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产品名称：SCH-1473759 (hydrochloride)
产品别名：SCH-1473759 hydrochloride

生物活性：

Description	SCH-1473759 hydrochloride is an aurora inhibitor with IC50s of 4 and 13 nM for aurora A and B, respectively.	
IC_{50} & Target	Aurora A	Aurora B
	4 nM (IC_{50})	13 nM (IC_{50})
In Vitro	SCH-1473759 directly binds to aurora A and B with Kds of 20 and 30 nM, respectively. SCH-1473759 also inhibits the Src family of kinases (IC50<10 nM), Chk1 (IC50=13 nM), VEGFR2 (IC50=1 nM), and IRAK4 (IC50=37 nM). It does not have significant activity (IC50>1000 nM) against 34 other kinases representing different families of the kinome. SCH-1473759 inhibits HCT116 cells proliferation with an IC50 of 6 nM[1]. SCH 1473759 inhibits tumor cell lines from different tissues (breast, ovarian, prostate, lung, colon, brain, gastric, renal, skin, and leukemia). The most sensitive cell lines includ A2780, LNCap, N87, Molt4, K562, and CCRF-CEM with IC50 values <5 nM[2].	
In Vivo	SCH-1473759 at a low dose of 5 mg/kg (ip, bid) is well-tolerated in a continuous dosing schedule and shows 50% tumor growth inhibition(TGI) on day 16. A higher dose of 10mg/kg(ip, bid) is well-tolerated in an intermittent schedule (5 days on, 5 days off) and gave 69% TGI on day 16. SCH-1473759 shows good exposure in all species with the clearance being high in rodents and moderate in dog and monkey. The half-life is also moderate, but the tissue distribution is high[1]. SCH 1473759 dose- and schedule-dependent anti-tumor activity in four human tumor xenograft models. Further, the efficacy is enhanced in combination with taxanes and found to be most efficacious when SCH 1473759 is dosed 12-h post-taxane treatment[2].	
Solvent&Solubility	***In Vitro:***	
	DMSO : 70 mg/mL (151.19 mM; Need ultrasonic)	

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1598 mL	10.7991 mL	21.5983 mL
	5 mM	0.4320 mL	2.1598 mL	4.3197 mL
	10 mM	0.2160 mL	1.0799 mL	2.1598 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

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	1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline Solubility: ≥ 2.75 mg/mL (5.94 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.94 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 27.5 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: ≥ 2.75 mg/mL (5.94 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.94 mM，饱和度未知) 的澄清溶液。 以 1 mL 工作液为例，取 100 μL 27.5 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: ≥ 2.75 mg/mL (5.94 mM); Clear solution 此方案可获得 ≥ 2.75 mg/mL (5.94 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 27.5 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中，混合均匀。
References	[1]. Yu T, et al. Discovery of a Potent, Injectable Inhibitor of Aurora Kinases Based on the Imidazo-[1,2-a]-Pyrazine Core. ACS Med Chem Lett. 2010 Jun 7;1(5):214-8. [2]. Basso AD, et al. SCH 1473759, a novel Aurora inhibitor, demonstrates enhanced anti-tumor activity in combination with taxanes and KSP inhibitors. Cancer Chemother Pharmacol. 2011 Oct;68(4):923-33.

实验参考：

Cell Assay	Cells are plated at a cell density ranging from 625 to 3,750 cells per well and treated in triplicate wells with SCH-1473759 (0.1% final DMSO concentration). A plate is stained at the start of the study (zero hour) and a second plate is incubated for 72 hour at 37°C and then stained. Cells are fixed with fixation solution plus 1,000 nM Hoechst 33342 dye and incubated for 30 minutes. The fixation solution is removed and cells are ished twice with PBS. Then 15 immunofluorescence images are captured at 10X using automated fluorescent microscope [1].
Animal Administration	Mice: Anti-tumor efficacy of SCH 1473759 dosed i.p. is evaluated in mice bearing established A2780 ovarian tumor xenografts. Three schedules are tested at their respective maximum tolerated doses: 10 mg/kg bid (twice daily), 20 mg/kg qd (daily), and 100 mg/kg day 0, 4, 7. Additionally, 60 mg/kg day 0, 4, 7 is tested[2].
Kinase Assay	Aurora A and Aurora B kinase assays are performed in low protein binding 384-well plates. SCH-1473759 is diluted in 100% DMSO to the desired concentrations. For the Aurora A assay, each reaction consists of 8 nM enzyme Aurora A, 100 nM Tamra-PKAtide, 25μM ATP, 1 mM DTT, and kinase buffer. For the Aurora B assay, each reaction consisted of 26 nM enzyme Aurora B, 100 nM Tamra-PKAtide, 50 μM ATP, 1 mM DTT, and kinase buffer. Dose-response curves are plotted from inhibition data generated in duplicate, from 8 point serial dilutions of SCH-1473759[1].
	[1]. Yu T, et al. Discovery of a Potent, Injectable Inhibitor of Aurora Kinases Based on the Imidazo-[1,2-a]-Pyrazine Core. ACS Med Chem Lett. 2010 Jun 7;1(5):214-8.

References	[2]. Basso AD, et al. SCH 1473759, a novel Aurora inhibitor, demonstrates enhanced anti-tumor activity in combination with taxanes and KSP inhibitors. Cancer Chemother Pharmacol. 2011 Oct;68(4):923-33.