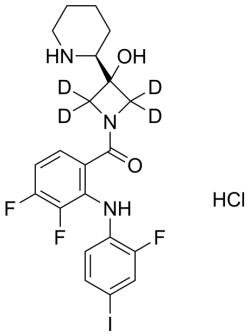
Cobimetinib-d_4 hydrochloride

Cat. No.:	HY-13064S1
Molecular Formula:	$C_{21}H_{18}D_4ClF_3IN_3O_2$
Molecular Weight:	571.8
Target:	MEK; Apoptosis; Isotope-Labeled Compounds
Pathway:	MAPK/ERK Pathway; Apoptosis; Others
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Cobimetinib-d_4 hydrochloride is deuterated labeled Cobimetinib (HY-13064). Cobimetinib (GDC-0973, RG7420) is a potent, selective and oral MEK1 inhibitor with an IC_{50} of 4.2 nM for MEK1.
In Vitro	Stable heavy isotopes of hydrogen, carbon, and other elements have been incorporated into drug molecules, largely as tracers for quantitation during the drug development process. Deuteration has gained attention because of its potential to affect the pharmacokinetic and metabolic profiles of drugs[1]. 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)[2]. Mitochondrial OXPHOS limits cell death induced by cobimetinib (100 nM) in melanoma with constitutive MAPK activation in A375 cells[5]. 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[2]. 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[3]. 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)[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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]. 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.

[3]. 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.

[4]. 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.

[5]. Russak EM, et al. Impact of Deuterium Substitution on the Pharmacokinetics of Pharmaceuticals. Ann Pharmacother. 2019 Feb;53(2):211-216.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA