

产品名称: **Crizotinib (hydrochloride)**

产品别名: 克里唑替尼盐酸

生物活性:				
Description	Crizotinib hydrochloride (PF-02341066 hydrochloride) is an orally bioavailable, selective, and ATP-competitive dual ALK and c-Met inhibitor with IC50s of 20 and 8 nM, respectively. Crizotinib hydrochloride (PF-02341066 hydrochloride) inhibits tyrosine phosphorylation of NPM-ALK and tyrosine phosphorylation of c-Met with IC50s of 24 and 11 nM in cell-based assays, respectively. It is also a ROS proto-oncogene 1 (ROS1) inhibitor. Crizotinib hydrochloride (PF-02341066 hydrochloride) has effective tumor growth inhibition[1][2][3].			
IC ₅₀ & Target	IC50: 20 nM (ALK), 8 nM (c-Met)[3]			
In Vitro	PF-2341066 displays similar potency against c-Met phosphorylation in mIMCD3 mouse or MDCK canine epithelial cells with IC50 of 5 nM and 20 nM, respectively. PF-2341066 shows improved or similar activity against NIH3T3 cells engineered to express c-Met ATP-binding site mutants V1092I or H1094R or the P-loop mutant M1250T with IC50 of 19 nM, 2 nM and 15 nM, respectively, compared with NIH3T3 cells expressing wild-type receptor with IC50 of 13 nM. In contrast, a marked shift in potency of PF-2341066 is observed against cells engineered to express c-Met activation loop mutants Y1230C and Y1235D with IC50 of 127 nM and 92 nM, respectively, compared with wild-type receptor. PF-2341066 also potently prevents the phosphorylation of c-Met in NCI-H69 and HOP92 cells, with IC50 of 13 nM and 16 nM, respectively, which express the endogenous c-Met variants R988C and T1010I, respectively[1]. PF-2341066 also potently inhibits NPM-ALK phosphorylation in Karpas299 or SU-DHL-1 ALCL cells with an IC50 of 24 nM. PF-2341066 potently prevents cell proliferation, which is associated with G(1)-S-phase cell cycle arrest and induction of apoptosis in ALK-positive ALCL cells with IC50 of 30 nM, but not ALK-negative lymphoma cells[2].			
In Vivo	PF-2341066 reveals the ability to cause marked regression of large established tumors (> 600 mm ³) in both the 50 mg/kg/day and 75 mg/kg/day treatment cohorts, with a 60% decrease in mean tumor volume over the 43-day administration schedule in the GTL-16 model. In an another study, PF-2341066 displays the ability to completely inhibits GTL-16 tumor growth for >3 months, with only 1 of 12 mice exhibiting a significant increase in tumor growth over the 3-month treatment schedule at 50 mg/kg/day. A significant dose-dependent reduction of CD31-positive endothelial cells is observed at 12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day in GTL-16 tumors, indicating that inhibition of MVD shows a dose-dependent correlation to antitumor efficacy. PF-2341066 displays a significant dose-dependent reduction of human VEGFA and IL-8 plasma levels in both the GTL-16 and U87MG models. Marked inhibition of phosphorylated c-Met, Akt, Erk, PLCA1, and STAT5 levels is observed in GTL-16 tumors following p.o. administration of PF-2341066[1]. Treatment of c-MET-amplified GTL-16 xenografts with 50 mg/kg PF-2341066 elicits tumor regression that is associated with a slow reduction in 18F-FDG uptake and decreases expression of the glucose transporter 1, GLUT-1[4].			
	<i>In Vitro:</i> H₂O : 50 mg/mL (102.71 mM; Need ultrasonic) DMSO : ≥ 4.9 mg/mL (10.07 mM) * "≥" means soluble, but saturation unknown.			
		Solvent Mass Concentration	1 mg	5 mg
				10 mg

Solvent&Solubility	Preparing	1 mM	2.0542 mL	10.2712 mL	20.5423 mL
	Stock Solutions	5 mM	0.4108 mL	2.0542 mL	4.1085 mL
		10 mM	0.2054 mL	1.0271 mL	2.0542 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℃, 6 months; -20℃, 1 month。-80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。				
References	[1]. Zou HY, et al. An orally available small-molecule inhibitor of c-Met, PF-2341066, exhibits cytoreductive antitumor efficacy through antiproliferative and antiangiogenic mechanisms. Cancer Res. 2007, 67(9), 4408-4417. [2]. Christensen JG, et al. Cytoreductive antitumor activity of PF-2341066, a novel inhibitor of anaplastic lymphoma kinase and c-Met, in experimental models of anaplastic large-cell lymphoma. Mol Cancer Ther. 2007, 6(12 Pt 1), 3314-3322. [3]. Cui JJ, et al. Structure based drug design of crizotinib (PF-02341066), a potent and selective dual inhibitor of mesenchymal-epithelial transition factor (c-MET) kinase and anaplastic lymphoma kinase (ALK). J Med Chem. 2011 Sep 22;54(18):6342-63. [4]. Cullinane C, et al. Differential (18)F-FDG and 3'-deoxy-3'-(18)F-fluorothymidine PET responses to pharmacologic inhibition of the c-MET receptor in preclinical tumor models. J Nucl Med. 2011 Aug;52(8):1261-7				
实验参考:					
Cell Assay	Tumor cells are seeded in 96-well plates at low density in media supplemented with 10% FBS (growth media) and transferred to serum-free media (0% FBS and 0.04% BSA) after 24 h. Appropriate controls or designated concentrations of PF-2341066 are added to each well, and cells are incubated for 24 to 72 h. Human umbilical vascular endothelial cells (HUVEC) are seeded in 96-well plates in EGM2 media for 5 to 6 h at > 20,000 cells per well and transferred to serum-free media overnight. The following day, appropriate controls or designated concentrations of PF-2341066 are added to each well, and after 1 h incubation, HGF is added to designated wells at 100 ng/mL. A 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay is done to determine the relative tumor cell or HUVEC numbers. [1]				
Animal Administration	Athymic mice bearing xenografts (300-800 mm³) are given PF-2341066 in water by oral gavage at designated dose levels. At designated times following PF-2341066 administration, mice are humanely euthanized, and tumors are resected. Tumors are snap frozen and pulverized using a liquid nitrogen-cooled cryomortar and pestle, protein lysates are generated, and protein concentrations are determined using a BSA assay. The level of total and phosphorylated protein is determined using a capture ELISA or immunoprecipitation-immunoblotting method. [1]				
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源叶生物