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产品名称：CCT-251921
产品别名：CCT-251921

生物活性：

Description	CCT-251921 is a potent, selective, and orally bioavailable CDK8 inhibitor with an IC_{50} of 2.3 nM.	
IC_{50} & Target	CDK8	CDK19
	2.3 nM (IC_{50})	2.6 nM (IC_{50})
In Vitro	CCT-251921 has acceptable aqueous solubility and demonstrates minimal activity when tested in a panel of 55 receptors, ion channels, and enzymes at 1 μM and in a panel of 279 kinases; weak inhibition of CYPs is observed. CCT-251921 demonstrates potent inhibition of reporter-based readouts measuring basal WNT pathway activity in human cancer cell lines that have constitutively activated WNT pathway signaling: LS174T (β-catenin mutant), SW480 and Colo205 (APC mutant) or PA-1 human teratocarcinoma cells that are WNT ligand dependent[1].	
In Vivo	CCT-251921 shows improved oral pharmacokinetics and pharmaceutical properties in order to facilitate further evaluation of CDK8/19 pharmacology and progression into preclinical efficacy and safety studies. In APC-mutant SW620 human colorectal carcinoma xenograft model, CCT-251921 treatment reduces mice tumor weight (54.2%) at day 15. The inhibition of STAT1SER727 phosphorylation is maintained for more than 6 h after the last dose[1].	

Solvent&Solubility

In Vitro:

DMSO： 33.33 mg/mL (81.11 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4337 mL	12.1684 mL	24.3368 mL
	5 mM	0.4867 mL	2.4337 mL	4.8674 mL
	10 mM	0.2434 mL	1.2168 mL	2.4337 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 (6.08 mM); Clear solution

此方案可获得 ≥ 2.5 mg/mL (6.08 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% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (6.08 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.08 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 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中，混合均匀。 3.请依序添加每种溶剂： 10% DMSO →90% corn oil Solubility: ≥ 2.5 mg/mL (6.08 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.08 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]. Mallinger A, et al. Discovery of Potent, Selective, and Orally Bioavailable Small-Molecule Modulators of the Mediator Complex-Associated Kinases CDK8 and CDK19. J Med Chem. 2016 Feb 11;59(3):1078-101.

实验参考：

Cell Assay	7dF3 cells are treated with CCT-251921 ranging in final concentration from 90 μM to 0.3 nM. After 2 h of further incubation, β-oestradiol is added to a final concentration of 10 μM. The cells are incubated and then 25 μL of luciferase reagent is added and mixed. After leaving the plate for 60 min at room temperature, luminescence is read on a plate luminescence reader[1].
Animal Administration	Mice: Animals are dosed orally by gavage every 24 h at 0.1 mL per 10 g body weight. Tumors are measured three times weekly by Vernier calipers and body weights recorded. At the end of the study, animals are culled at intervals: 3 control and 3 treated at 1, 2, 6, and 24 h after the final dose. Heparinized blood is collected by cardiac puncture, spun, and plasma snap frozen for analysis of compound exposure. Tumors are excised, weighed and samples snap frozen for compound quantification and PD analyses. The 30 mg/kg q.d. schedule is well tolerated with no significant body weight loss. Tumor growth is significantly inhibited[1].
References	[1]. Mallinger A, et al. Discovery of Potent, Selective, and Orally Bioavailable Small-Molecule Modulators of the Mediator Complex-Associated Kinases CDK8 and CDK19. J Med Chem. 2016 Feb 11;59(3):1078-101.