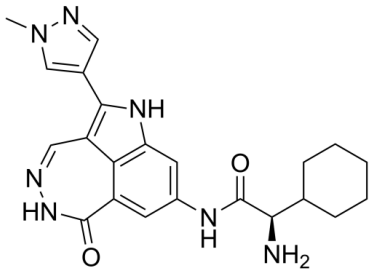
Data Sheet

Product Name:	PF 477736
Cat. No.:	CS-0026
CAS No.:	952021-60-2
Molecular Formula:	$C_{22}H_{25}N_7O_2$
Molecular Weight:	419.48
Target:	Aurora Kinase; CDK; c-Fms; Checkpoint Kinase (Chk); FGFR; FLT3; RET; Src; VEGFR
Pathway:	Cell Cycle/DNA Damage; Epigenetics; Protein Tyrosine Kinase/RTK
Solubility:	DMSO : 125 mg/mL (297.99 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

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]. IC50 & Target:Ki: 0.49 nM (Chk1), 47 nM (Chk2), 9.9 μM (CDK1)[1] **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]. **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].

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.

CAIndexNames:

Cyclohexaneacetamide, .alpha.-amino-N-[5,6-dihydro-2-(1-methyl-1H-pyrazol-4-yl)-6-oxo-1H-pyrrolo[4,3,2-ef][2,3]benzodiazepin-8-yl]-, (.alpha.R)-

SMILES:

O=C([C@@H](C1CCCCC1)N)NC2=CC3=C(C(C=NNC4=O)=C(N3)C5=CN(N=C5)C)C4=C2

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

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