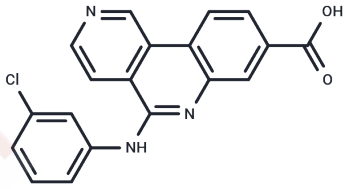
Data Sheet (Cat.No.T2259)

TargetMol

Silmitasertib

Chemical Properties



CAS No. : 1009820-21-6

Formula: C19H12ClN3O2

Molecular Weight: 349.77

Appearance: no data available

Storage: store at low temperature
Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Biological Description

Description	Silmitasertib (CX-4945) is a potent, orally bioavailable inhibitor of casein kinase 2 (CK2; Ki: 0.38 nM).
Targets(IC50)	Casein Kinase,Autophagy
In vitro	The antiproliferative activity of Silmitasertib (CX-4945) against cancer cells correlated with expression levels of the CK2α catalytic subunit. CX-4945 caused cell-cycle arrest and selectively induced apoptosis in cancer cells relative to normal cells. In models of angiogenesis, CX-4945 inhibited human umbilical vein endothelial cell migration, tube formation, and blocked CK2-dependent HIF-1α transcription in cancer cells [1]. Adding CX-4945 after bortezomib treatment, prevented leukemic cells from engaging a functional UPR in order to buffer the bortezomib-mediated proteotoxic stress in ER lumen. Bortezomib/CX-4945 treatment inhibited NF-κB signaling in T-ALL cell lines and primary cells from T-ALL patients, but, in B-ALL cells the drug combination activated NF-κB p65 pro-apoptotic functions [2]. CX-4945 was found to potently inhibit endogenous intracellular CK2 activity with an IC50 of 0.1 μM in Jurkat cells. CX-4945 induced dephosphorylation of Akt(S129) and a rapid dephosphorylation of the Akt substrate p21 (T145). CX-4945 induced apoptosis in multiple cancer cell lines [3].
In vivo	When administered orally in murine xenograft models, CX-4945 was well tolerated and demonstrated robust antitumor activity with concomitant reductions of the mechanism-based biomarker phospho-p21 (T145) [1]. Mice bearing subcutaneous PC3 tumors were treated with CX-4945 (25 mg/kg, 50 mg/kg, and 75 mg/kg, po, bid). Tumor growth inhibition compared to vehicle-treated control, and a dose-responsive efficacy was observed. Last, CX-4945 was well tolerated in mice as assessed by minimal changes in body weight during the course of treatment compared to vehicle control [3].
Kinase Assay	The 238 kinase selectivity panel was conducted using the Kinase Profiler service, which utilizes a radiometric filter-binding assay. The percent inhibition of each kinase was estimated using 0.5 μmol/L CX-4945 at ATP concentrations equivalent to the Km value for ATP for each respective human recombinant kinase. The determination of IC50 values was done at ATP concentrations equivalent to the Km for ATP for each kinase using 9 concentrations of CX-4945 over a range of 0.0001 to 1 μmol/L. The Ki value (inhibition constant) for CX-4945 against recombinant CK2 was determined by graphing the IC50 values of CX-4945 determined in the presence of various concentrations of ATP against the concentration of ATP. The Ki value is equivalent to the Y-intercept according

	to the Cheng-Prussoff equation (Ki = IC50/(1+[ATP]/Km), where Ki is the inhibition constant and Km is the Michaelis constant [1].
Cell Research	Various cell lines were seeded at a density of 3000 cells per well 24 h prior to treatment, in appropriate media, and then treated with indicated concentrations of CK2 inhibitors. Suspension cells were seeded and treated on the same day. Following 4 days of incubation, 20 μL of Alamar Blue (10% of volume/well) was added and the cells were further incubated at 37 °C for 4-5 h. Fluorescence with excitation wavelength at 530-560 nm and emission wavelength at 590 nm was measured [3].
Animal Research	Xenografts were initiated by subcutaneous injection of BxPC-3 cells into the right hind flank region of each mouse or BT-474 cells were injected into the mammary fat pad of mice implanted with estrogen pellets. When tumors reached a designated volume of 150-200 mm^3, animals were randomized and divided into groups of 9 to 10 mice per group. CX-4945 was administered by oral gavage twice daily at 25 or 75 mg/kg for 31 and 35 consecutive days for the BT-474 and BxPC-3 models, respectively. Tumor volumes and body weights were measured twice weekly. The length and width of the tumor were measured with calipers and the volume calculated using the following formula: tumor volume = (length × width^2)/2. Percent tumor growth inhibition (TGI) values were calculated on the final day of the study for CX-4945-treated compared to vehicle-treated mice and were calculated as 100 × {1 ? [(TreatedFinal day ? TreatedDay 1)/(ControlFinal day ? ControlDay 1)]}. The significance of the differences between the treated versus vehicle groups were determined using 1-way ANOVA [1].

Solubility Information

Solubility	H2O: < 1 mg/mL (insoluble or slightly soluble), Ethanol: < 1 mg/mL (insoluble or slightly soluble), DMSO: 50 mg/mL (142.95 mM),Sonication is recommended. (< 1 mg/ml refers to the product slightly soluble or insoluble)

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.859 mL	14.2951 mL	28.5902 mL
5 mM	0.5718 mL	2.859 mL	5.718 mL
10 mM	0.2859 mL	1.4295 mL	2.859 mL
50 mM	0.0572 mL	0.2859 mL	0.5718 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Reference

Siddiqui-Jain A, et al. CX-4945, an orally bioavailable selective inhibitor of protein kinase CK2, inhibits prosurvival and angiogenic signaling and exhibits antitumor efficacy. Cancer Res. 2010 Dec 15;70(24):10288-98.
Wang C, Tian L, He Q, et al.Targeting CK2-mediated phosphorylation of p53R2 sensitizes BRCA-proficient cancer cells to PARP inhibitors.Oncogene.2023: 1-14.
Werner C, Lindenblatt D, Viht K, et al.Discovery and Exploration of Protein Kinase CK2 Binding Sites Using CK2α′ Cys336Ser as an Exquisite Crystallographic Tool.Kinases and Phosphatases.2023, 1(4): 306-322.
Buontempo F, et al. Synergistic cytotoxic effects of bortezomib and CK2 inhibitor CX-4945 in acute lymphoblastic leukemia: turning off the prosurvival ER chaperone BIP/Grp78 and turning on the pro-apoptotic NF-κB. Oncotarget. 2016 Jan 12;7(2):1323-40.
Pierre F, et al. Discovery and SAR of 5-(3-chlorophenylamino)benzo[c][2,6]naphthyridine-8-carboxylic acid (CX-4945), the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer. J Med Chem. 2011 Jan 27; 54(2):635-54.
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