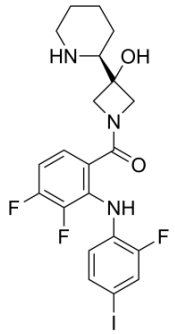
Cobimetinib



Cat. No.:	HY-13064
CAS No.:	934660-93-2
Molecular Formula:	$C_{21}H_{21}F_3IN_3O_2$
Molecular Weight:	531.31
Target:	MEK; Apoptosis
Pathway:	MAPK/ERK Pathway; Apoptosis
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month

SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (188.21 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8821 mL	9.4107 mL	18.8214 mL
	5 mM	0.3764 mL	1.8821 mL	3.7643 mL
	10 mM	0.1882 mL	0.9411 mL	1.8821 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 (4.71 mM); Clear solution
2. Add each solvent one by one: **10% DMSO >> 90% (20% SBE-β-CD in saline)**
   Solubility: ≥ 2.5 mg/mL (4.71 mM); Clear solution
3. Add each solvent one by one: **10% DMSO >> 90% corn oil**
   Solubility: ≥ 2.5 mg/mL (4.71 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Cobimetinib (GDC-0973, RG7420) is a potent, selective and oral **MEK1** inhibitor with an **IC_{50}** of 4.2 nM for **MEK1**.

IC_{50} & Target

MEK1
4.2 nM (IC_{50})

In Vitro	The EC_{50} values of Cobimetinib (GDC-0973) for 888MEL and A2058 cells are 0.2 μM, 10 μM, respectivelly. Melanoma cells are treated with EC_{50} concentration of MEK and PI3K inhibitors for 24 hours (888MEL: 0.05 μM GDC-0973, 2.5 μM GDC-0941; A2058: 2.5 μM GDC-0973, 2.5 μM GDC-0941)[1]. Mitochondrial OXPHOS limits cell death induced by cobimetinib (100 nM) in melanoma with constitutive MAPK activation in A375 cells[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In the NCI-H2122 KRASG12C mutant non-small cell lung carcinoma (NSCLC) xenograft model, treatment with up to 5 mg/kg Cobimetinib (GDC-0973) lead to moderate TGI and at 10 mg/kg approaches tumor stasis[1]. GDC-0973 and GDC-0941 are administered to A2058 tumor-bearing mice daily (QD) or every third day (Q3D) either as single agents or in combination. The population rate constants associated with tumor growth inhibition for GDC-0973 and GDC-0941 are 0.00102 and 0000651 μM^{-1} h^{-1}, respectively[2]. Following single doses of GDC-0973 (1, 3, or 10 mg/kg, p.o.) estimated in vivo IC_{50} values of %pERK decrease based on tumor concentrations in xenograft mice are 0.78 (WM-266-4) and 0.52 μM (A375)[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [3]	5 million WM-266-4 melanoma cells are resuspended in Hank balanced salt solution and implanted intradermally into the hind flank of female NCR nude mice. On days 11 or 13 after the implantation, xenograft mice with tumor volumes of approximately 100 to 120 mm^3 are randomLy assigned to 8 groups (n=27 per group), 4 single dose groups and 4 multiple dose groups. One day after randomization and group assignment, mice in the single dose groups are given a single oral dose of vehicle (water for injection USP), 1, 3, or 10 mg/kg of Cobimetinib (GDC-0973, expressed as free base equivalents). Mice in the multiple dose groups are given daily oral doses of vehicle (water for injection USP), 1, 3, or 10 mg/kg of GDC-0973 for 14 days. Plasma and tumor samples (n=3 per time point) are collected from euthanized mice predose and at 2, 4, 8, 16, 24, 72, 120, and 168 hours postdose on day 1 (single dose groups) or day 14 (multiple dose groups). Samples are stored at −80°C until analysis. GDC-0973 concentrations in plasma and tumor lysates are determined using liquid chromatography/tandem mass spectrometry (LC/MS-MS). The dynamic range of the assay is 0.004 to 35 μM. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- **Sci Transl Med**. 2018 Jul 18;10(450). pii: eaaq1093.
- **Neuro Oncol**. 2019 Mar 18;21(4):486-497.
- **J Control Release**. 2015 Oct 21;220(Pt A):160-168.
- **Sci Signal**. 2018 Oct 30;11(554). pii: eaar6795.
- **Sci Signal**. 2018 Oct 30;11(554):eaar6795.

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REFERENCES

[1]. Hoeflich KP, et al. Intermittent administration of MEK inhibitor GDC-0973 plus PI3K inhibitor GDC-0941 triggers robust apoptosis and tumor growth inhibition. Cancer Res. 2012 Jan 1;72(1):210-9.

[2]. Choo EF, et al. PK-PD modeling of combination efficacy effect from administration of the MEK inhibitor GDC-0973 and PI3K inhibitor GDC-0941 in A2058 xenografts. Cancer Chemother Pharmacol. 2013 Jan;71(1):133-43.

[3]. Wong H, et al. Bridging the gap between preclinical and clinical studies using pharmacokinetic-pharmacodynamic modeling: an analysis of GDC-0973, a MEK inhibitor. Clin Cancer Res. 2012 Jun 1;18(11):3090-9.

[4]. Corazao-Rozas P, et al. Mitochondrial oxidative phosphorylation controls cancer cell's life and death decisions upon exposure to MAPK inhibitors. Oncotarget. 2016 Feb 29. doi: 10.18632/oncotarget.7790.

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