产品名称：CCT245737
产品别名：CCT245737

生物活性：

Description	CCT245737 is an orally active and seletive Chk1 inhibitor, with an IC50 of 1.3 nM.				
IC_{50} & Target	Chk1	Chk2	ERK8	PKD1	RSK2
	1.3 nM (IC_{50})	2440 nM (IC_{50})	130 nM (IC_{50})	298 nM (IC_{50})	361 nM (IC_{50})
	RSK1	FLT3	MARK3	NUAK1	CLK2
	362 nM (IC_{50})	582 nM (IC_{50})	698 nM (IC_{50})	711 nM (IC_{50})	1370 nM (IC_{50})
	BRSK1	AMPK	PHK	CDK2/CyclA	CDK1/CyclB
	1660 nM (IC_{50})	2970 nM (IC_{50})	3470 nM (IC_{50})	3850 nM (IC_{50})	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 IC50s of 130, 298, 361 and 362 nM[1]. CCT245737 abrogates an etoposide-induced G2 checkpoint in HT29, SW620, MiaPaCa-2, and Calu6 cell lines, with IC50s ranging from 30 to 220 nM[2].				
In Vivo	CCT245737 (150 mg/kg p.o.) inhibits tumor growth in combination with gemcitabine (100 mg/kg iv) in HT29 colon cancer xenografts. CCT245737 (300 mg/kg, p.o.) also inhibits the gemcitabine (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].				

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

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

In Vivo:

请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 **In Vitro** 方式配制澄清的储备液，再依次添加助溶剂：

——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶

1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline

Solubility: ≥ 2.5 mg/mL (6.59 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.59 mM，饱和度未知) 的澄清溶液。

以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中，混合均匀；向上述体系中加入 50 μL Tween-80，混合均匀；然后继续加入 450 μL 生理盐水定容至 1 mL。

	2.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.59 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.59 mM，饱和度未知) 的澄清溶液，此方案不适用于实验周期在半个月以上的实验。 以 1 mL 工作液为例，取 100 μL 25.0 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
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.

实验参考：

Cell Assay	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 etoposide 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 gemcitabine or SN38 in combination with a range of CCT245737 concentrations to determine the combination GI_{50} of CCT245737. The ability of CCT245737 to enhance gemcitabine 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 ($\leq GI_{20}$) with a range of different concentrations of gemcitabine 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	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. Gemcitabine (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 gemcitabine. 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].
Kinase Assay	Commercial in vitro ^{33}P radiometric kinase assays are carried out against 124 human kinases using 10 μM CCT245737 at ATP concentrations corresponding to the kinase K_m, ATP. Other kinase IC_{50} determinations for CHK2 and FLT3 are performed using a commercial assay or in-house with recombinant human CHK1 on a LabChip® EZ Reader II or CDK1 in a DELFIA assay[2].
	[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

References	(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.