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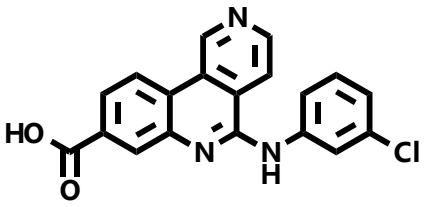
CK2 (Casein Kinase 2) Inhibitor – CX-4945 (Silmitasertib)

Chemical Name: 5-((3-chlorophenyl)amino)benzo[c][2,6]naphthyridine-8-carboxylic acid



Molecular Weight:	349.77
Formula:	$C_{19}H_{12}ClN_3O_2$
Purity:	≥98%
CAS#:	1009820-21-6
Solubility:	DMSO up to 40 mM
Storage	Powder: 4 °C 1 year DMSO: 4 °C 3 months -20 °C 1 year

Biological Activity:

CX-4945 (Silmitasertib) is a potent, selective and bioavailable CK2 (Casein Kinase 2) Inhibitor with IC_{50} of 1 nM. It only inhibits 7 of the 238 kinases by more than 90% at concentration of 0.5 μM, which is 500-fold selectivity over CK2. Although in cell-free systems CX-4945 inhibits FLT3, PIM1, and CDK1 with IC_{50} of 35 nM, 46 nM, and 56 nM, respectively, but it is inactive against FLT3, PIM1, and CDK1 in cell-based functional assays at 10 μM. CX-4945 exhibits a broad spectrum of antiproliferative activity, correlates with CK2α mRNA and protein levels but not the CK2α' catalytic subunit, the regulatory CK2β subunit, and the PI3K/Akt or PTEN mutational status. Combined inhibition of EGFR and CK2 augments the attenuation of PI3K-Akt-mTOR signaling and the killing of cancer cells. CX-4945 can potentiate senescence by blocking tumour progression in $Pten^{pc\ -/-}$ mice. Now CX-4945 is in phase I/II clinical trials to treat cancer.

How to Use:

In vitro: CX-4945 was used at 1 μM final concentration in various in vitro assays.

In vivo: Oral administration of CX-4945 at 25 mg/kg or 75 mg/kg twice daily displays potent antitumor activity in the BT-474 model, with TGI of 88% and 97%, respectively. In PC3 xenograft model, administration of CX-4945 at 25 mg/kg, 50 mg/kg, or 75 mg/kg causes tumor growth inhibition with TGI of 19%, 40%, and 86%, respectively.

Reference:

1. 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.(2010) Cancer Res. 70(24):10288-98.
2. 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. (2011) J Med Chem. 54(2):635-54.
3. Siddiqui-Jain A, et al. CK2 inhibitor CX-4945 suppresses DNA repair response triggered by DNA-targeted anticancer drugs and augments efficacy: mechanistic rationale for drug combination therapy. (2012) Mol Cancer Ther. 11(4):994-1005.
4. Buontempo F, et al. Cytotoxic activity of the casein kinase 2 inhibitor CX-4945 against T-cell acute lymphoblastic leukemia: targeting the unfolded protein response signaling. (2014) Leukemia. 28(3):543-53.
5. Kalathur M, et al. A chemogenomic screening identifies CK2 as a target for pro-senescence therapy in PTEN-deficient tumours. (2015) Nat Commun. 6:7227

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