Trametinib (DMSO solvate)

Cat. No.: HY-10999A

CAS No.: 1187431-43-1

Molecular Formula: $C_{28}H_{29}FIN_5O_5S$

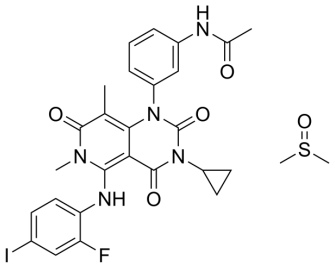
Molecular Weight: 693.53

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 : 3.33 mg/mL (4.80 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.4419 mL	7.2095 mL	14.4190 mL
	5 mM	---	---	---
	10 mM	---	---	---

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 (3.60 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (3.60 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (3.60 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Trametinib (DMSO solvate) (GSK-1120212 (DMSO solvate);JTP-74057 (DMSO solvate)) is an orally active MEK inhibitor that inhibits MEK1 and MEK2 with IC_{50}s of about 2 nM. Trametinib (DMSO solvate) activates autophagy and induces apoptosis[1] [2].

IC_{50} & Target

MEK1	MEK2
2 nM (IC_{50})	2 nM (IC_{50})

In Vitro	In BRAF mutant SK-MEL-28 cells and KRAS mutant HCT116 cells, Trametinib (GSK1120212;JTP-74057) DMSO solvate causes dose-dependent inhibition of ERK1/2 phosphorylation as well as dose-dependent growth inhibition. In both SK-MEL-28 and HCT116 cells, Trametinib DMSO solvate inhibits 50% p-ERK1/2 at nearly equivalent concentrations (0.8 and 1.8 nM, respectively). However, as the slopes of the curves reflect, in SK-MEL-28 cells, Trametinib DMSO solvate inhibits 90% p-ERK1/2 at a lower concentration (3.4 nM) than in HCT116 (33.3 nM). Furthermore, in both cell lines, 50% growth inhibition is only achieved at concentrations Trametinib DMSO solvate that produces near complete ERK1/2 inhibition (85 and 90%, respectively)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Trametinib (GSK1120212;JTP-74057) is evaluated in vivo in an A549 (KRAS mutant cell line) xenograft model, orally dosing daily for 21 days (qd×21). In this study, near complete tumor growth inhibition is observed at 5.0 and 2.5 mg/kg [92 and 87% tumor growth inhibition (TGI), respectively] and to a lesser degree at 0.5 and 0.1 mg/kg (62 and 58% TGI). Although 5 mg/kg is the maximally tolerated dose (MTD) in this study, 3 mg/kg is the typically observed MTD. Dose-dependent antitumor activity with Trametinib treatment has been similarly reported for several other KRAS and BRAF mutant tumor models[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	SK-MEL-28, and HCT116 cell lines are plated in triplicate 96 well microtitre plates at 5000 cells per well in culture media. Trametinib dissolved in DMSO or negative control (0.1% DMSO) are added the following day and one plate is harvested with 50 µL of CellTiter-Glo for a time 0 (T=0) measurement. Remaining duplicate cell plates are typically incubated for 72 h. Cells are then lysed with 50 µL CellTiter-Glo, and chemiluminescent signal is read on the Wallac EnVision 2100 plate reader. For measurement of cellular ERK1/2 phosphorylation, cells are seeded and treated with Trametinib, and lysed after 72 h in Tris lysis buffer supplemented with phosphatase and protease inhibitors. All samples are analyzed with a phospho-ERK1/2 ELISA. Plates are read on MSD.SI6000 and curves are analyzed using the XLfit curve-fitting tool. For comparison of the growth assay curve and pERK1/2 assay curve, data are background subtracted and normalized to the vehicle treatment control[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] A549 (human non-small cell lung carcinoma) model is established from cells grown in tissue culture and harvested aseptically using a trypsin digest. Female athymic mice (strain nu/nu) are injected subcutaneously with between 5×10^6 and 10^7 cells in 50% martigel. Tumors are allowed to establish for one to four weeks before use. Trametinib is administered orally at the indicated doses in 0.2 mL/20 g by weight. Tumors are measured twice weekly using Vernier calipers. Antitumor activity is defined as tumor growth inhibition representing the % volume differential in tumor growth between the treated and control tumors at the time vehicle tumors exceeded a volume of 1000 mm^3. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell. 2018 Aug 9;174(4):843-855.e19.
- Cancer Cell. 2023 Dec 11;41(12):2083-2099.e9.
- Cancer Cell. 2021 Aug 9;39(8):1135-1149.e8.
- Cancer Cell. 2021 May 10;39(5):678-693.e11.
- Cancer Cell. 2020 Mar 16;37(3):387-402.e7.

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REFERENCES

[1]. Yamaguchi T, et al. Suppressive effect of an orally active MEK1/2 inhibitor in two different animal models for rheumatoid arthritis: a comparison with HWA486. Inflamm Res, 2012, 61(5), 445-454.

[2]. Abe H, et al. Discovery of a Highly Potent and Selective MEK Inhibitor: GSK1120212 (JTP-74057 DMSO Solvate). ACS Med Chem Lett. 2011 Feb 28;2(4):320-4.

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