CCT245737

Cat. No.: HY-18958

CAS No.: 1489389-18-5

Molecular Formula: $C_{16}H_{16}F_3N_7O$

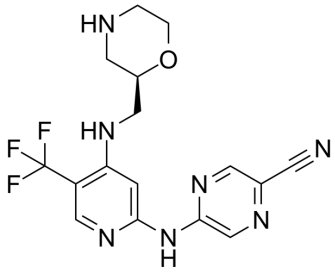
Molecular Weight: 379.34

Target: Checkpoint Kinase (Chk)

Pathway: Cell Cycle/DNA Damage

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 32 mg/mL (84.36 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
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

1. 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
2. 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 (SRA737) is an orally active and seletive Chk1 inhibitor, with an IC_{50} of 1.3 nM.

IC_{50} & 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 (GI_{50}) 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 IC_{50} 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 IC_{50}: 96 h SRB GI_{50}). Routine potentiation studies are carried out using a fixed concentration (GI_{50}) of either LY 188011 or SN38 in combination with a range of CCT245737 concentrations to determine the combination GI_{50} 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 GI_{50} for CCT245737 alone versus the combination GI_{50} 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 (≤GI_{20}) 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 GI_{50} genotoxic alone: GI_{50} 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.

CUSTOMER VALIDATION

- University of London. 2021 Sep.

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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.

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