产品名称：Dinaciclib (SCH727965)
产品别名：SCH 727965；Dinaciclib

生物活性：

Description	Dinaciclib is a potent inhibitor of CDK, with IC_{50}s of 1, 1, 3, and 4 nM for CDK2, CDK5, CDK1, and CDK9, respectively.			
IC_{50} & Target	CDK2	CDK5	CDK1	CDK9
	1 nM (IC_{50})	1 nM (IC_{50})	3 nM (IC_{50})	4 nM (IC_{50})
In Vitro	Dinaciclib (SCH 727965) is a potent DNA replication inhibitor that blocks thymidine (dThd) DNA incorporation in A2780 cells with an IC50 of 4 nM. Dinaciclib (100 nM) inhibits phosphorylation of the retinoblastoma (Rb) tumor suppressor protein and induces accumulation of the p85 PARP caspase cleavage product[1]. In vitro cell growth of pancreatic cancer cells is inhibited by Dinaciclib (SCH727965) in a dose-dependent manner. Upon incubation with Dinaciclib for 72 h, the GI50s are approximately 10 and 20 nM for MIAPaCa-2 and Pa20C cells, respectively. These results are consistent with studies of Dinaciclib in other cancer cell lines. In soft agar assays, 5 to 10 nM of Dinaciclib significantly reduces colony formation and anchorage independent growth of MIAPaCa-2 cells. Moreover, in vitro cell migration of Pa20C and MIAPaCa-2 cells is significantly reduced by Dinaciclib-concentrations starting from 2-5 nM, as demonstrated using BD FluoroChrom, modified Boyden Chamber and wound healing assays[2].			
In Vivo	Dinaciclib (8, 16, 32, and 48 mg/kg, i.p.) results in tumor inhibition by 70%, 70%, 89%, and 96%, respectively; Dinaciclib (SCH 727965) is well tolerated, and the maximum body weight loss in the highest dosage group is 5%. Dinaciclib has a short plasma half-life in mouse. A dose of 5 mg/kg Dinaciclib given i.p. in mice is associated with a plasma half-life of ~0.25 hour[1]. Treatment with Dinaciclib (SCH727965) given as twice weekly i.p. doses of 40 mg/kg for 4 weeks causes significant tumor growth inhibition (TGI) in 10/10 (100%) of low-passage subcutaneous pancreatic xenografts tested[2].			
Solvent&Solubility	***In Vitro:***			
	DMSO : ≥ 56 mg/mL (141.24 mM)			
	H_2O : < 0.1 mg/mL (insoluble)			
	* "≥" means soluble, but saturation unknown.			

	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
Preparing Stock Solutions	1 mM	2.5221 mL	12.6107 mL	25.2213 mL
	5 mM	0.5044 mL	2.5221 mL	5.0443 mL
	10 mM	0.2522 mL	1.2611 mL	2.5221 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 (6.31 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (6.31 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 (6.31 mM); Suspended solution 此方案可获得 ≥ 2.5 mg/mL (6.31 mM，饱和度未知) 的均匀悬浊液，悬浊液可用于口服和腹腔注射。 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。
References	[1]. Parry D, et al. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010 Aug;9(8):2344-53. [2]. Feldmann G, et al. Cyclin-dependent kinase inhibitor Dinaciclib (SCH727965) inhibits pancreatic cancer growth and progression in murine xenograft models. Cancer Biol Ther. 2011 Oct 1;12(7):598-609.

实验参考：

Cell Assay	A2780 cells are plated onto tissue culture dishes and propagated with the appropriate growth media. Growing cultures are exposed to increasing concentrations of Dinaciclib (0.75, 1.5, 3.15, 6.25, 12.5, 25, and 500 nM) or a vehicle control, typically for 7 days. After removing the medium, cells are fixed with 50% methanol/50% acetone for 5 minutes and stained with 0.2% crystal violet in 2% ethanol for 5 minutes. Following staining, cells are washed with 5 to 10 mL of water. Stained cells are solubilized in 1% deoxycholic acid, and the absorbance of the resulting solution is measured at 600 nm using a SOFTmax PRO 4.3 plate reader. Absorbance of Dinaciclib-treated samples is plotted as a percent of that of a vehicle-treated control, and data are reported as an IC50 value relative to these controls. For suspension cell lines, assessments of cell viability are obtained using the alamarBlue Cell Viability Assay kit[1].
Animal Administration	Mice[1] For tumor implantation, specific cell lines are grown in vitro, washed once with PBS, and resuspended in 50% Matrigel in PBS to a final concentration of 4×10^7 to 5×10^7 cells per milliliter. Nude mice are injected with 0.1 mL of this suspension s.c. in the flank region. Tumor length (L), width (W), and height (H) are measured by a caliper twice weekly on each mouse and then used to calculate tumor volume using the formula (L×W×H)/2. When the tumor volume reaches 100 mm^3, the animals are randomized to treatment groups (10 mice/group) and treated i.p. with either Dinaciclib (8, 16, 32, and 48 mg/kg daily, i.p.) or individual chemotherapeutic agents according to the dosing schedule indicated in table and figure legends. Tumor volumes and body weights are measured during and after the treatment periods.
Kinase Assay	Recombinant cyclin/CDK holoenzymes are purified from Sf9 cells engineered to produce baculoviruses that express a specific cyclin or CDK. Cyclin/CDK complexes are typically diluted to a final concentration of 50 μg/mL in a kinase reaction buffer containing 50 mM Tris-HCl (pH 8.0), 10 mM $MgCl_2$, 1 mM DTT, and 0.1 mM sodium orthovanadate. For each kinase reaction, 1 μg of enzyme and 20 μL of a 2 μM substrate solution (a biotinylated peptide derived from histone H1) are mixed and combined with 10 μL of diluted Dinaciclib (SCH 727965). The reaction is started by the addition of 50 μL of 2 μM ATP and 0.1 μCi of ^{33}P-ATP. Kinase reactions are incubated for 1 hour at room temperature and are stopped by the addition of 0.1% Triton X-100, 1 mM ATP, 5 mM EDTA,

	and 5 mg/mL streptavidin-coated SPA beads. SPA beads are captured using a 96-well GF/B filter plate and a Filtermate universal harvester. Beads are washed twice with 2 M NaCl and twice with 2 M NaCl containing 1% phosphoric acid. The signal is then assayed using a TopCount 96-well liquid scintillation counter. Dose-response curves are generated from duplicate, eight-point serial dilutions of inhibitory compounds. IC50 values are derived by nonlinear regression analysis[1].
References	[1]. Parry D, et al. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther. 2010 Aug;9(8):2344-53. [2]. Feldmann G, et al. Cyclin-dependent kinase inhibitor Dinaciclib (SCH727965) inhibits pancreatic cancer growth and progression in murine xenograft models. Cancer Biol Ther. 2011 Oct 1;12(7):598-609.