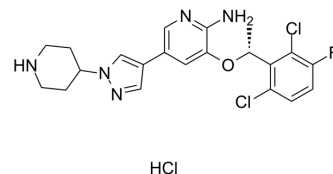


## Crizotinib hydrochloride

<b>Cat. No.:</b>	HY-50878A
<b>CAS No.:</b>	1415560-69-8
<b>Molecular Formula:</b>	C <sub>21</sub> H <sub>23</sub> Cl <sub>3</sub> FN <sub>5</sub> O
<b>Molecular Weight:</b>	486.8
<b>Target:</b>	Anaplastic lymphoma kinase (ALK); c-Met/HGFR; ROS Kinase; Autophagy
<b>Pathway:</b>	Protein Tyrosine Kinase/RTK; Autophagy
<b>Storage:</b>	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



### SOLVENT & SOLUBILITY

<b>In Vitro</b>	H <sub>2</sub> O : 50 mg/mL (102.71 mM; Need ultrasonic)																				
	DMSO : ≥ 4.9 mg/mL (10.07 mM) * "≥" means soluble, but saturation unknown.																				
<b>Preparing Stock Solutions</b>	<table border="1"> <thead> <tr> <th rowspan="2">Solvent Concentration</th> <th>Mass</th> <th>1 mg</th> <th>5 mg</th> <th>10 mg</th> </tr> </thead> <tbody> <tr> <td>1 mM</td> <td></td> <td>2.0542 mL</td> <td>10.2712 mL</td> <td>20.5423 mL</td> </tr> <tr> <td>5 mM</td> <td></td> <td>0.4108 mL</td> <td>2.0542 mL</td> <td>4.1085 mL</td> </tr> <tr> <td>10 mM</td> <td></td> <td>0.2054 mL</td> <td>1.0271 mL</td> <td>2.0542 mL</td> </tr> </tbody> </table>	Solvent Concentration	Mass	1 mg	5 mg	10 mg	1 mM		2.0542 mL	10.2712 mL	20.5423 mL	5 mM		0.4108 mL	2.0542 mL	4.1085 mL	10 mM		0.2054 mL	1.0271 mL	2.0542 mL
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Please refer to the solubility information to select the appropriate solvent.																					
<b>In Vivo</b>	1. Add each solvent one by one: PBS Solubility: 55 mg/mL (112.98 mM); Clear solution; Need ultrasonic																				

### BIOLOGICAL ACTIVITY

<b>Description</b>	Crizotinib hydrochloride (PF-02341066 hydrochloride) is an orally bioavailable, selective, and ATP-competitive dual ALK and c-Met inhibitor with IC <sub>50</sub> s of 20 and 8 nM, respectively. Crizotinib hydrochloride (PF-02341066 hydrochloride) inhibits tyrosine phosphorylation of NPM-ALK and tyrosine phosphorylation of c-Met with IC <sub>50</sub> s 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 <sup>[1][2][3]</sup> .
<b>IC<sub>50</sub> &amp; Target</b>	IC <sub>50</sub> : 20 nM (ALK), 8 nM (c-Met) <sup>[3]</sup>
<b>In Vitro</b>	PF-2341066 displays similar potency against c-Met phosphorylation in mIMCD3 mouse or MDCK canine epithelial cells with IC <sub>50</sub> 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 IC <sub>50</sub> of 19 nM, 2 nM and 15 nM, respectively, compared with NIH3T3 cells expressing wild-type receptor with IC <sub>50</sub> 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 IC<sub>50</sub> 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 IC<sub>50</sub> of 13 nM and 16 nM, respectively, which express the endogenous c-Met variants R988C and T1010I, respectively<sup>[1]</sup>.

PF-2341066 also potently inhibits NPM-ALK phosphorylation in Karpas299 or SU-DHL-1 ALCL cells with an IC<sub>50</sub> 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 IC<sub>50</sub> of 30 nM, but not ALK-negative lymphoma cells<sup>[2]</sup>.

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

#### In Vivo

PF-2341066 reveals the ability to cause marked regression of large established tumors (> 600 mm<sup>3</sup>) 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 another study, PF-2341066 displays the ability to completely inhibit 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, PLC $\lambda$ 1, and STAT5 levels is observed in GTL-16 tumors following p.o. administration of PF-2341066<sup>[1]</sup>.

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<sup>[4]</sup>.

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

## PROTOCOL

#### Cell Assay <sup>[1]</sup>

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.

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

#### Animal Administration <sup>[1]</sup>

Athymic mice bearing xenografts (300-800 mm<sup>3</sup>) 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.

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

## CUSTOMER VALIDATION

- J Hematol Oncol. 2018 Aug 29;11(1):109.
- Cancer Discov. 2018 Mar;8(3):354-369.
- Nat Biomed Eng. 2018 Aug;2(8):578-588.
- Blood. 2021 Oct 17;blood.2020008136.
- Sci Transl Med. 1 Sep 2021.

## REFERENCES

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- [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
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**Caution: Product has not been fully validated for medical applications. For research use only.**

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