Toreforant

Cat. No.: HY-16756

CAS No.: 952494-46-1

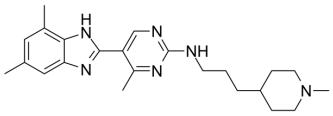
Molecular Formula: $C_{23}H_{32}N_6$

Molecular Weight: 392.54

Target: Histamine Receptor

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

Storage: 4°C, sealed storage, away from moisture and light
* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture and light)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (254.75 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5475 mL	12.7376 mL	25.4751 mL
	5 mM	0.5095 mL	2.5475 mL	5.0950 mL
	10 mM	0.2548 mL	1.2738 mL	2.5475 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 (6.37 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.37 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.37 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Toreforant is a potent and selective histamine H_4 receptor (H4R) antagonist, with a K_i at the human receptor of 8.4 nM.

IC_{50} & Target

H_4 receptor
8.4±2.2 nM (IC_{50})

In Vitro

In human polymorphonuclear leukocytes, Toreforant inhibits the histamine-induced shape change of human eosinophils and produces a rightward shift in the histamine dose response curves indicating that it is acting as an antagonist of the human H4R in these primary cells. This is not an equilibrium measurement and therefore the calculation of a pA2 is

	complicated. The pA2 can be estimated using the shift seen the lowest concentration of antagonist. This yields a pA2 of around 7.5 consistent with the results in the transfected system. This assay can also be performed in whole blood and, as for the purified cells, Toreforant is able to inhibit the actions of histamine. The IC_{50} values are 296 nM and 780 nM when 100 nM and 300 nM histamine are used, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The animals treated with 100 mg/kg toreforant have reduced disease severity scores. The reduction in scores is similar to JNJ 28307474. A model of histamine-induced scratching in CD-1 mice (n=5 per group) is used to judge the anti-pruritic effects of Toreforant. Unlike other H4R antagonists, Toreforant is not efficacious in reducing histamine-mediated pruritus. After oral administration to rats, Toreforant-derived radioactivity is widely distributed into tissues; however, it is not quantifiable in cerebellum, cerebrum, medulla, and spinal cord in either Long Evans or Sprague Dawley rats, suggesting that drug-derived radioactivity does not cross the blood-brain barrier. Neuropathic pain models in rats are conducted with Toreforant and an H4R antagonist that does cross the blood-brain barrier, JNJ 39758979. In a rat spinal nerve ligation model JNJ 39758979 was able to significantly attenuate the mechanical allodynia induced in the model, however Toreforant has no activity[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice[1] The ovalbumin mouse asthma model and the collageninduced arthritis model are conducted. Toreforant is dosed orally in 20% hydroxypropyl-β-cyclodextrin. In the collagen-induced arthritis model Toreforant is given orally twice a day starting with the first signs of disease onset around Day 30 and continued for 14 days. CD-1 mice (5 per group) are dosed with vehicle (20% hydroxypropyl-β-cyclodextrin), Toreforant or JNJ 28307474, as a positive control, at 50 mg/kg orally, 60 mins prior to the intra-dermal injection of histamine. Bouts of scratching are recorded over a 20 minute period. In a subsequent experiment mice are orally dosed with Toreforant (100 mg/kg) at 24, 8, 4 and 1 h prior to intra-dermal injection of histamine and similarly monitored. The area at the back of the neck of mice is shaved 24 hours prior to an intra-dermal injection of 20 µL of 100 µg compound 48/80. Both knockout and wild-type mice (five mice per group) are dosed with vehicle, Toreforant (50 mg/kg) or JNJ 28307474 (50 mg/kg), orally, 60 mins prior to the intradermal injection. Bouts of scratching are recorded over a 20 minute period. Terminal (t=80 min) plasma and brain samples are analyzed for drug concentration. Male Sprague-Dawley rats are deeply anesthetized with isoflurane/oxygen inhalational anesthesia [1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Robin L Thurmond, Pharmacology and Clinical Activity of Toreforant, a Histamine H4 Receptor Antagonist. Annals of Pharmacology and Pharmaceutics. 21 Jan, 2017.

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