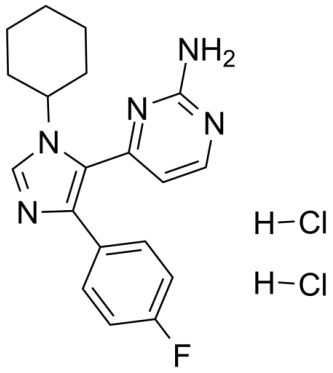
Data Sheet

Product Name:	PF-670462
Cat. No.:	CS-1015
CAS No.:	950912-80-8
Molecular Formula:	C19H22Cl2FN5
Molecular Weight:	410.32
Target:	Casein Kinase
Pathway:	Cell Cycle/DNA Damage; Stem Cell/Wnt
Solubility:	DMSO : ≥ 32 mg/mL (77.99 mM)



BIOLOGICAL ACTIVITY:

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. IC50 & Target: IC50: 7.7 nM (CKIε), 14 nM (CKIδ), 150 nM (EGFR), 190 nM (SAPK2A/p38)[1], 17 nM (Wnt/β-catenin)[2] **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 CKIε-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 μM) 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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **Animal Administration:** PF-670462 is formulated in 40% β-cyclodextrin.[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].

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.

CAIndexNames:

2-Pyrimidinamine, 4-[1-cyclohexyl-4-(4-fluorophenyl)-1H-imidazol-5-yl]-, hydrochloride (1:2)

SMILES:

NC1=NC=CC(C2=C(C3=CC=C(F)C=C3)N=CN2C4CCCCC4)=N1.[H]Cl.[H]Cl

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

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