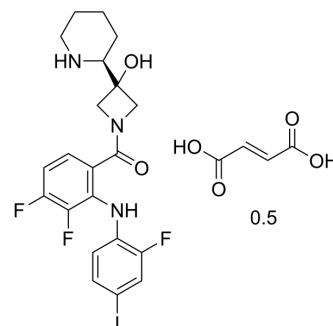


Cobimetinib hemifumarate

Cat. No.:	HY-13064A
CAS No.:	1369665-02-0
Molecular Formula:	C ₂₁ H ₂₁ F ₃ IN ₃ O ₂ ·1/2C ₄ H ₄ O ₄
Molecular Weight:	589.25
Target:	MEK; Apoptosis
Pathway:	MAPK/ERK Pathway; Apoptosis
Storage:	4°C, sealed storage, away from moisture * In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro	DMSO : 50 mg/mL (84.85 mM; Need ultrasonic)					
	Preparing Stock Solutions	Solvent	Mass	1 mg	5 mg	10 mg
		Concentration				
		1 mM		1.6971 mL	8.4854 mL	16.9707 mL
5 mM			0.3394 mL	1.6971 mL	3.3941 mL	
	10 mM		0.1697 mL	0.8485 mL	1.6971 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 (4.24 mM); Clear solution					
	2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.24 mM); Clear solution					
	3. Add each solvent one by one: 10% DMSO >> 90% corn oil Solubility: ≥ 2.5 mg/mL (4.24 mM); Clear solution					
	4. Add each solvent one by one: 5% DMSO >> 40% PEG300 >> 5% Tween-80 >> 50% saline Solubility: ≥ 2.5 mg/mL (4.24 mM); Clear solution					
	5. Add each solvent one by one: 5% DMSO >> 95% (20% SBE-β-CD in saline) Solubility: ≥ 2.5 mg/mL (4.24 mM); Clear solution					

BIOLOGICAL ACTIVITY

Description	Cobimetinib hemifumarate is a novel selective MEK1 inhibitor, and the IC ₅₀ value against MEK1 is 4.2 nM.
IC₅₀ & Target	MEK1 4.2 nM (IC ₅₀)

In Vitro	<p>The EC₅₀ values of Cobimetinib (GDC-0973) for 888MEL and A2058 cells are 0.2 μM, 10 μM, respectively. Melanoma cells are treated with EC₅₀ 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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>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 IC₅₀ values of %pERK decrease based on tumor concentrations in xenograft mice are 0.78 (WM-266-4) and 0.52 μM (A375)^[3].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

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 mm³ 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

- Nat Nanotechnol. 2021 Jul;16(7):830-839.
- Sci Transl Med. 2021 Jan 27;13(578):eaba7308.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- J Exp Med. 2022 Apr 4;219(4):e20210739.
- Bioact Mater. 8 September 2021.

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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.

Caution: Product has not been fully validated for medical applications. For research use only.

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