产品名称：AT13148
产品别名：AT13148

生物活性：

Description	AT13148 is an orally active and ATP-competitive, multi-AGC kinase inhibitor with IC_{50}s of 38 nM/402 nM/50 nM, 8 nM, 3 nM, and 6 nM/4 nM for Akt1/2/3, p70S6K, PKA, and ROCKI/II, respectively.					
IC_{50} & Target	Akt1	Akt3	Akt2	PKA	ROCKII	ROCKI
	38 nM (IC_{50})	50 nM (IC_{50})	402 nM (IC_{50})	3 nM (IC_{50})	4 nM (IC_{50})	6 nM (IC_{50})
	SGK3	RSK1	CHK2	Aurora		
	63 nM (IC_{50})	85 nM (IC_{50})	860 nM (IC_{50})	1840		
In Vitro	AT13148 inhibits a panel of kinases at 10 μM, and the IC50 values for p70S6K, PKA, ROCKI, and ROCKII are all less than 10 nM and those for AKT1, 2, and 3 are 38, 402, and 50 nM, respectively. For the related AGC kinases RSK1 and SGK3, the IC50 values are 85 and 63 nM, respectively. In contrast, IC50 values for the non-AGC kinases CHK2 and Aurora B are both greater than 800 nM. AT13148 potently inhibits proliferation with GI50 values of 1.5 to 3.8 μM across a selected panel of cancer cell lines[1]. AT13148 treatment in gastric cancer cells dramatically suppresses activation of multiple AGC kinases, including Akt (at p-Thr-308), p70S6 kinase (p70S6K), glycogen synthase kinase 3β (GSK-3β) and p90 ribosomal S6 kinase (RSK)[2]..					
In Vivo	Oral drug administration of 5 mg/kg of AT13148 results in complete bioavailability. Clear inhibition of phosphorylation of the AKT substrates GSK3β, tuberin, and the p70S6K target S6RP are also observed in PTEN-deficient MES-SA human uterine tumor xenografts after treatment with 40 and 50 mg/kg p.o. of AT13148[1]. Oral gavage of AT13148 at well-tolerated doses significantly inhibits HGC27 xenograft tumor growth in nude mice. AGC activity is also dramatically decreased in AT13148-administrated HGC27 tumors[2].					
Solvent&Solubility	***In Vitro:*** **DMSO : 50 mg/mL (159.35 mM;** Need ultrasonic)					

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.1869 mL	15.9347 mL	31.8695 mL
	5 mM	0.6374 mL	3.1869 mL	6.3739 mL
	10 mM	0.3187 mL	1.5935 mL	3.1869 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 (7.97 mM); Clear solution

	此方案可获得 ≥ 2.5 mg/mL (7.97 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 (7.97 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.97 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 (7.97 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (7.97 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]. Yap TA, et al. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 2012 Jul 15;18(14):3912-23. [2]. Xi Y, et al. AT13148, a first-in-class multi-AGC kinase inhibitor, potently inhibits gastric cancer cells both in vitro and in vivo. Biochem Biophys Res Commun. 2016 Sep 9;478(1):330-6.

实验参考：

Cell Assay	Cells are seeded onto 96-well micro-plates at a density of 1×10^4 cells per well. After treatment, MTT solution (0.5 mg/mL) is added for 2-3 h. The MTT-purple formazan productions are dissolved in 0.1 N hydrochloric acid, and optical density (OD) is obtained through the micro-plate reader at 570 nm wavelength. [2]
Animal Administration	For pharmacokinetic analysis, male athymic BALB/c mice are obtained from Harlan. AT13148 is formulated in 10% DMSO, 1% Tween-20, and 89% saline and administered at 5 mg/kg i.v. or p.o. Duplicate samples of heparinized whole blood are collected by cardiac puncture at 1, 2, 4, 6, 8, 16, 24, and 72 hours after dosing. Plasma and tissues (liver, kidney, spleen, and muscle are also taken) are prepared and frozen at −20°C until analysis. AT13148 is extracted from plasma and tissues using acetonitrile containing an internal standard and quantified using a liquid chromatography tandem mass spectrometry (LC-MS/MS) method and appropriate standard curves. Pharmacokinetic parameters are determined using WinNonLin software version 5.2. [1]
Kinase Assay	AT13148 is assayed against 40 kinases and the percentage inhibition at 10 μM of AT13148 is determined. Individual IC_{50} values are measured for selected kinases using ATP concentrations equivalent to the K_m for each enzyme. [1]
References	[1]. Yap TA, et al. AT13148 is a novel, oral multi-AGC kinase inhibitor with potent pharmacodynamic and antitumor activity. Clin Cancer Res. 2012 Jul 15;18(14):3912-23. [2]. Xi Y, et al. AT13148, a first-in-class multi-AGC kinase inhibitor, potently inhibits gastric cancer cells both in vitro and in vivo. Biochem Biophys Res Commun. 2016 Sep 9;478(1):330-6.