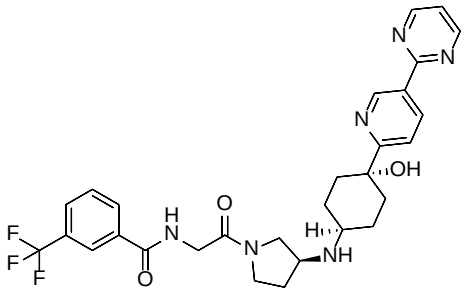
Product data sheet

MedKoo Cat#: 510288 Name: PF4136309 CAS#: 1341224-83-6 Chemical Formula: $C_{29}H_{31}F_3N_6O_3$ Exact Mass: 568.2410 Molecular Weight: 568.59	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

PF-4136309, also known as INCB8761, is an orally available human chemokine receptor 2 (CCR2) antagonist with potential immunomodulating and antineoplastic activities. Upon oral administration, CCR2 antagonist PF-04136309 specifically binds to CCR2 and prevents binding of the endothelium-derived chemokine ligand CLL2 (monocyte chemoattractant protein-1 or MCP1) to its receptor CCR2, which may result in inhibition of CCR2 activation and signal transduction. This may inhibit inflammatory processes as well as angiogenesis, tumor cell migration, and tumor cell proliferation.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	5.0	8.8
Ethanol	20.0	35.2

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.76 mL	8.79 mL	17.59 mL
5 mM	0.35 mL	1.76 mL	3.52 mL
10 mM	0.18 mL	0.88 mL	1.76 mL
50 mM	0.04 mL	0.18 mL	0.35 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Xue CB, Wang A, Han Q, Zhang Y, Cao G, Feng H, Huang T, Zheng C, Xia M, Zhang K, Kong L, Glenn J, Anand R, Meloni D, Robinson DJ, Shao L, Storace L, Li M, Hughes RO, Devraj R, Morton PA, Rogier DJ, Covington M, Scherle P, Diamond S, Emm T, Yeleswaram S, Contel N, Vaddi K, Newton R, Hollis G, Metcalf B. Discovery of INCB8761/PF-4136309, a Potent, Selective, and Orally Bioavailable CCR2 Antagonist. ACS Med Chem Lett. 2011 Oct 5;2(12):913-8. doi: 10.1021/ml200199c. PMID: 24900280; PMCID: PMC4018168.

In vivo study

1. Xue CB, Wang A, Han Q, Zhang Y, Cao G, Feng H, Huang T, Zheng C, Xia M, Zhang K, Kong L, Glenn J, Anand R, Meloni D, Robinson DJ, Shao L, Storace L, Li M, Hughes RO, Devraj R, Morton PA, Rogier DJ, Covington M, Scherle P, Diamond S, Emm T, Yeleswaram S, Contel N, Vaddi K, Newton R, Hollis G, Metcalf B. Discovery of INCB8761/PF-4136309, a Potent, Selective, and Orally Bioavailable CCR2 Antagonist. ACS Med Chem Lett. 2011 Oct 5;2(12):913-8. doi: 10.1021/ml200199c. PMID: 24900280; PMCID: PMC4018168.

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7. Bioactivity

Biological target: PF-4136309 is a CCR2 antagonist with IC50s of 5.2 nM, 17 nM and 13 nM for human, mouse and rat CCR2.

In vitro activity

In addition to being a potent human CCR2 antagonist (Table 2), PF-4136309 is also a potent murine CCR2 antagonist, exhibiting IC50 values of 17 and 13 nM in mouse and rat binding assays and 16 and 2.8 nM in mouse and rat chemotaxis assays. In signaling assays, PF-4136309 is potent in inhibiting CCR2 mediated signaling events such as intracellular calcium mobilization and ERK (extracellular signal-regulated kinase) phosphorylation with IC50 values of 3.3 and 0.5 nM, respectively. Cerep screens revealed that PF-4136309 is a selective CCR2 inhibitor, showing no significant inhibitory activity at a concentration of 1 μM when tested against a panel of >50 ion channels, transporters, chemokine receptors including CCR1, CCR3, CCR5, CXCR3, and CXCR5, and additional GPCRs. In hERG patch clamp assay, PF-4136309 inhibited hERG potassium current with an IC50 of 20 μM.

Reference: ACS Med Chem Lett. 2011 Oct 5;2(12):913-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018168/

In vivo activity

The pharmacokinetics of PF-4136309 was assessed in rats and dogs (Table 4). Following iv administration of PF-4136309, the total systemic clearance was moderate in rats but low in dogs. The apparent steady-state volume of distribution (Vss) followed the same trend as in clearance, with high Vss in rats and low Vss in dogs. As a result, PF-4136309 exhibited a moderate half-life in both species after iv administration (2.5 and 2.4 h). When administered orally, PF-4136309 was absorbed rapidly, with peak concentration time (Tmax) at 1.2 h for rats and 0.25 h for dogs. A similar half-life was observed in both species between iv dosing and po dosing. PF-4136309 was well absorbed, with an oral bioavailability of 78% in both species.

Reference: ACS Med Chem Lett. 2011 Oct 5;2(12):913-8. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4018168/