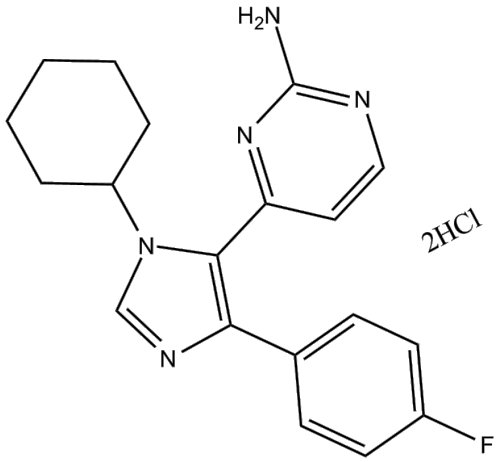
Product Data Sheet

Product Name: PF-670462
Cat. No.: GC10556

Chemical Properties

Cas. No.	950912-80-8		
Chemical Name	4-[3-cyclohexyl-5-(4-fluorophenyl)imidazol-4-yl]pyrimidin-2-amine;dihydrochloride		
SMILES	C1CCC(CC1)N2C=NC(=C2C3=NC(=NC=C3)N)C4=CC=C(C=C4)F.Cl.Cl		
Formula	$C_{19}H_{22}Cl_2FN_5$	M.Wt	410.32
Solubility	≥ 20.5 mg/mL in DMSO, ≥ 20.8 mg/mL in EtOH with ultrasonic and warming, ≥ 94 mg/mL in Water with ultrasonic and warming	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20°C for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		

Structure



Protocol

Kinase experiment [1]:

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Kinase assays	The CK1ε and CK1δ kinase assays were performed in a 20-μL volume in buffer containing 50 mM Tris, pH 7.5, 10 mM MgCl2, 1 mM DTT, 10 μM ATP and 42 μM peptide substrate (PLSRTLpSVASLPGL). The final enzyme concentrations were 2.5 nM for CK1ε and 2 nM for CK1δ. Assays were run in a panel format in the presence 1 μL of CK1 inhibitor or 5% DMSO. The reactions were incubated for 2 hrs at room temperature, followed by detection with 20 μL of the Kinase-Glo Plus Assay reagent. Luminescence was measured by using Enhanced Lum detection on an Envision plate reader.

Cell experiment [1]:

Cell lines	Rat1 cells
Preparation method	The solubility of this compound in DMSO is > 20.5 mg/mL. General tips for obtaining a higher concentration: Please warm the tube at 37 °C for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below - 20 °C for several months.
Reacting condition	0 ~ 50 μM
Applications	In Rat1 cells, PF-670462 significantly lengthened the circadian period. At the concentration as low as 1 μM, PF-670462 started to dramatically increase the circadian period in a dose-dependent manner. PF-670462 began to increase the period of the clock at approximately 3- to 10-fold over the whole-cell CK1δ IC50 and approximately 3-fold lower for CK1ε.

Animal experiment [1]:

Animal models	C57BL/6J mice

Caution: Product has not been fully validated for medical applications. For research use only.
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Dosage form	32 mg/kg; s.c.; a single dose
Applications	After a single subcutaneous dose of 32 mg/kg PF-670462, the brain-to-plasma concentration ratio of PF-670462 was constant throughout the 24-hr time course, with an average value of 1.3. The free brain Cmax of PF-670462 was 3-fold above its CK1δ whole-cell IC50, along with a 0.7-fold CK1ε whole-cell IC50, which indicated that PF-670462 inhibited most of the CK1δ and CK1ε activity.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:

[1]. Walton KM, Fisher K, Rubitski D, et al. Selective inhibition of casein kinase 1 epsilon minimally alters circadian clock period. J Pharmacol Exp Ther, 2009, 330(2): 430-439.

Background

PF-670462 is a potent and selective inhibitor of CK1ε and CK1δ with IC50 value of 80 nM and 13 nM, respectively [1].
CK1ε and CK1δ belong to the casein kinase 1 family which is serine/threonine-selective enzyme and plays an important role in regulating circadian rhythm [1].
In COS-7 cells cotransfected with GFP-tagged PER3 and the human CK1ε enzyme, PF-670462 inhibited PER3 nuclear translocation in a concentration-dependent way [2]. In primary lung fibroblast cells obtained from WT mice, PF-670462 significantly lengthened the circadian period in a dose-dependent way. And with a dose of 1 μM, the period in WT fibroblast cells extended to 33 h [3].
In WT, Ck1ε–/– and Ck1εtau mice, PF-670462 (10 mg/kg/d) significantly lengthened the period of activity rhythms in all three genotypes (WT: 0.44 h, Ck1εtau: 0.39 h, Ck1ε–/–: 0.42 h). In WT mice, the activity onset occurred 10.4 h after 24 d of treatment. Also, PF-670462 caused identical period lengthening in WT and Ck1ε–/– mice, which suggested that the effect of CK1δ on the circadian

period [3].

References:

[1]. Walton KM, Fisher K, Rubitski D, et al. Selective inhibition of casein kinase 1 epsilon minimally alters circadian clock period. J Pharmacol Exp Ther, 2009, 330(2): 430-439.

[2]. Badura L, Swanson T, Adamowicz W, 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, 322(2): 730-738.

[3]. Meng QJ, Maywood ES, Bechtold DA, et al. Entrainment of disrupted circadian behavior through inhibition of casein kinase 1 (CK1) enzymes. Proc Natl Acad Sci U S A, 2010, 107(34): 15240-15245.

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