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产品名称: **PF-06282999**
 产品别名: **PF-06282999**

生物活性:					
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] .				
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 (t _{1/2}) 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 (V _{dss}) ranging from 0.5-2.1 L/kg in mice, rats, dogs, and monkeys. Following oral administration, PF-06282999 is rapidly (T _{max} =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] .				
Solvent&Solubility	In Vitro: DMSO : ≥ 32 mg/mL (98.23 mM) * "≥" means soluble, but saturation unknown.				
		Solvent Mass Concentration	1 mg	5 mg	10 mg
	Preparing	1 mM	3.0697 mL	15.3483 mL	30.6965 mL
	Stock Solutions	5 mM	0.6139 mL	3.0697 mL	6.1393 mL
		10 mM	0.3070 mL	1.5348 mL	3.0697 mL
	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。 储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。				
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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实验参考:

Animal Administration	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.
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 H ₂ O ₂ .
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. <i>Drug Metab Dispos.</i> 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. <i>J Med Chem.</i> 20

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