Biological Activity

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 V1091I or H1049R or the F-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 R688C and T1010I, respectively. PF-2341066 is >1,000-fold selective for the VEGFR2 and PDGFRβ RTKs, >250-fold selective for IRK and Lck, and >40- to 60-fold selective for Tie2, TrkA, and TrkB, all compared with c-Met. PF-2341066 is 20- to 30-fold selective for RON and Axl RTKs. In contrast, PF-2341066 shows a near-equivalent IC50 of 24 nM against the nucleophosmin (NPM)-anaplastic lymphoma kinase (ALK) oncogenic fusion variant of the ALK RTK expressed by the Karpas299 human anaplastic large cell lymphoma (ALCL) cell line. PF-2341066 inhibits c-Met-dependent neoplastic phenotypes of cancer cells and angiogenic phenotypes of endothelial cells. PF-2341066 suppresses human GTL-16 gastric carcinoma cell growth with IC50 of 9.7 nM. PF-2341066 induces apoptosis in GTL-16 cells with IC50 of 8.4 nM. PF-2341066 inhibits HGF-stimulated human NCI-H441 lung carcinoma cell migration and invasion with IC50 of 11 nM and 6.1 nM, respectively. PF-2341066 inhibits MDCK cell scattering with IC50 of 16 nM. PF-2341066 prevents HGF-stimulated c-Met phosphorylation, cell survival, and Matrigel invasion with IC50 of 11 nM, 14 nM, and 35 nM, respectively. In addition, PF-2341066 prevents serum-stimulated HMVEC branching tubulogenesis (formation of vascular tubes) in fibrin gels. [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 G1-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] Besides, PF-2341066 prevents osteosarcoma behavior associated with primary tumor growth (i.e., proliferation and survival) as well as metastasis (eg, invasion and colonization).

In vivo

In the GTL-16 model, PF-2341066 reveals the ability to cause marked regression of large established tumors (>600 mm³) 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 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. In the NCI-H441 NSCLC model, a 43% decrease in mean tumor volume is observed at 50 mg/kg/day during the 38-day PF-2341066 administration cycle. In the Caki-1 RCC model, a 53% decrease in mean tumor volume is observed to be associated with decreased volume of each tumor by at least 30% at 50 mg/kg/day during the 33-day PF-2341066 administration cycle. PF-2341066 also reveals near-complete prevention of the growth of established tumors at 50 mg/kg/day in the U87MG glioblastoma or PC-3 prostate carcinoma xenograft models, with 97% or 84% inhibition on the final study day, respectively. In contrast, PF-2341066 p.o. given at 50 mg/kg/day does not significantly inhibit tumor growth in the MDA-MB-231 breast carcinoma model, or the DLD-1 colon carcinoma model. 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, PLCγ1, and STAT5 levels is observed in GTL-16 tumors following p.o. administration of PF-2341066.[1] P.o. administration of PF-2341066 to severe combined immunodeficient (SCID) mice bearing Karpas299(ALCL) tumor xenografts leads to dose-dependent, antitumor efficacy with complete regression of all tumors at the 100 mg/kg/day dose within 15 days of initial compound administration. In addition, inhibition of key NPM-ALK signaling mediators, including phospholipase C-gamma, signal transducers and activators of transcription 3, extracellular signal-regulated kinases, and Akt by PF-2341066 are observed at concentrations or dose levels, which correlated with inhibition of NPM-ALK phosphorylation and function.[2] PF-2341066 prevents osteosarcoma behavior associated with primary tumor growth (eg, proliferation and survival) as well as metastasis (eg, invasion and colonization).

Crizotinib (PF-02341066) Chemical Structure

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Toll Free: (877) 796-6397
-- USA and Canada only--
Fax: +1-713-796-9816
Orders: +1-832-582-8158
sales@selleckchem.com
Tech Support: +1-832-582-8158
Ext3
Monday-Friday
9:00 AM–5:00 PM (Central Time)
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**Clinical Trials**
Pf-2341066 is currently in a Phase III clinical trial in the treatment of non squamous lung cancer.

**Features**

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<th>Protocol (Only for Reference)</th>
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**Kinase Assay**

**Biochemical kinase assays**
c-Met catalytic activity is quantitated using a continuous-coupled spectrophotometric assay in which the time-dependent production of ADP by c-Met is determined by analysis of the rate of consumption of NADH. NADH consumption is measured by a decrease in absorbance at 340 nm by spectrophotometry at designated time points. To determine K_i values, PF-2341066 is introduced into test wells at various concentrations in the presence of assay reagents and incubated for 10 minutes at 37 °C. The assay is initiated by the addition of the c-Met enzyme.

**Cell Assay**

**Cell Lines**
GTL-16 gastric carcinoma cells and T47D breast carcinoma cells

**Concentrations**
0-256 nM

**Incubation Time**
1 hour

**Methods**
Cells including GTL-16 gastric carcinoma cells and T47D breast carcinoma cells are seeded in 96-well plates in media supplemented with 10% fetal bovine serum (FBS) and transferred to serum-free media (with 0.04% bovine serum albumin (BSA)) after 24 hours. In experiments investigating ligand-dependent RTK phosphorylation, corresponding growth factors are added for up to 20 minutes. After incubation of cells with PF-2341066 for 1 hour and/or appropriate ligands for the designated times, cells are washed once with HBSS supplemented with 1 mM Na_3VO_4, and protein lysates are generated from cells. Subsequently, phosphorylation of selected protein kinases is assessed by a sandwich ELISA method using specific capture antibodies used to coat 96-well plates and a detection antibody specific for phosphorylated tyrosine residues. Antibody-coated plates are (a) incubated in the presence of protein lysates at 4 °C overnight; (b) washed seven times in 1% Tween 20 in PBS; (c) incubated in a horseradish peroxidase–conjugated anti–total-phosphotyrosine (PY-20) antibody (1:500) for 30 min; (d) washed seven times again; (e) incubated in 3,3',5,5'-tetramethyl benzidine peroxidase substrate to initiate a colorimetric reaction that is stopped by adding 0.09 N H_2SO_4; and (f) measured for absorbance in 450 nm using a spectrophotometer.

**Animal Study**

**Animal Models**
Female or male nu/nu mice bearing NCI-H441, or DLD-1, or MDA-MB-231

**Formulation**

**Doses**
12.5 mg/kg/day, 25 mg/kg/day, and 50 mg/kg/day

**Administration**
Administered via p.o.

**References**


**Customer Reviews**

Data from [Int J Proteomics, 2011, 2011, Article ID 215496]
Crizotinib (PF-02341066) purchased from Selleck
Inhibition of signaling pathway activation in lung tumor cell lines by kinase inhibitors. Lung tumor cells were cultured in 10% FBS until reaching ~80% confluence and then the cells were starved in serum-free medium for overnight, followed by 4-hour treatment with the inhibitors. Cell lysates were then prepared and used for determination of the pathway activation signals by the CEER assay.

Data from [Nat Med, 2011, 17, 1116-1120]
Crizotinib (PF-02341066) purchased from Selleck
(c) Western blot analyses of p-Akt (Ser473) and p-S6RP (Ser235 and Ser236) in two RCT-E565 transplanted tumors treated with vehicle or PF-02341066 at 10 mg/kg/day.
last dose from mice treated with PF02341066 for 3 d. (d) Responses of RCT-E565 transplanted tumors in athymic mice to PF02341066 or vehicle. Data are means ± s.e.m. (each group, n = 6). *P < 0.005, **P < 0.001 (Student’s t test).

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