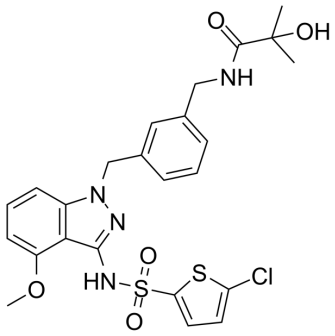
GSK2239633A

Cat. No.:	HY-100183
CAS No.:	1240516-71-5
Molecular Formula:	$C_{24}H_{25}ClN_4O_5S_2$
Molecular Weight:	549.06
Target:	CCR
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 : ≥ 250 mg/mL (455.32 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8213 mL	9.1065 mL	18.2129 mL
5 mM	0.3643 mL	1.8213 mL	3.6426 mL
10 mM	0.1821 mL	0.9106 mL	1.8213 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: ≥ 2.08 mg/mL (3.79 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.79 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GSK2239633A is a CC-chemokine receptor 4 (CCR4) antagonist, which inhibits the binding of [^{125}I]-TARC to human CCR4 with a pIC_{50} of 7.96 ± 0.11.

IC_{50} & Target

[^{125}I]-TARC-CCR4

7.96 (pIC_{50})

In Vitro

The GSK2239633A is an allosteric antagonist of human CCR4. GSK2239633A inhibits the binding of [^{125}I]-TARC to human CCR4 with a pIC_{50} of 7.96±0.11 and also inhibits thymus- and activation-regulated chemokine-induced (TARC)-induced increases in the F-actin content of isolated human $CD4^+$ $CCR4^+$ T-cells with a pA_2 of 7.11±0.29[1]. The effect of GSK2239633A

	(Compound 3) on CCL17-induced increases in the F-actin content of human $CD4^+$ $CCR4^+$ T cells is measured. The pEC_{50} value is 8.79±0.22[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Following intravenous dosing, plasma GSK2239633A displays rapid, bi-phasic distribution and slow terminal elimination ($t_{1/2}$: 13.5 hours), suggesting that GSK2239633A is a low to moderate clearance drug. Following oral dosing, blood levels of GSK2239633A reach C_{max} rapidly (median t_{max}: 1.0-1.5 hours). Estimated GSK2239633A bioavailability is low with a maximum value determined of only 16%[1]. GSK2239633A (Compound 9) demonstrates good pharmacokinetic data in preclinical animal studies (bioavailability in rats and beagle dogs 85% and 97% respectively)[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Blood is taken from normal volunteers who have taken no medication within the previous 10 days and chemokine-induced increases in the filamentous (F)-actin content of $CD4^+$ $CCR4^+$ T cells are measured. Briefly, the peripheral blood mononuclear cells (PBMC) are isolated and stained with fluorescein isothiocyanate-conjugated anti-human CD4 and phycoerythrin-conjugated anti-CCR4 antibodies. The cells are then incubated with GSK2239633A (1 μM) or vehicle (0.1% DMSO) for 30 min at 37°C before stimulation with agonist for 15 sec. The assay is terminated by addition of 3% formaldehyde. The fixed cells are stained with Alexa fluor-647 phalloidin and the mean fluorescence intensity of 1000 $CD4^+$ $CCR4^+$ cells per sample is determined. This is expressed as a fraction of the mean intensity of the $CD4^+$ $CCR4^-$ cells in the same sample[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Rats and Dogs[3] Pharmacokinetics are determined in male Wistar Han rats (277-305 g) or male Sprague Dawley (crl:CD(SD)) rats 277-305 g) and male Beagle dogs (14-16 kg; aged approximately 3-4 years) following single oral and intravenous administration to aid prediction of the likely human pharmacokinetics using precedented physiological scaling techniques. In the rat, compounds (e.g., GSK2239633A) are dosed intravenously and orally to 2 rats per compound per route. Nominal doses of 1 mg/kg are used for intravenous (iv) and oral (po) administration and studies are conducted following routine animal husbandry methods. Rats are housed in standard holding cages and maintained in a controlled environment with free access to food and water. Serial blood samples are collected via a temporary cannula inserted into the tail vein of all animals. For the intravenously dosed animals the cannula is inserted into a vein discrete from that used for dosing. The dogs are kept in slings for no longer than 2 h following the end of dosing on each phase of the study. Compounds (e.g., GSK2239633A) are dosed intravenously (bolus, 0.5 mg/kg) using an angiocath and orally (gavage; 1 mg/kg) to two male Beagle dogs per compound in a cross over design. Serial blood samples are collected from the cephalic vein via an angiocath for the first 2 h post dose and via direct venipuncture for the remainder of the study. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Cahn A, et al. Safety, tolerability, pharmacokinetics and pharmacodynamics of GSK2239633, a CC-chemokine receptor 4 antagonist, in healthy male subjects: results from an open-label and from a randomised study. BMC Pharmacol Toxicol. 2013 Feb 28;14:14.

[2]. Slack RJ, et al. Antagonism of human CC-chemokine receptor 4 can be achieved through three distinct binding sites on the receptor. Pharmacol Res Perspect. 2013 Dec;1(2):e00019.

[3]. Miah AH, et al. Identification of pyrazolopyrimidine arylsulfonamides as CC-chemokine receptor 4 (CCR4) antagonists. Bioorg Med Chem. 2017 Oct 15;25(20):5327-5340.

Caution: Product has not been fully validated for medical applications. For research use only.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA