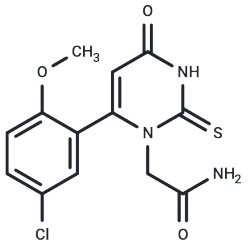
Data Sheet (Cat.No.T4090)

TargetMol

PF-06282999

Chemical Properties



CAS No. : 1435467-37-0

Formula: C13H12ClN3O3S

Molecular Weight: 325.77

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year
Actual storage temperature shall be subject to the COA.

Biological Description

Description	PF-06282999, a potent and selective myeloperoxidase inhibitor, is potentially useful for the treatment of cardiovascular diseases.
Targets(IC50)	Glutathione Peroxidase
In vitro	The estimated EC50 for total 8 concentration in plasma is 3.8 μM, which corresponds well with the IC50 value obtained in the human whole blood assay of 1.9 μM.
In vivo	Approximately 26-32% of the intravenous (iv) dose of PF-06282999 is excreted unchanged in the urine of rats, dogs, and monkeys, indicating the compound's distribution and excretion patterns across different species. It demonstrates favorable distribution characteristics, with steady state distribution volumes (Vdss) between 0.5-2.1 L/kg across mice, rats, dogs, and monkeys. Upon oral administration, PF-06282999 is rapidly absorbed (Tmax=0.78-1.70 h) with high oral bioavailability of 100%, 86%, 75%, and 76% in mice, rats, dogs, and monkeys, respectively. Blood/plasma ratios of PF-06282999 in these species, along with humans, suggest consistent distribution into both plasma and red blood cells. The pharmacokinetic profile of PF-06282999 reveals low clearance (CLp) in mice, dogs, and monkeys, and moderate CLp in rats, coupled with terminal plasma elimination half-lives (t1/2) spanning from 0.75 to 3.3 hours across the four species, underlining its pharmacokinetic behavior and potential for further pharmacological exploration.
Kinase Assay	Test compound is incubated with human whole blood stimulated with bacterial LPS for 4 h, followed by capture of MPO on immobilized anti-MPO antibody coated plates. The captured MPO is washed and residual MPO activity is determined using Amplex Red and H2O2.
Animal Research	In order to ascertain whether the advances noted in the in vitro and ex vivo assays for candidate thiouracil derivatives translated to effective irreversible inhibition of MPO in vivo, PF-06282999 is also advanced to an in vivo pharmacology study in cynomolgus monkeys using iv endotoxin (LPS) challenge, a classic model of inflammatory leukocyte activation with corresponding MPO activation demonstrated in various species including human. In this randomized crossover study, cynomolgus monkeys are orally administered either vehicle or PF-06282999 (5, 20, and 80 mg/kg) 1 h after iv administration of LPS. Blood is sampled throughout the study and heparinized plasma prepared for MPO activity measurements as well as determination of 8 plasma concentrations. Total MPO is captured using anti-MPO antibody coated plates, and

Animal Research	following exchange of plasma for drug-free assay media, the residual activity of the captured MPO is measured using the peroxidation of Amplex Red. A mixed effect sigmoid model is applied to study the relationship between plasma exposure of PF-06282999 and the MPO capture activity at 2 h after dose and 3 h after LPS administration, which corresponds to the peak of MPO activity.

Solubility Information

Solubility	DMSO: 55 mg/mL (168.83 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2 mg/mL (6.14 mM),Sonication is recommended. *Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.*

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	3.0697 mL	15.3483 mL	30.6965 mL
5 mM	0.6139 mL	3.0697 mL	6.1393 mL
10 mM	0.307 mL	1.5348 mL	3.0697 mL
50 mM	0.0614 mL	0.307 mL	0.6139 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Dong JQ, et al. Pharmacokinetics and Disposition of the Thiouracil Derivative PF-06282999, an Orally Bioavailable, Irreversible Inactivator of Myeloperoxidase Enzyme, Across Animals and Humans. Drug Metab Dispos. 2016 Feb;44 (2):209-19.

Ruggeri RB, et al. Discovery of 2-(6-(5-Chloro-2-methoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl) acetamide (PF-062821999): A Highly Selective Mechanism-Based Myeloperoxidase Inhibitor for the Treatment of Cardiovascular Diseases. J Med Chem. 20