SCH 546738

Cat. No.: HY-10017

CAS No.: 906805-42-3

Molecular Formula: $C_{23}H_{31}Cl_2N_7O$

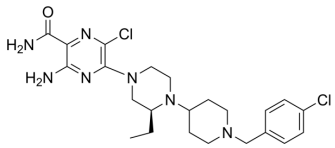
Molecular Weight: 492.44

Target: CXCR

Pathway: GPCR/G Protein; Immunology/Inflammation

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 4.5 mg/mL (9.14 mM; Need ultrasonic)

H_2O : 1 mg/mL (2.03 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.0307 mL	10.1535 mL	20.3070 mL
5 mM	0.4061 mL	2.0307 mL	4.0614 mL
10 mM	---	---	---

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

In Vivo

1. Add each solvent one by one: 0.5% Methylcellulose/saline water
   Solubility: 5 mg/mL (10.15 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: corn oil
   Solubility: 1 mg/mL (2.03 mM); Suspended solution; Need ultrasonic and warming

BIOLOGICAL ACTIVITY

Description

SCH 546738 is a potent, orally active and non-competitive CXCR3 antagonist, the affinity constant (K_i) of SCH 546738 binding to human CXCR3 receptor is determined to be 0.4 nM in multiple experiments.

IC_{50} & Target

Human CXCR3
0.4 nM (Ki)

In Vitro

The affinity of SCH 546738 binding to human CXCR3 receptor is determined by competition binding analysis using ^{35}S radiolabeled SCH 535390 (a sulfonamide analog of the CXCR3 compound series with a K_d of 0.6 nM) as a competitive tracer. In addition, SCH 546738 displaces radiolabeled CXCL10 and CXCL11 from human CXCR3 with IC_{50} ranging from 0.8 to 2.2 nM

	in a non-competitive manner. SCH 546738 potently and specifically inhibits CXCR3-mediated chemotaxis in human activated T cells with IC_{90} about 10 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	SCH 546738 has strong cross-species activities with IC_{50} of 1.3 nM, 6.4 nM, 5.9 nM and 4.2 nM in inhibiting the binding of [^{125}I]hCXCL10 to CXCR3 of monkey, dog, mouse and rat origin, respectively. SCH 546738 is a selective and potent CXCR3 antagonist with a good PK for in vivo studies[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	The preparation of human activated T cells is performed. Human peripheral blood lymphocytes are prepared, depleted of monocytes, and stimulated for 2 days with 1 μg/mL PHA and 100 U/mL IL-2 in RPMI 1640 supplemented with 10% fetal bovine serum (FBS), 2 mM L-Glutamine, 1% non-essential amino acids and 2 mM HEPES. Following stimulation, peripheral blood lymphocytes are cultured in above media containing 5% conditioned media for up to 15 days. uman activated T cell chemotaxis assays ae performed using 96-well ChemoTx microplates with a 3 μm filter. Activated T cells are washed with RPMI medium twice, and then resuspended in the medium containing 20% FBS. 1.25×10^5 cells/reaction are mixed with indicated concentrations of SCH 546738 (1, 10 or 100 nM) and placed on the filter. SCH 546738 and chemokines are mixed and placed in the bottom well of the ChemoTx system. After 2.5 hours incubation at 37°C/5% CO_2, the cells are scraped off and the plate system is centrifuged for 5 minutes at 1000 RPM. The filter screen is then removed and the ChemoTx plate is inverted into a 96 well plate with a funnel plate. The plate system is centrifuged for 5 minutes at 1000 RPM. The volume in the wells is brought to 100 μL with assay buffer and the plates are rested for approximately 15 minutes at room temperature. The number of migrated cells is measured using the Cell Titer Glo Luminescent Assay. Chemotaxis is expressed as a chemotactic index, which is a ratio versus the one without chemokines[1] MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Female C57BL/6 mice are used. For immunization, 150 μg MOG35-55 peptide prepared by Princeton Biomolecules and 300 μg killed Mycobacterium tuberculosis are mixed in CFA and injected s.c. in two 50-μL injections over the flanks on day 1. Also, 200 ng of pertussis toxin is injected i.v. on days 0 and 2. SCH 546738 is administered orally 30 mpk in C57BL/6 mice twice daily. Dosing with SCH 546738 started at day 0, 24 h prior to MOG35-55 immunization (day 1). Mice are monitored daily and assessed for clinical signs of disease in a blinded fashion according to the following criteria: 0, no signs of disease; 1, tail paralysis; 2, limp tail and hind limb weakness; 3, hind limb paralysis; 4, hind limb plus forelimb paralysis; and 5, moribund or dead. Cumulative clinical scores are calculated by adding daily scores from the day of immunization until the end of the experiment. Mean clinical scores at separate days and mean maximal scores are calculated by adding the scores of individual mice and dividing with the number of mice in each group, including mice not developing signs of EAE. Rats[1] Male Lewis rats challenged by injection of 50 μL (30 mg) of a guinea pig spinal cord homogenate in complete Freund's adjuvant (CFA) into one footpad. SCH 546738 or 0.4% methylcellulose (vehicle) is orally administered at the indicated dose (0.2 mL) twice a day, starting on the day before transplantation until the day of graft rejection. SCH 546738 is administered orally at 10 mg/kg (mpk) in Lewis rats. To test whether SCH 546738 enhances the effect of conventional immunosuppressive reagent, the recipients are received treatment with subtherapeutic dose of CsA for one week combined with treatment with SCH 546738. Graft survival is analyzed using the log-rank test. The parametric data are analyzed by Student t test (2-tailed) using GraphPad InStat version. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Hepatol. 2016 Jan;64(1):160-70.

- Nat Struct Mol Biol. 2024 Jan 4.
- Nat Commun. 2017 Nov 17;8(1):1571.
- J Allergy Clin Immunol. 2016 Jul;138(1):114-122.e4.
- Sci Adv. 2023 Apr 28;9(17):eadg0654.

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REFERENCES

[1]. Jenh CH, et al. A selective and potent CXCR3 antagonist SCH 546738 attenuates the development of autoimmune diseases and delays graft rejection. BMC Immunol. 2012 Jan 10;13:2.

[2]. Zhang X, et al. CXC chemokine receptor 3 promotes steatohepatitis in mice through mediating inflammatory cytokines, macrophages and autophagy. J Hepatol. 2016 Jan;64(1):160-70.

[3]. Yue C, et al. STAT3 in $CD8^+$ T Cells Inhibits Their Tumor Accumulation by Downregulating CXCR3/CXCL10 Axis. Cancer Immunol Res. 2015 Aug;3(8):864-870.

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