN_3O_2$

Molecular Weight: 349.86

Target: Histamine Receptor

Pathway: GPCR/G Protein; Immunology/Inflammation; Neuronal Signaling

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Irdabisant (CEP-26401) hydrochloride is a selective, orally active and blood-brain barrier (BBB) penetrant histamine H3 receptor (H3R) inverse agonist/inverse agonist with K_i values of 7.2 nM and 2.0 nM for rat H3R and human H3R, respectively. Irdabisant hydrochloride has relatively low inhibitory activity against hERG current with an IC_{50} of 13.8 μM. Irdabisant hydrochloride has cognition-enhancing and wake-promoting activities in the rat social recognition model. Irdabisant hydrochloride can be used to research schizophrenia or cognitive impairment[1][2].

IC_{50} & Target

rat H_3 receptor	human H_3 receptor
7.2 nM (Ki)	2 nM (Ki)

In Vitro

Irdabisant (CEP-26401, compound 8a) shows antagonist activity with $K_{b,\ app}$ values of 1.0 nM and 0.4 nM for rat H3R and human H3R, respectively; shows inverse agonist activity with EC_{50} values of 2.0 nM and 1.1 nM for rat H3R and human H3R, respectively[1].

Irdabisant has moderate activity at Muscarinic M_2 (K_i = 3.7 ± 0.0 μM) and Adrenergic α_{1A} (K_i = 9.8 ± 0.3 μM) receptors, Dopamine transporters (K_i = 11 ± 2 μM), Norepinephrine transporters (K_i = 10 ± 1 μM), and phosphodiesterase PDE3 (IC_{50} = 15 ± 1 μM)[1].

Irdabisant inhibits the cytochrome P450 enzymes CYP1A2, 2C9, 2C19, 2D6, and 3A4 with IC_{50} values of greater than 30 μM, indicating less potential for drug-drug interactions[1].

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

In Vivo

CEP-26401 (0.01-0.3 mg/kg; p.o.; single dosage) dose-dependently inhibits H3R agonist RAMH-induced dipsogenia[1].

CEP-26401 (0.0001-0.1 mg/kg; i.v. or p.o.; single dosage) improves performance in the rat social recognition model of short-term memory[1].

CEP-26401 (3-30 mg/kg; p.o.; single dosage) exhibits wake-promoting activity in rat[2].

CEP-26401 (3-30 mg/kg; i.p.) increases prepulse inhibition (PPI) in DBA/2NCrl mice[2].

CEP-26401 (1 mg/kg for i.v. and 3 mg/kg for p.o.; single dosage) is rapidly absorbed with high oral bioavailability in rat and monkey, and shows a moderate clearance in monkey and dog compared to the rat[1].

Pharmacokinetic Parameters of Irdabisant (compound 8a) in rats, dogs and monkeys[1].

	Rat	Dog	Monkey
i.v. $t_{1/2}$ (h)	2.6	2.9	5.4

i.v. V_d (L/kg)	9.4	3.5 ± 1.1	3.8 ± 0.9
i.v. CL (mL/min/kg)	42	13.2 ± 1.5	7.7 ± 1.8
p.o. $t_{1/2}$ (L/kg)	2.9	2.7	5.0
p.o. AUC (ng·h/mL)	984	1190 ± 180	1919 ± 611
p.o. C_{max} (ng/mL)	270	230 ± 70	760 ± 74
p.o. F (%)	83	22 ± 2	83 ± 18
Brain to plasma ratio	2.6 ± 0.2	2.4 ± 0.4	/

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Animal Model:	Male Sprague-Dawley rats (i.p. 10 mg/kg RAMH-induced dipsogenia model)[1]
Dosage:	0.01-0.3 mg/kg
Administration:	p.o.; single dosage
Result:	Dose-dependently inhibited H3R agonist RAMH (HY-100999)-induced dipsogenia (which manifests as water drinking) with an EC_{50} value of 0.06 mg/kg.

Animal Model:	Male Sprague-Dawley rats (adult rats were briefly exposed to a juvenile rat for build social recognition model)[2]
Dosage:	0.0001, 0.001, 0.01 and 0.1 mg/kg for i.p.; 0.01 and 0.1 mg/kg for p.o.
Administration:	i.v. or p.o.; single dosage
Result:	Effectively reduced the ratio of investigation duration (RID) at doses over the range from 0.001 to 0.1 mg/kg i.p. and at 0.01 and 0.1 mg/kg p.o., demonstrating potent enhancement of short-term sensory memory in this model.

Animal Model:	Male Sprague-Dawley rats[2]
Dosage:	3, 10 and 30 mg/kg
Administration:	p.o.; single dosage
Result:	Exhibited robust wake promotion with the treated animals awake 90% of the time up to 3 h postdosing at 30 mg/kg.

Animal Model:	Male Sprague-Dawley rats, male beagle dogs and male cynomolgus monkeys[1]
Dosage:	1 mg/kg for i.v. and 3 mg/kg for p.o.
Administration:	i.v. and p.o.

Result:	Exhibited rapid absorption with high oral bioavailability in rat and monkey, and showed a moderate clearance in monkey and dog compared to the rat.

Animal Model:	Male DBA/2NCrl mice (19-27 g; 7-9 weeks)[2]
Dosage:	3, 10 and 30 mg/kg
Administration:	i.p.; single dosage
Result:	Increased prepulse inhibition (PPI) in DBA/2NCrl mice, whereas the antipsychotic Risperidone (HY-11018) is effective at 0.3 and 1 mg/kg i.p..

REFERENCES

[1]. Hudkins RL, et al. Discovery and characterization of 6-{4-[3-(R)-2-methylpyrrolidin-1-yl)propoxy]phenyl}-2H-pyridazin-3-one (CEP-26401, irdabisant): a potent, selective histamine H3 receptor inverse agonist. J Med Chem. 2011 Jul 14;54(13):4781-92.

[2]. Raddatz R, et al. CEP-26401 (irdabisant), a potent and selective histamine H_3 receptor antagonist/inverse agonist with cognition-enhancing and wake-promoting activities. J Pharmacol Exp Ther. 2012 Jan;340(1):124-33.

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