PF-03814735

Cat. No.: HY-14574

CAS No.: 942487-16-3

Molecular Formula: $C_{23}H_{25}F_3N_6O_2$

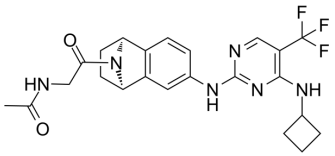
Molecular Weight: 474.48

Target: Aurora Kinase; VEGFR

Pathway: Cell Cycle/DNA Damage; Epigenetics; Protein Tyrosine Kinase/RTK

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (210.76 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1076 mL	10.5379 mL	21.0757 mL
5 mM	0.4215 mL	2.1076 mL	4.2151 mL
10 mM	0.2108 mL	1.0538 mL	2.1076 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: ≥ 2.5 mg/mL (5.27 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.27 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.27 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-03814735 is a potent, orally available, ATP-competitive and reversible aurora A and aurora B inhibitor with IC_{50}s of 0.8 and 0.5 nM, respectively.

IC_{50} & Target

Aurora 1 0.8 nM (IC_{50})	Aurora 2 5 nM (IC_{50})	Flt-1 10 nM (IC_{50})	FAK 22 nM (IC_{50})
TrkA	Met	FGFR1	

	30 nM (IC_{50})	100 nM (IC_{50})	100 nM (IC_{50})

In Vitro

In intact cells, the inhibitory activity of PF-03814735 on the Aurora1 and Aurora2 kinases reduces levels of phospho-Aurora1, phosphohistone H3, and phospho-Aurora2. PF-03814735 produces a block in cytokinesis, resulting in inhibition of cell proliferation and the formation of polyploid multinucleated cells[1]. Small cell lung cancer (SCLC) and, to a lesser extent, colon cancer lines are very sensitive to PF-03814735. The status of the Myc gene family and retinoblastoma pathway members significantly correlates with the efficacy of PF-03814735[2].

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

In Vivo

Once-daily oral administration of PF-03814735 to mice bearing human xenograft tumors produces a reduction in phosphohistone H3 in tumors at doses that are tolerable and that result in significant inhibition of tumor growth. The combination of PF-03814735 and docetaxel in xenograft mouse tumor models shows additive tumor growth inhibition[1]. PF-03814735 is much more effective in NCI-H82 xenografts when administered on a weekly dosing schedule at 80 mg/kg compared with a daily schedule at 15 mg/kg. PF-03814735 delayed growth by 23.5 days on the weekly schedule, which corresponds to 0.9 logs of net cell kill during the course of treatment[2].

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

PROTOCOL

Kinase Assay [1]

Aurora1 and Aurora2 proteins are produced as full-length His-tag recombinant proteins expressed in insect cells. For the Aurora2 kinase assay, phosphorylation of the substrate peptide by recombinant Aurora2 protein is assessed at 3 to 300 μM ATP and various concentrations of PF-03814735 over 60 min, at a substrate peptide concentration of 2 μM. Phosphorylation is linear over this time for all conditions. For the Aurora1 kinase assay, phosphorylation of the substrate peptide by recombinant Aurora1 protein is assessed by a scintillation proximity assay in a 96-well plate format in which the incorporation of 33P into the peptide substrate is measured by capturing the peptide on a streptavidin scintillation proximity assay bead[1].

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Cell Assay [1]

Cell lines are grown in appropriate media and evaluated after 48 h of exposure to either PF-03814735 or vehicle. Proliferation (as measured by an increase in cell number) is expressed as a percent of untreated controls. To evaluate the PF-03814735 exposure time required for antiproliferative activity, HL-60 cell cultures are cultured in RPMI medium supplemented with 15% heat-inactivated fetal bovine serum and exposed to various PF-03814735 concentrations for 4, 8, 12, 24, and 48 h, followed by a washout step and incubation with growth media without PF-03814735 for the remainder of the 72-h assay period. Continuous exposure to PF-03814735 for 72 h is also evaluated. Cell counts are determined by a Coulter Counter[1].

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Animal Administration [1]

Mice: Mice bearing s.c. HCT-116 xenograft tumors (250-400mm^3) are evaluated for plasma drug concentrations and tumor levels of phosphohistone H3 Ser10. Mice are treated with a single dose of PF-03814735 or vehicle by oral gavage and are sacrificed at 0.5, 1, 2, 3, 7, 16, or 24 h postdose (3-4 mice/time point)[1].

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CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Patent. US20180263995A1.

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REFERENCES

[1]. Jani JP, et al. PF-03814735, an orally bioavailable small molecule aurora kinase inhibitor for cancer therapy. Mol Cancer Ther. 2010 Apr;9(4):883-94.

[2]. Hook KE, et al. An integrated genomic approach to identify predictive biomarkers of response to the aurora kinase inhibitor PF-03814735. Mol Cancer Ther. 2012 Mar;11(3):710-9.

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