产品名称：**R547**
产品别名：**R547**

生物活性：

Description

R547 is a potent ATP-competitive inhibitor of CDK1/2/4 with Ki of 2 nM/3 nM/1 nM. IC50 Value: 2 nM(Ki for CDK1); 3 nM(Ki for CDK2); 1 nM(Ki for CDK4) Target: CDK in vitro: R547 effectively inhibits CDK1/cyclinB, CDK2/cyclinE, and CDK4/cyclinD1(Ki=1-3nM) and is inactive(Ki>5,000nM) against a panel of >120 unrelated kinases. R547 effectively inhibits the proliferation of tumor cell lines independent of multidrug resistant status, histologic type, retinoblastoma protein, or p53 status, with IC50s <0.60 μM. R547 reduces phosphorylation of the cellular retinoblastoma protein at specific CDK phosphorylation sites at the same concentrations that induced cell cycle arrest, suggesting a potential pharmaco dynamics marker for clinical use. R547 inhibits the proliferation of tumor cell lines and is active in all 19 cell lines tested irrespective of tissue of origin, multidrug resistance (MDR), p53, or retinoblastoma status. R547 possessing both 5-and 6-fluoro substitution culminated in an Inhibitor with low, single-digit nanomolar potency against the CDKs(Ki=0.001,0.003,and 0.001 μM for CDK1,CDK2, and CDK4,respectively) and excellent cellular potency (IC50=0.08 μM,HCT116 cell line). in vivo: R547 administered with oral and i.v. dosing in multiple established human tumor significantly inhibits tumor activity(P < 0.01). R547 administered orally at dose of 40 mg/kg daily in colon, lung, breast, prostate, and melanoma human tumor xenograft models shows significant TGI (79-99%). R547 is equally efficacious (TGI, 61-95%) when dosed with 40 mg/kg i.v. once weekly. These doses of R547 are not toxic and did not result in body weight loss. R547 does not show signs of overt toxicity during the course of the 3-week study and any gross pathology at necropsies done at the end of the studies. R547 inhibits tumor growth up to 95% in the HCT116 human colorectal tumor xenograft model in nude mice . R547 causes significant TGI in all of the models tested when dosed orally and i.v. at or below the maximum tolerated dose. R547 inhibits phosphorylation of retinoblastoma protein in tumors at the efficacious exposures in tumor xenograft models, providing a pharmacodynamic biomarker for clinical use. R547 reported here suggests that this is a promising molecule for evaluation in the treatment of solid tumors.

IC_{50} & Target [1]

Cdk1/cyclin B	CDK4/cyclin D	CDK2/cyclinE
2 nM (Ki)	1 nM (Ki)	3 nM (Ki)

In Vitro:

DMSO : ≥ 50 mg/mL (**113.26 mM**)

H_2O : < 0.1 mg/mL (insoluble)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.2653 mL	11.3263 mL	22.6526 mL
5 mM	0.4531 mL	2.2653 mL	4.5305 mL
10 mM	0.2265 mL	1.1326 mL	2.2653 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

Solvent&Solubility	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 (5.66 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.66 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 (5.66 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (5.66 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]. Chu XJ, DePinto W, Bartkovitz D, So SS, Vu BT, Packman K, Lukacs C, Ding Q, Jiang N, Wang K, Goelzer P, Yin X, Smith MA, Higgins BX, Chen Y, Xiang Q, Moliterni J, Kaplan G, Graves B, Lovey A, Fotouhi N.Discovery of [4-Amino-2-(1-methanesulfonylpiperidin-4 [2]. Bayés M, Rabasseda X, Prous JR.Gateways to clinical trials.Methods Find Exp Clin Pharmacol. 2007 Jul-Aug;29(6):427-37. [3]. Martin F, Thomson TM, Sewer A, Drubin DA, Mathis C, Weisensee D, Pratt D, Hoeng J, Peitsch MC.Assessment of network perturbation amplitudes by applying high-throughput data to causal biological networks.BMC Syst Biol. 2012 May 31;6:54. [4]. DePinto, Wanda et al In vitro and in vivo activity of R547: a potent and selective cyclin-dependent kinase inhibitor currently in phase I clinical trials Molecular Cancer Therapeutics (2006), 5(11), 2644-2658 [5]. Jones, Clifford D.; Andrews, David M. Imidazole pyrimidine amides as potent, orally bioavailable cyclin-dependent kinase inhibitors Bioorganic & Medicinal Chemistry Letters (2008), 18(24), 6486-6489