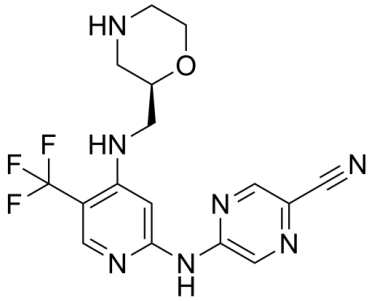
Data Sheet

Product Name:	CCT245737
Cat. No.:	CS-5863
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
Solubility:	DMSO : ≥ 32 mg/mL (84.36 mM)



BIOLOGICAL ACTIVITY:

CCT245737 is an orally active and seletive **Chk1** inhibitor, with an **IC_{50}** of 1.3 nM. IC50 & Target: IC50: 1.3 nM (Chk1), 2440 nM (Chk2)[1] ***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]. ***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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **Animal Administration:** CCT245737 is formulated in 10% DMSO 20% PEG 400, 5% Tween 80, 65% water.[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].

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.

CAIndexNames:

2-Pyrazinecarbonitrile, 5-[[4-[[(2R)-2-morpholinylmethyl]amino]-5-(trifluoromethyl)-2-pyridinyl]amino]-

SMILES:

FC(F)(F)C(C=NC(NC1=CN=C(C#N)C=N1)=C2)=C2NC[C@H]3CNCCO3

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