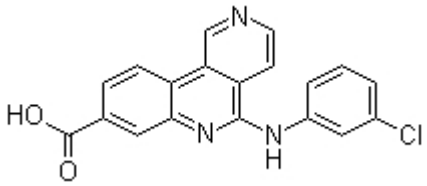
Product Introduction

CX-4945 (Silmitasertib)

CX-4945 is a potent and selective inhibitor of **CK2 (casein kinase 2)** with **IC50** of 1 nM, less potent to Flt3, Pim1 and CDK1 (inactive in cell-based assay). Phase 1.

Technical Data:

Molecular Weight (MW):	349.77	
Formula:	$C_{19}H_{12}ClN_3O_2$	
Solubility (25°C) *** <1 mg/ml means slightly soluble or insoluble:**	DMSO 16 mg/mL	
	Water <1 mg/mL	
	Ethanol <1 mg/mL	
Purity:	>98%	
Storage:	3 years -20℃Powder	
	6 months-80℃in DMSO	
CAS No.:	1009820-21-6	

Biological Activity

CX-4945 is selective for CK2, as it only inhibits 7 of the 238 kinases by more than 90% at concentration of 0.5 μM, which is 500-fold greater than the IC50 of CK2. Although in cell-free systems CX-4945 inhibits FLT3, PIM1, and CDK1 with IC50 of 35 nM, 46 nM, and 56 nM, respectively, CX-4945 treatment at 10 μM is inactive against FLT3, PIM1, and CDK1 in cell-based functional assays. CX-4945 exhibits a broad spectrum of antiproliferative activity, and the breast cancer cell lines displays the widest range of sensitivity to CX-4945 with EC50 of 1.71-20.01 μM. The antiproliferative activity of CX-4945 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. CX-4945 inhibits PI3K/Akt signaling by directly blocking the phosphorylation of Akt at Serine 129 by CK2 rather than through activation of PTEN. CX-4945 treatment causes reduced phosphorylation of p21 (T145), increased levels of total p21 and p27, and induction of caspase 3/7 activity. CX-4945 treatment induces a G2/M cell-cycle arrest in BT-474 cells and a G1 arrest in BxPC-3 cells. CX-4945 inhibits HUVEC proliferation, migration, and tube formation with IC50 of 5.5 μM, 2 μM, and 4 μM, respectively. Under hypoxic conditions in BT-474 and BxPC-3 cells, CX-4945 treatment prevents downregulation of p53 and pVHL and reduces activation of HIF-1α transcription. [1] CX-4945 potently inhibits endogenous intracellular CK2 activity with IC50 of 0.1 μM in Jurkat cells. [2]

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, and 2 of 9 animals in each group showing more than 50% reduction in tumor size compared with the initial tumor volume. In the BxPC-3 model, CX-4945 treatment at 75 mg/kg twice daily shows 93% TGI with 3 animals having no evidence of tumor remaining at the end of the treatment period. [1] 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. [2]

References

[1] Siddiqui-Jain A, et al. Cancer Res, 2010, 70(24), 10288-10298.
[2] Pierre F, et al. J Med Chem, 2011, 54(2), 635-654.
[3] Siddiqui-Jain A, et al. Mol Cancer Ther, 2012, 11(4), 994-1005.
[4] Bliesath J, et al. Cancer Lett, 2012, 322(1), 113-118.

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