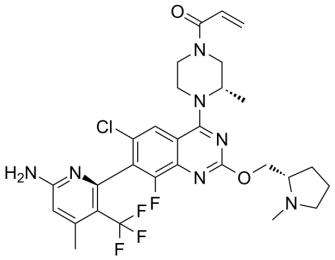
Divarasib

Cat. No.:	HY-145928
CAS No.:	2417987-45-0
Molecular Formula:	$C_{29}H_{32}ClF_4N_7O_2$
Molecular Weight:	622.06
Target:	Ras
Pathway:	GPCR/G Protein
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 (160.76 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6076 mL	8.0378 mL	16.0756 mL
	5 mM	0.3215 mL	1.6076 mL	3.2151 mL
	10 mM	0.1608 mL	0.8038 mL	1.6076 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 (4.02 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (4.02 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.02 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Divarasib (GDC-6036) is an orally bioavailable, highly potent, and selective KRAS G12C inhibitor with an IC_{50} of <0.01 μM. Divarasib covalently binds to the switch II (SW-II) pocket of KRAS G12C and irreversibly locks it in the inactive GDP-bound state.

IC_{50} & Target

K-Ras(G12C)
<0.01 μM (IC_{50})

In Vitro	Divarasib (compound 17a) has an EC_{50} of 2 nM in K-Ras G12C-alkylation HCC1171 cells[2] MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Divarasib (10-100 mg/kg/day; PO for 7 days) decreases the ratio of free KRAS G12C[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Female C.B-17 SCID (Inbred) mice (20-21 weeks old; 24.1 g) with human NSCLC NCI-H2030.X1.1 cells[1]
Dosage:	10, 25, or 100 mg/kg
Administration:	Oral gavage (PO) every day (QD) for 7 days (vehicle: 0.5% methylcellulose)
Result:	Decreased the ratio of free KRAS G12C to internal standard. Dose-dependent target engagement was observed for all time points (2, 8, and 24 h post-last dose), with over 90% KRAS G12C engagement observed for the highest dose 100 mg/kg assessed.

REFERENCES

[1]. Lingyao Meng, et al. Assessment of KRAS G12C Target Engagement by a Covalent Inhibitor in Tumor Biopsies Using an Ultra-Sensitive Immunoaffinity 2D-LC-MS/MS Approach. Anal Chem. 2022 Sep 20;94(37):12927-12933.

[2]. Sushant Malhotra, et al. Fused ring compounds. WO2020097537A2.

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