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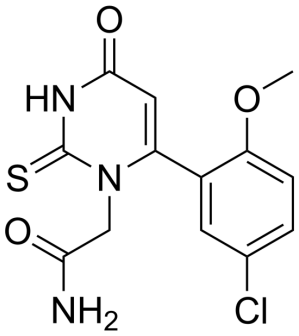
PF-06282999

Cat. No.:	HY-19321
CAS No.:	1435467-37-0
Molecular Formula:	$C_{13}H_{12}ClN_3O_3S$
Molecular Weight:	325.77
Target:	Glutathione Peroxidase
Pathway:	Apoptosis; Metabolic Enzyme/Protease
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 : 100 mg/mL (306.97 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.0697 mL	15.3483 mL	30.6965 mL
	5 mM	0.6139 mL	3.0697 mL	6.1393 mL
	10 mM	0.3070 mL	1.5348 mL	3.0697 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: 2.5 mg/mL (7.67 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (7.67 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.5 mg/mL (7.67 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

PF-06282999 is a potent and selective myeloperoxidase inhibitor which is potential useful for the treatment of cardiovascular diseases.

In Vitro

PF-06282999 (Compound 8) is a potent and selective myeloperoxidase inhibitor. The estimated EC_{50} for total PF-06282999 concentration in plasma is 3.8 μM, which corresponds well with the IC_{50} value obtained in the human whole blood assay of 1.9 μM[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo	PF-06282999 is moderately bound to plasma proteins across preclinical species and humans. The blood/plasma ratios for PF-06282999 are 1.1, 1.1, 0.91, 1.2, and 0.94 in mice, rats, dogs, monkeys, and humans, respectively, suggesting that PF-06282999 is equally distributed into plasma and red blood cells[1]. The in vivo pharmacokinetics of PF-06282999 are examined in greater detail in mice, rats, dogs, and monkeys, wherein it is demonstrated to have low CLp in mice (10.1 mL/min/kg), dogs (3.39 mL/min/kg), monkeys (10.3 mL/min/kg) and moderate CLp in rats (41.8 mL/min/kg). The terminal plasma elimination half-lives (t1/2) range from 0.75 to 3.3 h in the four species. Approximately 26-32% of the iv dose of PF-06282999 is excreted in the unchanged form in rat, dog, and monkey urine, wherein it is also shown that it is well distributed with steady state distribution volumes (Vdss) ranging from 0.5-2.1 L/kg in mice, rats, dogs, and monkeys. Following oral administration, PF-06282999 is rapidly (Tmax=0.78-1.70 h) and well absorbed in mice, rats, dogs, and monkeys with oral bioavailability values of 100%, 86%, 75%, and 76%, respectively[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	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 H_2O_2. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	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 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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. 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.

[2]. Ruggeri RB, et al. Discovery of 2-(6-(5-Chloro-2-methoxyphenyl)-4-oxo-2-thioxo-3,4-dihydropyrimidin-1(2H)-yl)acetamide (PF-06282999): A Highly Selective Mechanism-Based Myeloperoxidase Inhibitor for the Treatment of Cardiovascular Diseases. J Med Chem. 20

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