PF-670462

Cat. No.: HY-15490

CAS No.: 950912-80-8

Molecular Formula: $C_{19}H_{22}Cl_2FN_5$

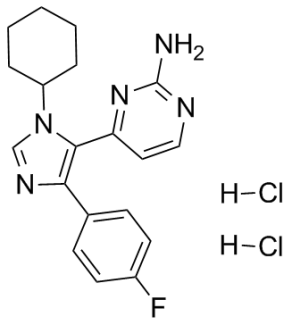
Molecular Weight: 410.32

Target: Casein Kinase

Pathway: Cell Cycle/DNA Damage; Stem Cell/Wnt

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 : ≥ 32 mg/mL (77.99 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4371 mL	12.1856 mL	24.3712 mL
5 mM	0.4874 mL	2.4371 mL	4.8742 mL
10 mM	0.2437 mL	1.2186 mL	2.4371 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 (5.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (5.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-670462 is a potent and selective inhibitor of casein kinase (CK1ε and CK1δ), with IC_{50}s of 7.7 nM and 14 nM, respectively.

IC_{50} & Target

CKI	CKIδ	EGFR	SAPK2A/p38
7.7 nM (IC_{50})	14 nM (IC_{50})	150 nM (IC_{50})	190 nM (IC_{50})

In Vitro

PF-670462 is a potent and selective inhibitor of CKIε and CKIδ, with IC_{50}s of 7.7 nM and 14 nM, respectively. PF-670462 shows less than 30-fold selevtivity for EGFR and SAPK2A/p38, with IC_{50}s of 150 nM and 190 nM, respectively. PF-670462 also causes a redistribution of the GFP signal to the cytoplasm in a concentration-dependent manner, with an EC_{50} of 290 ± 39 nM in CKI ε-transfected COS7 cells[1]. PF-670462 is a potent inhibitor of Wnt/β-catenin signaling, with an IC_{50} of -17 nM. PF-670462 (1 μ

	M) is a weak inhibitor of proliferation, and only modestly suppresses the growth of HEK293 and HT1080 cells. PF-670462 (100 nM) strongly inhibits CK1ε and CK1δ, consistent with its effect on Wnt/β-catenin signaling[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PF-670462 (50 mg/kg, s.c.) produces robust phase delays, and the activity remains persistent, with no discernible correction in the absence of exogenous zeitgebers in rats. PF-670462 (25, 50, and 100 mg/kg, s.c.) induces dose-dependent phase shift [1]. PF-670462 (50 mg/kg; s.c.) significantly phase delays the rhythmic transcription of Bmal1, Per1, Per2 and Nr1d1 in both liver and pancreas by 4.5 ± 1.3 h and 4.5 ± 1.2 h, respectively, 1 day after administration. In the suprachiasmatic nucleus (SCN), the rhythm of Nr1d1 and Dbp mRNA expression is also delayed by 4.2 and 4 h, respectively[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The CKIε kinase assay is performed in a 40-μL final volume in buffer containing 50 mM Tris, pH 7.5, 10 mM $MgCl_2$, 5 mM dithiothreitol with 5 μM ATP, 3 nM CKIεΔ319, and 15 μM peptide substrate PLSRTLpSVASLPGL in the presence of 5 μL of CKIε inhibitor (PF-670462) or 5% dimethyl sulfoxide. The reaction is incubated for 3 h at 27°C; detection is carried out as described for the Kinase-Glo Assay. Luminescent output is measured[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Adult male CD rats (initial weight 175-225 g) are released into constant darkness (DD) for 2 weeks, and their individual free-running periods and times of activity onset are determined from the 7 to 10 days at the end of the 2-week period. Dosing of 50 mg/kg PF-670462 or vehicle (40% β-cyclodextrin) takes place at circadian time (CT)9 or 3 h before the predicted onset of activity; night vision goggles facilitated the subcutaneous administration. CT9 is chosen based on preliminary data demonstrating robust responses to CKIε inhibition at this circadian time. Animals are maintained under DD for an additional 4 to 5 days postdose, and the data from that time period are used in the estimation of the magnitude and direction of the putative phase shifts[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450). pii: eaaq1093.
- Proc Natl Acad Sci U S A. 2018 Aug 7;115(32):E7522-E7531.
- Biochem Biophys Res Commun. 2020 Jan.

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REFERENCES

[1]. Badura L, et al. An inhibitor of casein kinase I epsilon induces phase delays in circadian rhythms under free-running and entrained conditions. J Pharmacol Exp Ther. 2007 Aug;322(2):730-8. Epub 2007 May 14.

[2]. Cheong JK, et al. IC261 induces cell cycle arrest and apoptosis of human cancer cells via CK1δ/? and Wnt/β-catenin independent inhibition of mitotic spindle formation. Oncogene. 2011 Jun 2;30(22):2558-69.

[3]. Kennaway DJ, et al. Acute inhibition of casein kinase 1δ/ε rapidly delays peripheral clock gene rhythms. Mol Cell Biochem. 2015 Jan;398(1-2):195-206.

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

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