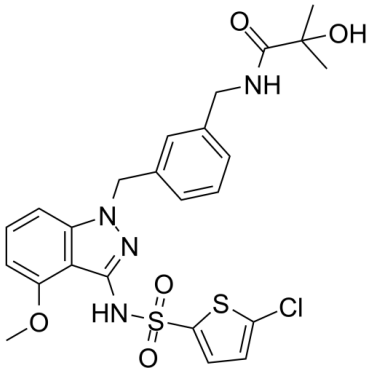
Data Sheet

Product Name:	GSK2239633A
Cat. No.:	CS-0018178
CAS No.:	1240516-71-5
Molecular Formula:	C24H25ClN4O5S2
Molecular Weight:	549.06
Target:	CCR
Pathway:	GPCR/G Protein; Immunology/Inflammation
Solubility:	DMSO : ≥ 250 mg/mL (455.32 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: CCR4[1] **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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: GSK2239633A is prepared in vehicle (0.1% DMSO)[2].[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].
Animal Administration: GSK2239633A is formulated as solutions in DMSO:PEG 200:Water (5:45:50)[3].[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.

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.

CAIndexNames:

Propanamide, N-[[3-[[3-[[(5-chloro-2-thienyl)sulfonyl]amino]-4-methoxy-1H-indazol-1-yl]methyl]phenyl]methyl]-2-hydroxy-2-methyl-

SMILES:

CC(C)(O)C(NCC1=CC=CC(CN2N=C(NS(=O)(C3=CC=C(Cl)S3)=O)C4=C2C=CC=C4OC)=C1)=O

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

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