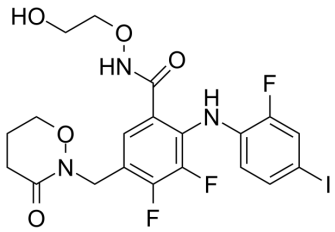
RO4987655

Cat. No.:	HY-14719
CAS No.:	874101-00-5
Molecular Formula:	$C_{20}H_{19}F_3IN_3O_5$
Molecular Weight:	565.28
Target:	MEK
Pathway:	MAPK/ERK Pathway
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



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

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.42 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

RO4987655 is an orally active and highly selective MEK inhibitor with an IC_{50} 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 IC_{50} of 5.2 nM for inhibition of MEK1/2[1]. RO4987655 inhibits proliferation of NCI-H2122 cells in a dose-dependent

	manner with an IC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Science. 2017 Dec 1;358(6367):eaan4368.
- Cancer Discov. 2021 Jul;11(7):1716-1735.
- ACS Comb Sci. 2019 Dec 9;21(12):805-816.

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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.

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