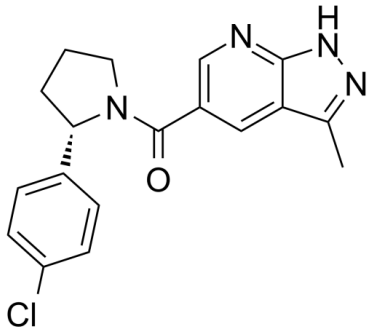
Data Sheet

Product Name:	MSC2530818
Cat. No.:	CS-6912
CAS No.:	1883423-59-3
Molecular Formula:	C18H17ClN4O
Molecular Weight:	340.81
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : ≥ 125 mg/mL (366.77 mM)



BIOLOGICAL ACTIVITY:

MSC2530818 is a potent, selective and orally available **CDK8** inhibitor with an **IC_{50}** of 2.6 nM for CDK8. IC50 & Target: IC50: 2.6 nM (CDK8)[1] **In Vitro:** MSC2530818 binds to CDK8 and CDK19 with similar affinity (4 nM). Potent inhibition of phospho-$STAT1^{SER727}$, an established biomarker of CDK8 activity, in SW620 human colorectal carcinoma cells is also observed ($pSTAT1^{SER727}$ IC_{50}=8±2 nM). MSC2530818 demonstrates potent inhibition of WNT-dependent transcription in human cancer cell lines that have constitutively activated WNT signaling. For example, MSC2530818 inhibits the reporter-based luciferase readout in several cell lines bearing activating WNT-pathway mutations; LS174T (β-catenin mutant, IC_{50}=32±7 nM), COLO205 (APC mutant, IC_{50}=9±1 nM) and demonstrates inhibition of WNT3a ligand-dependent reporter readout in PA-1 cells (IC_{50}=52±30 nM). MSC2530818 demonstrates minimal activity in the CEREP panel, being active on the dopamine transporter (IC_{50}=8.5 μM) as the only activity below 10 μM, and demonstrates minimal hERG inhibition. Furthermore, MSC2530818 is a soluble CDK8 inhibitor with high permeability and low efflux ratio in Caco-2 cells and does not inhibit any cytochrome P450 subtypes[1]. **In Vivo:** Tumor-bearing mice treated with MSC2530818 shows reduction in tumor growth with T/C ratios (based on final tumor weights) of 49% and 57%, respectively. MSC2530818 is generally well tolerated, with no effects on mouse body weight in the qd administration schedule and manageable body weight loss. The human clearance and volume of distribution at steady-state are estimated to be low (0.14 L/h/kg) and small (0.48 L/kg), respectively, resulting in a short predicted terminal half-life (2.4 h). Physiologically based pharmacokinetics simulations suggested that human oral bioavailability may be ≥75% up to dose level of 500 mg daily[1].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: MSC2530818 is prepared in kolliphor 20% w/v in water.[1]Mouse: MSC2530818 is then assessed in an established SW620 human colorectal cancer xenograft model in female NCr athymic mice. Tumor-bearing mice are treated orally with MSC2530818 (50 mg/kg bid or 100 mg/kg qd) for 16 days. Tumor weights are measured and body weights are monitored[1].

References:

[1]. Czodrowski P, et al. Structure-Based Optimization of Potent, Selective, and Orally Bioavailable CDK8 Inhibitors Discovered by High-Throughput Screening. J Med Chem. 2016 Oct 27;59(20):9337-9349.

CAIndexNames:

Methanone, [(2S)-2-(4-chlorophenyl)-1-pyrrolidinyl](3-methyl-1H-pyrazolo[3,4-b]pyridin-5-yl)-

SMILES:

O=C(N1[C@H](C2=CC=C(Cl)C=C2)CCC1)C3=CN=C(NN=C4C)C4=C3

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

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA