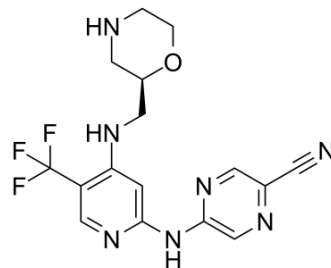


CCT245737

Cat. No.:	HY-18958		
CAS No.:	1489389-18-5		
Molecular Formula:	C ₁₆ H ₁₆ F ₃ N ₇ O		
Molecular Weight:	379.34		
Target:	Checkpoint Kinase (Chk)		
Pathway:	Cell Cycle/DNA Damage		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 32 mg/mL (84.36 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent		1 mg	5 mg	10 mg
	Concentration	Mass			
	1 mM		2.6362 mL	13.1808 mL	26.3616 mL
	5 mM		0.5272 mL	2.6362 mL	5.2723 mL
	10 mM		0.2636 mL	1.3181 mL	2.6362 mL

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

In Vivo

- Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
 Solubility: ≥ 2.5 mg/mL (6.59 mM); Clear solution
- Add each solvent one by one: 10% DMSO >> 90% corn oil
 Solubility: ≥ 2.5 mg/mL (6.59 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

CCT245737 is an orally active and selective Chk1 inhibitor, with an IC₅₀ of 1.3 nM.

IC₅₀ & Target

Chk1 1.3 nM (IC ₅₀)	Chk2 2440 nM (IC ₅₀)	ERK8 130 nM (IC ₅₀)	PKD1 298 nM (IC ₅₀)
RSK2 361 nM (IC ₅₀)	RSK1 362 nM (IC ₅₀)	FLT3 582 nM (IC ₅₀)	MARK3 698 nM (IC ₅₀)
NUAK1	CLK2	BRSK1	AMPK

	711 nM (IC ₅₀)	1370 nM (IC ₅₀)	1660 nM (IC ₅₀)	2970 nM (IC ₅₀)
	PHK 3470 nM (IC ₅₀)	CDK2/CyclA 3850 nM (IC ₅₀)	CDK1/CyclB 9030 nM (IC ₅₀)	
In Vitro	CCT245737 (10 μM) shows >80% inhibition of a panel of 124 kinases, including ERK8, PKD1, RSK2 and RSK1 with IC ₅₀ s of 130, 298, 361 and 362 nM ^[1] . CCT245737 abrogates an VP-16-induced G2 checkpoint in HT29, SW620, MiaPaCa-2, and Calu6 cell lines, with IC ₅₀ s ranging from 30 to 220 nM ^[2] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.			
In Vivo	CCT245737 (150 mg/kg p.o.) inhibits tumor growth in combination with LY 188011 (100 mg/kg iv) in HT29 colon cancer xenografts. CCT245737 (300 mg/kg, p.o.) also inhibits the LY 188011 (60 mg/kg iv) induced pSer296 CHK1 autophosphorylation at 24 h in SW620 human colon cancer xenografts ^[1] . CCT245737 (150 mg/kg, p.o) alone significantly inhibits tumor growth in an Eμ-Myc mouse model of human B-cell lymphocytic leukemia ^[2] . MCE has not independently confirmed the accuracy of these methods. They are for reference only.			

PROTOCOL

Cell Assay ^[2]

Cytotoxicity is determined as the drug concentration that gives 50% inhibition of tumor cell proliferation (GI₅₀) using a 96 h Sulforhodamine B (SRB) assay. Inhibition of intracellular CHK1 activity is measured using a cell based ELISA for the abrogation of an VP-16 induced G2 checkpoint (mitosis induction assay, MIA). The IC₅₀ for G2 checkpoint abrogation (MIA) is determined in the presence of nocodazole using UCN01 as a positive control. The activity index (AI) is used as a measure of the compounds ability to induce mitosis relative to its toxicity (i.e., ratio of MIA IC₅₀: 96 h SRB GI₅₀). Routine potentiation studies are carried out using a fixed concentration (GI₅₀) of either LY 188011 or SN38 in combination with a range of CCT245737 concentrations to determine the combination GI₅₀ of CCT245737. The ability of CCT245737 to enhance LY 188011 or SN38 cell killing is expressed as a potentiation index (PI) equal to the ratio of the GI₅₀ for CCT245737 alone versus the combination GI₅₀ for CCT245737. PI values > 1 indicate potentiation of the genotoxic activity. In addition, a series of experiments is carried out using fixed, non- or minimally toxic concentrations of CCT245737 (≤GI₂₀) with a range of different concentrations of LY 188011 or SN38 to determine the extent to which CCT245737 enhances drug cytotoxicity compared with the genotoxic agent alone, i.e. conventional PI (ratio GI₅₀ genotoxic alone: GI₅₀ genotoxic combined with non-toxic CCT245737 concentration, Con PI)^[2].

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

Animal Administration ^[1]

Human HT29 colorectal carcinoma cells are injected s.c into the flanks of female NCr athymic mice 6-8 weeks of age. Dosing commenced 5 days after transplantation when tumors reach a mean diameter of 5.5 mm. LY 188011 (100 mg/kg i.v.) is dosed in saline on days 0, 7 and 14 and compounds 4 (CCT245737) and 41 (150 mg/kg p.o.) in 10% DMSO 20% PEG 400, 5% Tween 80, 65% water, 24 and 48 h after each dose of LY 188011. Tumors are measured and body weights recorded three times weekly. Animals are culled on an individual basis when tumors reach a predetermined humane endpoint (mean diameter <15 mm)^[1].

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

REFERENCES

[1]. Osborne JD, et al. Multiparameter Lead Optimization to Give an Oral Checkpoint Kinase 1 (CHK1) Inhibitor Clinical Candidate: (R)-5-((4-((Morpholin-2-ylmethyl)amino)-5-(trifluoromethyl)pyridin-2-yl)amino)pyrazine-2-carbonitrile (CCT245737). *J Med Chem.* 2016 Jun 9;59(11):5221-37.

[2]. Walton MI, et al. The clinical development candidate CCT245737 is an orally active CHK1 inhibitor with preclinical activity in RAS mutant NSCLC and Eμ-MYC driven B-cell lymphoma.

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

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