Avutometinib

Cat. No.: HY-18652

CAS No.: 946128-88-7

Molecular Formula: $C_{21}H_{18}FN_5O_5S$

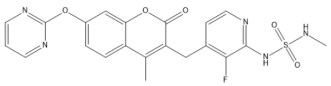
Molecular Weight: 471.46

Target: MEK; Raf

Pathway: MAPK/ERK Pathway

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 : 125 mg/mL (265.13 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1211 mL	10.6054 mL	21.2107 mL
5 mM	0.4242 mL	2.1211 mL	4.2421 mL
10 mM	0.2121 mL	1.0605 mL	2.1211 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: ≥ 2.08 mg/mL (4.41 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.41 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.41 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Avutometinib (Ro 5126766) is a first-in-class dual MEK/RAF inhibitor that allosterically inhibits $BRAF^{V600E}$, CRAF, MEK, and BRAF (IC_{50}: 8.2, 56, 160 nM, and 190 nM, respectively).

IC_{50} & Target

MEK	$BRaf^{V600E}$	Braf	CRAF
160 nM (IC_{50})	8.2 nM (IC_{50})	190 nM (IC_{50})	56 nM (IC_{50})

In Vitro

Avutometinib (Ro 5126766) is an allosteric inhibitor that binds directly to MEK and prevents its phosphorylation by RAF

	through the formation of a stable RAF-MEK complex. Ro 5126766 inhibits both the phosphorylation of MEK by RAF and the activation of ERK by MEK. In cell-free MEK and RAF kinase assays, Avutometinib effectively inhibits activation of ERK2 by MEK1 with an IC_{50} of 160 nM (SD=±0.043) and inhibits the phosphorylation of MEK1 protein by BRAF (IC_{50}=190 nM, SD=±0.003), $BRAF^{V600E}$ (IC_{50}=8.2 nM, SD=±0.0015), and CRAF (IC_{50}=56 nM, SD=±0.016). Avutometinib effectively inhibits both MEK and ERK phosphorylation in a panel of human tumor cell lines including KRAS/HRAS and BRAF mutant cell lines and KRAS/HRAS and BRAF wild-type cells[1]. In order to investigate whether the mevalonate pathway affects the sensitivity to MEK inhibitors, human breast cancer MDA-MB-231 cells harboring KRAS and BRAF mutations are treated Avutometinib, with or without statins, which inhibits HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway. The combined treatment of Avutometinib with XU 62-320 demonstrates more significant reduction in cell growth in a dose-dependent manner than the single treatment of Avutometinib. The marked combined effects of Avutometinib at 40 nM and XU 62-320 at 0.3 μM is also confirmed on the suppression of the colony formation of the cells[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	In KRAS-mutant xenograft models, Avutometinib (Ro 5126766) inhibits growth and causes tumor regressions more effectively than another allosteric MEK inhibitor, PD0325901. Preclinical data from a series of human tumor mouse xenograft models indicates an ED_{50} for Ro 5126766 of 0.03 to 0.23 mg/kg and an ED_{90} of 0.15 to 1.56 mg/kg. These effective doses are associated with target trough concentrations of 17 to 133 ng/L and 87 to 901 ng/mL, respectively. [1]. In this experiment, Avutometinib or PD0325901 is administrated at their maximum tolerated dose (MTD) in the HCT116 model (1.5 and 25 mg/kg, respectively). These doses inhibit pERK and ERK signaling output at similar degrees in the tumors from the drug-treated mice at 4 hours from the first drug administration. Moreover, in HCT116 models, the ED_{50} for Avutometinib and PD0325901 are 0.056 and 0.80 mg/kg, respectively. Therefore, the doses used for this experiment are 26.8- and 31.3-fold higher doses than the 50% effective doses, respectively. Daily oral administration of either drug causes significant tumor regression of each these tumors. However, whereas inhibition of tumor growth is maintained for the entire 28-day treatment period in Avutometinib-treated mice, tumor models receiving PD0325901 become refractory after 10 days of treatment[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	The number of viable cells is assessed with a Cell Counting Kit-8 assay. Human breast cancer MDA-MB-231 cells, human melanoma SK-MEL-28 cells, and human non-small cell lung cancer A549 cells are seeded at a density of 2,000 cells per well in 96-well plates and incubated for 24 h, and then treated with Ro 5126766 (10, 20, 40, and 80 nM) for 72 h. After a further 4 h incubation with the kit reagent, the absorbance at 450 nm of the samples is measured using a multi-plate reader[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Mice[3] Female BALB-***nu***/***nu*** mice (CAnN.Cg-Foxn1nu/CrlCrlj nu/nu) are given access to standard mouse chow and water ad libitum. A total of 5×10^6 (HCT116) or 1×10^7 (Calu-6 and COLO205) tumor cells per mouse are injected subcutaneously into the right flank of the 7- to 9-week-old mice. When tumor volume reaches to 200 mm^3 (day 0), the mice are randomized and vehicle [5% DMSO and 10% 2-hydroxypropyl-β-cyclodextrin (HPCD) solution in distilled water], Avutometinib (1.5 mg/kg or 2.0 mg/kg) or PD0325901 (25 mg/kg) is administered orally once a day. Drugs are administrated at the maximum tolerated dose (MTD). Tumor growth inhibition (TGI) is calculated. The value of the 50% effective dose (ED_{50}) for each compound is calculated[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Clin Sci (Lond). 2019 Apr 16;133(8):919-932.

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REFERENCES

[1]. Martinez-Garcia M, et al. First-in-human, phase I dose-escalation study of the safety, pharmacokinetics, and pharmacodynamics of RO5126766, a first-in-class dual MEK/RAF inhibitor in patients with solid tumors. Clin Cancer Res. 2012 Sep 1;18(17):4806-19.

[2]. Iizuka-Ohashi M, et al. Blockage of the mevalonate pathway overcomes the apoptotic resistance to MEK inhibitors with suppressing the activation of Akt in cancer cells. Oncotarget. 2018 Apr 13;9(28):19597-19612.

[3]. Ishii N, et al. Enhanced inhibition of ERK signaling by a novel allosteric MEK inhibitor, CH5126766, that suppresses feedback reactivation of RAF activity. Cancer Res. 2013 Jul 1;73(13):4050-4060.

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