PF 477736

Cat. No.: HY-10032

CAS No.: 952021-60-2

Molecular Formula: $C_{22}H_{25}N_7O_2$

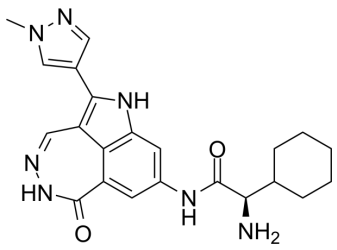
Molecular Weight: 419.48

Target: Checkpoint Kinase (Chk); VEGFR; Src; c-Fms; Aurora Kinase; FGFR; FLT3; RET; CDK

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

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 : 125 mg/mL (297.99 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3839 mL	11.9195 mL	23.8390 mL
	5 mM	0.4768 mL	2.3839 mL	4.7678 mL
	10 mM	0.2384 mL	1.1920 mL	2.3839 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: ≥ 2.08 mg/mL (4.96 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.96 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF 477736 (PF 00477736) is a potent, selective and ATP-competitive inhibitor of Chk1, with a K_i of 0.49 nM, it is also a Chk2 inhibitor, with a K_i of 47 nM. PF 477736 shows <100-fold selectivity for Chk1 over VEGFR2, Fms, Yes, Aurora-A, FGFR3, Flt3, and Ret (IC_{50}=8 (K_i), 10, 14, 23, 23, 25, and 39 nM, respectively). PF 477736 can enhance Gemcitabine antitumor activity in vitro and in vivo[1][2].

IC_{50} & Target

Chk1 0.49 nM (Ki)	Chk2 47 nM (Ki)	VEGFR2 8 nM (Ki)	Fms 10 nM (IC_{50})
Yes 14 nM (IC_{50})	Aurora-A 23 nM (IC_{50})	FGFR3 23 nM (IC_{50})	Flt3 25 nM (IC_{50})

	Ret 39 nM (IC_{50})	CDK1 9.9 μM (Ki)
In Vitro	PF 477736 is a poor inhibitor of CDK1 activity (K_i=9.9 μM, 20,000-fold versus Chk1)[1]. PF 477736 (0.01-1 μM; 16 h) dose-dependently abrogates the camptothecin-induced DNA damage checkpoint in CA46 cells[1]. PF 477736 (10-48 h) abrogates the Gemcitabine-induced S-phase arrest and induces increase in apoptotic cell death in HT29 cells[1]. PF 477736 (180-540 nM; 4-48 h) enhances Gemcitabine cytotoxicity in dose- and time-dependent manner in HT29 cells[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	PF 477736 (4-60 mg/kg; i.p. for once a day or twice a day for four treatments) potentiates Gemcitabine antitumor activity in Colo205 xenografts[1]. PF 477736 (15 and 30 mg/kg; i.p.) induces histone H3 phosphorylation and DNA damage and increases apoptosis in vivo[1]. PF 477736 (4 mg/kg; i.v.) exhibits low systemic plasma clearance (11.8 mL/min/kg) and terminal half-life (2.9 h) in rats[1]. PF 477736 (4-40 mg/kg; i.p.) exhibits a dose dependent pharmacokinetics[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Cancers. 2019 Oct 25;11(11):1654.
- Research Square Preprint. 2022 Jul.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Blasina A, et al. Breaching the DNA damage checkpoint via PF-00477736, a novel small-molecule inhibitor of checkpoint kinase 1. Mol Cancer Ther. 2008 Aug;7(8):2394-404

[2]. Ashwell S, et, al. DNA damage detection and repair pathways--recent advances with inhibitors of checkpoint kinases in cancer therapy. Clin Cancer Res. 2008 Jul 1; 14(13): 4032-7.

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