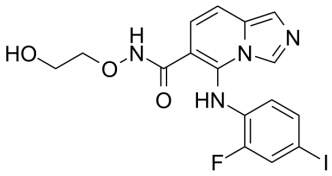
GDC-0623

Cat. No.:	HY-15610
CAS No.:	1168091-68-6
Molecular Formula:	$C_{16}H_{14}FIN_4O_3$
Molecular Weight:	456.21
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 : 50 mg/mL (109.60 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1920 mL	10.9599 mL	21.9197 mL
	5 mM	0.4384 mL	2.1920 mL	4.3839 mL
	10 mM	0.2192 mL	1.0960 mL	2.1920 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 (5.48 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.48 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GDC-0623 (RG 7421) is a potent, ATP-uncompetitive inhibitor of MEK1 (K_i=0.13 nM, +ATP), and displays 6-fold weaker potency against HCT116 (KRAS (G13D), EC_{50}=42 nM) versus A375 ($BRAF^{V600E}$, EC_{50}=7 nM).

IC_{50} & Target

MEK1
0.13 nM (Ki, +ATP)

In Vitro

GDC-0623 (RG 7421) and G-573 are able to prevent MEK phosphorylation by CRAF in vitro, and able to block MEK phosphorylation by BRAF(V600E)[1]. GDC-0623 (RG 7421) is potent, ATP-uncompetitive inhibitors of MEK1 but shows distinct shifts in cellular activity compared with the other two inhibitors, only 6-fold half-maximum effective concentration (EC_{50}) decreases[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	GDC-0623 (RG 7421) (40 mg/kg, p.o.) shows percent tumour growth inhibition (%TGI) in MiaPaCa-2 xenograft model. GDC-0623 (RG 7421) and G-573 show superior antitumour activity compared to GDC-0623 (RG 7421) in all three KRAS models[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Flag-MEK1 mutants, S212P and S212A, are generated using the QuickChange site directed mutagenesis kit. Mammalian expression vectors for N-terminal Flag tagged MEK-1 are expressed in HCT116 cells. 1.8×10^6 HCT116 cells are plated in 10 cm plate and transfected on the following day with 17 μg of expression constructs using lipofectamine 2000. After 48 hours cells are treated with inhibitors for the indicated times, harvested and lysed in 100 μL cell extraction buffer. Cell lysates from each sample are analyzed by SDS-PAGE. Membranes are incubated with phospho-MEK S221, phospho-ERK1/2 and MEK1 primary antibodies and immunoreactive proteins are analyzed by SuperSignal West Pico Chemiluminescent Substrate. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Colo205 xenografts are established by inoculating 5×10^6 cells resuspended in Hank's Balanced Salt Solution (HBSS) subcutaneously (s.c.) in the rear right flank of 6-8 week old female nude (nu/nu) mice. NCI-H2122 xenografts are established by inoculating 1×10^7 cells resuspended in Hank's Balanced Salt Solution (HBSS) plus matrigel (growth factor reduced) s.c. in the rear right flank of 6-8 week old female nu/nu mice. Both A375 and MiaPaca-2 xenografts are initiated by transplanting 1 mm^3 tumor fragments from their respective passaged tumors s.c. into the flank of athymic nu/nu mice. When tumors reached appr 200 mm^3, mice are randomized and treated with daily (QD) oral gavage (PO) with either vehicle [methylcellulose 0.1% tween 80 0.1% (MCT)], GDC-0973 (at 10 mg/kg), GDC-0623 (RG 7421) (40 mg/kg), or G-573 (100 mg/kg). All doses of MEK inhibitors represented maximal tolerated doses (MTDs), resulting in no more than 15-20% body weight loss. Tumor volumes are determined using digital calipers using the formula (L×W×W)/2. Tumor growth inhibition (%TGI) iscalculated as the percentage of the area under the fitted curve (AUC) for the respective dose group per day in relation to the vehicle. Animal weights are recorded twice per week and mice are removed from study if body weights dropped ≥20%. Partial responses (PRs) are defined as any tumor demonstrating a ≥ 50% decrease in tumor volume, whereas complete responses (CRs) are defined as any tumor demonstrating 100% reduction in tumor volume at any point during the study. 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):eaaq1093.
- Sci Signal. 2018 Oct 30;11(554):eaar6795.
- Cancers. 2019 Feb 1;11(2):164.
- ACS Comb Sci. 2019 Dec 9;21(12):805-816.
- Patent. US20170326205A1.

See more customer validations on www.MedChemExpress.com

REFERENCES

[1]. Hatzivassiliou G, et al. Mechanism of MEK inhibition determines efficacy in mutant KRAS- versus BRAF-driven cancers. Nature. 2013 Sep 12;501(7466):232-6.

[2]. Takahashi RH, et al. Elucidating the Mechanisms of Formation for Two Unusual Cytochrome P450-Mediated Fused Ring Metabolites of GDC-0623, a MAPK/ERK Kinase Inhibitor. Drug Metab Dispos. 2015 Dec;43(12):1929-1933.

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

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