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产品名称：RO4987655(CH4987655)
产品别名：RO4987655

生物活性：

Description	RO4987655 is an orally active and highly selective MEK inhibitor with an IC50 of 5.2 nM for inhibition of MEK1/MEK2.	
IC_{50} & Target	MEK1	MEK2
	5.2 nM (IC_{50})	5.2 nM (IC_{50})
In Vitro	RO4987655 potently inhibits mitogen-activated protein kinase signaling pathway activation and tumor cell growth, with an in vitro IC50 of 5.2 nM for inhibition of MEK1/2[1]. RO4987655 inhibits proliferation of NCI-H2122 cells in a dose-dependent manner with an IC50 value of 0.0065 μM. RO4987655 at doses ranging from 0.1 to 1.0 μM suppresses pERK1/2 already at 2 h after the start of treatment[2].	
In Vivo	Single-agent oral administration of RO4987655 (CH4987655) results in complete tumor regressions in xenograft models. RO4987655 is rapidly absorbed with a t_{max} of ~1 h. Exposures are dose proportional from 0.5 to 4 mg. The disposition is biphasic with a terminal $t_{1/2}$ of ~25 hr. Intersubject variability is low, 9% to 23% for C_{max} and 14% to 25% for area-under-the-curve (AUC). pERK inhibition is exposure dependent and is greater than 80% inhibition at higher doses. The pharmacokinetic-pharmacodynamic relationship is characterized by an inhibitory E_{max} model (E_{max} ~100%; IC_{50} 40.6 ng/mL) using nonlinear mixed-effect modeling[1]. Female athymic nude mice are randomized into study groups. The tumors size is estimated with digital caliper and PET scans performed on days 0, 1, and 3 with 1.0, 2.5, and 5.0 mg/kg RO4987655. The vehicle treatment does not inhibit the NCI-H2122 tumor xenograft growth over this time frame. In contrast, RO4987655 treatment results in 119% tumor growth inhibition (TGI) at 1.0 mg/kg, 145% TGI at 2.5 mg/kg and 150% TGI at 5.0 mg/kg on day 3. PET imaging shows that [^{18}F] FDG uptake in the xenografts decreases within 24 h (day 1) from the administration of RO4987655[2].	

Solvent&Solubility

In Vitro:

DMSO : 100 mg/mL (**176.90 mM**; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7690 mL	8.8452 mL	17.6903 mL
	5 mM	0.3538 mL	1.7690 mL	3.5381 mL
	10 mM	0.1769 mL	0.8845 mL	1.7690 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 (4.42 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.42 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 (4.42 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.42 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 (4.42 mM); Clear solution 此方案可获得 ≥ 2.5 mg/mL (4.42 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]. Lee L, et al. The safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of CH4987655 in healthy volunteers: target suppression using a biomarker. Clin Cancer Res. 2009 Dec 1;15(23):7368-74. [2]. Tegnebratt T, et al. Evaluation of efficacy of a new MEK inhibitor, RO4987655, in human tumor xenografts by [(18)F] FDG-PET imaging combined with proteomic approaches. EJNMMI Res. 2014 Dec;4(1):34.

实验参考：

Cell Assay	The human lung adenocarcinoma cell line NCI-H2122 are maintained in the designated media and indicated concentrations of heat-inactivated fetal bovine serum and L-glutamine. Cells are grown at 37°C in an atmosphere of 5%CO_2. Cells are treated with various concentrations of RO4987655 (0.00001, 0.001, 0.1, and 10 μM) for 72 h in 96-well plates and viable cells were quantified with Cell Counting Kit-8[2].
Animal Administration	Mice[2] Female athymic nude mice Balb nu/nu, age 5 to 6 weeks (18 to 22 g) are used. NCI-H2122 cells (4×10^6/mouse) are inoculated subcutaneously in the right flank of Balb-nu/nu mice. Once tumors are established (100 to 200 mm^3), mice are randomized into groups with similar mean tumor volumes at the start of the study. The tumors size is estimated with digital caliper and PET scans performed on days 0, 1, and 3 with 1.0, 2.5, and 5.0 mg/kg RO4987655. Tumor volume and body weight are measured on days 0 (baseline), 1, 2, 3, and 9 of [18F] FDG-PET imaging. Tumor growth inhibition is calculated[2].
	[1]. Lee L, et al. The safety, tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of CH4987655 in healthy volunteers: target suppression using a biomarker. Clin Cancer Res. 2009 Dec 1;15(23):7368-74.

References	[2]. Tegnebratt T, et al. Evaluation of efficacy of a new MEK inhibitor, RO4987655, in human tumor xenografts by [(18)F] FDG-PET imaging combined with proteomic approaches. EJNMMI Res. 2014 Dec;4(1):34.