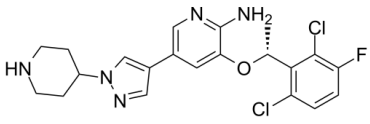
Data Sheet

Product Name:	Crizotinib (hydrochloride)
Cat. No.:	CS-1156
CAS No.:	1415560-69-8
Molecular Formula:	C21H23Cl3FN5O
Molecular Weight:	486.80
Target:	ALK; Autophagy; c-Met/HGFR; ROS
Pathway:	Autophagy; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : ≥ 4.9 mg/mL (10.07 mM); H2O : 50 mg/mL (102.71 mM; Need ultrasonic)



H−Cl

BIOLOGICAL ACTIVITY:

Crizotinib hydrochloride (PF-02341066 hydrochloride) is an orally bioavailable, selective, and ATP-competitive dual **ALK** and **c-Met** inhibitor with **IC_{50}**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_{50}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[1][2][3]. IC50 & 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 IC_{50} of 5 nM and 20 nM, respectivly. 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_{50} of 19 nM, 2 nM and 15 nM, respectively, compared with NIH3T3 cells expressing wild-type receptor with IC_{50} 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_{50} 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_{50} 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 IC_{50} 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_{50} 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, PLCλ1, 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]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. **Animal Administration:** PF-2341066 is formulated in water.[1]Athymic mice bearing xenografts (300-800 mm^3) 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.

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

CAIndexNames:

2-Pyridinamine, 3-[(1R)-1-(2,6-dichloro-3-fluorophenyl)ethoxy]-5-[1-(4-piperidinyl)-1H-pyrazol-4-yl]-, hydrochloride (1:1)

SMILES:

ClC1=C(F)C=CC(Cl)=C1[C@H](OC2=CC(C3=CN(N=C3)C4CCNCC4)=CN=C2N)C.[H]Cl

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA