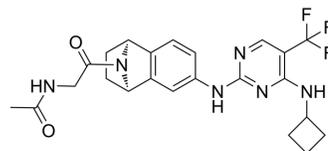


PF-03814735

Cat. No.:	HY-14574												
CAS No.:	942487-16-3												
Molecular Formula:	C ₂₃ H ₂₅ F ₃ N ₆ O ₂												
Molecular Weight:	474.48												
Target:	Aurora Kinase; VEGFR												
Pathway:	Cell Cycle/DNA Damage; Epigenetics; Protein Tyrosine Kinase/RTK												
Storage:	<table border="0"> <tr> <td>Powder</td> <td>-20°C</td> <td>3 years</td> </tr> <tr> <td></td> <td>4°C</td> <td>2 years</td> </tr> <tr> <td>In solvent</td> <td>-80°C</td> <td>2 years</td> </tr> <tr> <td></td> <td>-20°C</td> <td>1 year</td> </tr> </table>	Powder	-20°C	3 years		4°C	2 years	In solvent	-80°C	2 years		-20°C	1 year
Powder	-20°C	3 years											
	4°C	2 years											
In solvent	-80°C	2 years											
	-20°C	1 year											



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (210.76 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	Mass		
		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

- 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
- 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
- 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 IC₅₀s of 0.8 and 0.5 nM, respectively.

IC₅₀ & 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	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>		
In Vivo	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>		

PROTOCOL

Kinase Assay ^[1]	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Cell Assay ^[1]	<p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[1]	<p>Mice: Mice bearing s.c. HCT-116 xenograft tumors (250-400mm³) 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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

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

Tel: 609-228-6898

Fax: 609-228-5909

E-mail: tech@MedChemExpress.com

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