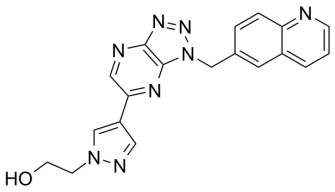
PF-04217903

Cat. No.:	HY-12017
CAS No.:	956905-27-4
Molecular Formula:	$C_{19}H_{16}N_8O$
Molecular Weight:	372.38
Target:	c-Met/HGFR
Pathway:	Protein Tyrosine Kinase/RTK
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (53.71 mM; Need ultrasonic)
Ethanol : < 1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6854 mL	13.4271 mL	26.8543 mL
5 mM	0.5371 mL	2.6854 mL	5.3709 mL
10 mM	0.2685 mL	1.3427 mL	2.6854 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2 mg/mL (5.37 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2 mg/mL (5.37 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2 mg/mL (5.37 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-04217903 is a potent ATP-competitive c-Met kinase inhibitor with K_i of 4.8 nM for human c-Met. PF-04217903 shows more than 1,000-fold selectivity relative to 208 kinases. Antiangiogenic properties[1][2].

IC_{50} & Target

Ki: 4.8 nM (human c-Met)[1]

In Vitro

PF-04217903 (0.1-10000 nM; 48-72 hours) inhibits proliferation of c-Met–amplified human GTL-16 gastric carcinoma and

H1993 NSCLC cells with IC_{50} values of 12 and 30 nM, respectively[1].
PF-04217903 (1.5-3333 nM; 48 hours) induces apoptosis of GTL-16 cells (IC_{50}=31 nM)[1].
PF-04217903 also inhibits HGF-mediated cell migration and Matrigel invasion in several c-Met–overexpressing tumor cell lines such as human NCI-H441 lung carcinoma and HT29 colon carcinoma with IC_{50} values comparable with those for inhibition of c-Met phosphorylation in these cell lines (IC_{50}=7-12.5 nM)[1].PF-04217903 displays similar potency to inhibit the activity of c-Met-H1094R, c-Met-R988C, and c-Met-T1010I with IC_{50} of 3.1 nM, 6.4 nM, and 6.7 nM, respectively, but has no inhibitory activity against c-Met-Y1230C with IC_{50} of >10 μM[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[1]

Cell Line:	GTL-16, H1993 cells
Concentration:	0.1, 1, 10, 100, 1000, 10000 nM
Incubation Time:	48-72 hours
Result:	Inhibited proliferation of c-Met–amplified human GTL-16 gastric carcinoma and H1993 NSCLC cells with IC_{50} values of 12 and 30 nM, respectively.

Apoptosis Analysis[1]

Cell Line:	GTL-16 cells
Concentration:	1.5-3333 nM
Incubation Time:	48 hours
Result:	Induced apoptosis of GTL-16 cells (IC_{50}=31 nM).

In Vivo

PF-04217903 (1-30 mg/kg; p.o.; daily for 16 days) shows dose-dependent tumor growth inhibition, which correlated with the inhibition in c-Met phosphorylation in these tumors[1].
PF-04217903 (5-50 mg/kg, p.o.; once daily for 3 days) dose dependently inhibits c-Met, Gab-1, Erk1/2, and AKT phosphorylation and induced apoptosis (cleaved caspase-3) in U87MG xenograft tumors at all dose levels. PF-04217903 phenolsulfonate shows a significant dose-dependent reduction of human IL-8 levels in both the U87MG and GTL-16 models and decreases human VEGFA levels in the GTL-16 model. PF-04217903 strongly induces phospho-PDGFRβ levels in U87MG xenograft tumors[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Female nu/nu mice (GTL-16 xenograft model)[1]
Dosage:	1, 3, 10, 30 mg/kg
Administration:	Oral; daily for 16 days
Result:	Showed dose-dependent tumor growth inhibition, and was correlated with the inhibition in c-Met phosphorylation in these tumors.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Timofeevski SL, et al. Enzymatic characterization of c-Met receptor tyrosine kinase oncogenic mutants and kinetic studies with aminopyridine and triazolopyrazine inhibitors. Biochemistry, 2009, 48(23), 5339-5349.

[2]. Zou HY, et al. Sensitivity of selected human tumor models to PF-04217903, a novel selective c-Met kinase inhibitor. Mol Cancer Ther. 2012 Apr;11(4):1036-47.

[3]. Cui JJ, et al. Discovery of a novel class of exquisitely selective mesenchymal-epithelial transition factor (c-MET) protein kinase inhibitors and identification of the clinical candidate 2-(4-(1-(quinolin-6-ylmethyl)-1H-[1,2,3]triazolo[4,5-b]pyrazin-6-yl)

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