Navarixin

Cat. No.: HY-10198

CAS No.: 473727-83-2

Molecular Formula: $C_{21}H_{23}N_3O_5$

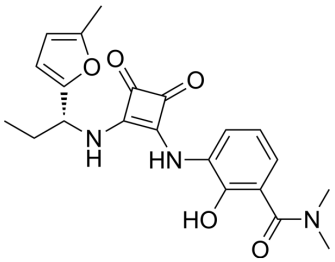
Molecular Weight: 397.42

Target: CXCR

Pathway: GPCR/G Protein; Immunology/Inflammation

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 : ≥ 50 mg/mL (125.81 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.5162 mL	12.5811 mL	25.1623 mL
5 mM	0.5032 mL	2.5162 mL	5.0325 mL
10 mM	0.2516 mL	1.2581 mL	2.5162 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 (6.29 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.29 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution
4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution
5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (6.29 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Navarixin (SCH 527123) is a potent, allosteric and orally active antagonist of both CXCR1 and CXCR2, with K_d values of 41 nM for cynomolgus CXCR1 and 0.20 nM, 0.20 nM, 0.08 nM for mouse, rat and cynomolgus monkey CXCR2, respectivelly[1][2].

IC_{50} & Target	^{125}I-CXCL8-CXCR2 0.97 nM (IC_{50})	Cynomolgus CXCR2 0.08 nM (Kd)	Mouse CXCR2 0.2 nM (Kd)	Rat CXCR2 0.2 nM (Kd)
	^{125}I-CXCL8-CXCR1 43 nM (IC_{50})	Cynomolgus CXCR1 41 nM (Kd)		

In Vitro

Navarixin is a potent, allosteric antagonist of both CXCR1 and CXCR2, with K_d values of 41 nM for cynomolgus CXCR1 and 0.20 nM, 0.20 nM, 0.08 nM for mouse, rat and cynomolgus monkey CXCR2, respectivelly[1]. Navarixin (1 nM) reduces CXCL8 potency in stimulating Ba/F3-hCXCR2 chemotaxis. Navarixin (3 nM) significantly inhibits the potency and efficacy of CXCL1-induced neutrophils (PMN) chemotaxis. Navarixin (300 nM) significantly decreases chemokine potency and slightly decreases maximal cell movement for Ba/F3-CXCR1 cells[2]. Navarixin (25 μM) is sufficient to block IL-8-mediated CXCR2 activation in HCT116, E2, Caco2, and IIIe cells, in which phosphorylation of downstream kinases of CXCR2 is reduced in a concentration-dependent manner[3].

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

In Vivo

Navarixin (0.1-10 mg/kg, p.o.) blocks pulmonary neutrophilia (ED_{50}=1.2 mg/kg) and goblet cell hyperplasia (32-38% inhibition at 1-3 mg/kg) in mice following the intranasal lipopolysaccharide (LPS) administration. In rats, Navarixin (0.1-3 mg/kg p.o.) suppresses the pulmonary neutrophilia (ED=1.8 mg/kg) and increase in bronchoalveolar lavage (BAL) mucin content (ED_{50}=0.1 mg/kg) induced by intratracheal (i.t.) LPS[1].

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PROTOCOL

Cell Assay [2]

Recombinant cells are resuspended at 1×10^6/mL in assay buffer (phenol red free-RPMI 1640 supplemented with 2% FBS). Human neutrophils are resuspended at 2×10^6/mL in the same assay buffer containing 5% FBS. CXCL1 binds only CXCR2 with high affinity, whereas CXCL8 binds both CXCR1 and CXCR2 with high affinity. Chemoattractants (30 μL) diluted in assay buffer are dispensed into the bottom wells of disposable microchemotaxis plates, which are then covered with filter. Cells are preincubated with Navarixin (1-300 nM) in a CO_2 incubator for 90 min. Cell aliquots (25 μL) are applied to each spot on the filter. After incubation (90 min for BaF/3 cells and 30 min for PMN in a CO_2 incubator), the filters are removed[2].

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

Animal Administration [1]

Mice[1]

Male BALB/c mice weighing between 20 and 25 g are used. Control mice receive intranasal injection of 50 μL of isotonic (0.9%) saline. Navarixin (0.1-10 mg/kg, p.o.) is suspended in 0.4% methylcellulose and given orally by gavage 2 h before and 4 h after each intranasal administration of LPS. Control animals receive 0.4% methylcellulose (10 mL/kg). In total, four doses of Navarixin or vehicle are given[1].

Rats[1]

Male Sprague-Dawley rats (200 g) are used. Control animals receive 100 μL of isotonic saline. Navarixin (0.1-3 mg/kg, p.o.) is suspended in 0.4% methylcellulose vehicle and given orally 2 h before the LPS challenge. Control rats receive oral methylcellulose (10 mL/kg). Only one dose of Navarixin or vehicle is given in these experiments[1].

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

CUSTOMER VALIDATION

- Nat Immunol. 2019 Nov;20(11):1444-1455.
- Nat Microbiol. 2017 May 15;2:17072.
- J Hepatol. 2023 Jun 20;S0168-8278(23)00423-3.
- Nat Commun. 2021 May 5;12(1):2547.

- J Allergy Clin Immunol. 2016 Jul;138(1):114-122.e4.

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REFERENCES

[1]. Gonsiorek W, et al. Pharmacological characterization of Sch527123, a potent allosteric CXCR1/CXCR2 antagonist. J Pharmacol Exp Ther. 2007 Aug;322(2):477-85.

[2]. Chapman RW, et al. A novel, orally active CXCR1/2 receptor antagonist, Sch527123, inhibits neutrophil recruitment, mucus production, and goblet cell hyperplasia in animal models of pulmonary inflammation. J Pharmacol Exp Ther. 2007 Aug;322(2):486-93.

[3]. Ning Y, et al. The CXCR2 antagonist, SCH-527123, shows antitumor activity and sensitizes cells to NSC 266046 in preclinical colon cancer models. Mol Cancer Ther. 2012 Jun;11(6):1353-64.

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