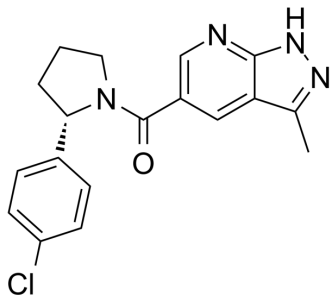
MSC2530818

Cat. No.:	HY-101611
CAS No.:	1883423-59-3
Molecular Formula:	$C_{18}H_{17}ClN_4O$
Molecular Weight:	340.81
Target:	CDK
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 110 mg/mL (322.76 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.9342 mL	14.6709 mL	29.3419 mL
	5 mM	0.5868 mL	2.9342 mL	5.8684 mL
	10 mM	0.2934 mL	1.4671 mL	2.9342 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.75 mg/mL (8.07 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.75 mg/mL (8.07 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (8.07 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

MSC2530818 is a potent, selective and orally available CDK8 inhibitor with an IC_{50} of 2.6 nM for CDK8.

IC_{50} & Target

CDK8
2.6 nM (IC_{50})

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, 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	Mice: 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.

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