# Ro 5126766

**Cat. No.:** HY-18652

**CAS No.:** 946128-88-7

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

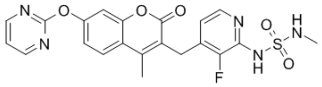
**Molecular Weight:** 471.46

**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 : 100 mg/mL (212.11 mM; Need ultrasonic)

$H_2O$ : < 0.1 mg/mL (insoluble)

**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**

Ro 5126766 (CH5126766) 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** | Ro 5126766 (RO5126766) 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, Ro 5126766 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). Ro 5126766 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 Ro 5126766 (CH5126766), with or without statins, which inhibits HMG-CoA reductase, the rate-limiting enzyme in the mevalonate pathway. The combined treatment of Ro 5126766 with XU 62-320 demonstrates more significant reduction in cell growth in a dose-dependent manner than the single treatment of Ro 5126766. The marked combined effects of Ro 5126766 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].<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |
| **In Vivo** | In KRAS-mutant xenograft models, Ro 5126766 (RO5126766) 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, Ro 5126766 (CH5126766) 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 Ro 5126766 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 Ro 5126766-treated mice, tumor models receiving PD0325901 become refractory after 10 days of treatment[3].<br>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].<br>MCE has not independently confirmed the accuracy of these methods. They are for reference only. |
| **Animal Administration** [3] | Mice[3]<br>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 $5\times10^6$ (HCT116) or $1\times10^7$ (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], Ro 5126766 (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].<br>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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