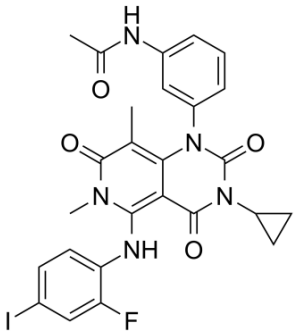
Trametinib



Cat. No.:	HY-10999
CAS No.:	871700-17-3
Molecular Formula:	$C_{26}H_{23}FIN_5O_4$
Molecular Weight:	615.39
Target:	MEK; Autophagy; Apoptosis
Pathway:	MAPK/ERK Pathway; Autophagy; 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 : 33.33 mg/mL (54.16 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.6250 mL	8.1249 mL	16.2499 mL
	5 mM	0.3250 mL	1.6250 mL	3.2500 mL
	10 mM	0.1625 mL	0.8125 mL	1.6250 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 (4.06 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.06 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Trametinib (GSK1120212; JTP-74057) is an orally active MEK inhibitor that inhibits MEK1 and MEK2 with IC_{50}s of about 2 nM. Trametinib activates autophagy and induces apoptosis[1][2].

IC_{50} & Target

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

In Vitro

Trametinib (GSK1120212;JTP-74057) (0.1-100 nM) blocks tumor necrosis factor-α and interleukin-6 production from peripheral blood mononuclear cells (PBMCs). Trametinib (JTP-74057) inhibits the growth of 9 out of 10 human colorectal cancer cell lines, and they shows cell-cycle arrest at the G1 phase after drug tratment[1].
The combination of GSK2118436 and Trametinib (GSK1120212) effectively inhibits cell growth, decreases ERK

	phosphorylation, decreases cyclin D1 protein, and increases p27(kip1) protein in the resistant clones[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Adjuvant-induced arthritis (AIA) and type II collageninduced arthritis (CIA) development are suppressed almost completely by 0.1 mg/kg of Trametinib (GSK1120212; JTP-74057) or 10 mg/kg of HWA486[1]. Trametinib (0.3 mg/kg, 1 mg/kg, p.o.) is effective in inhibiting the HT-29 xenograft growth in a nude mouse xenograft model [2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	The nonphosphorylated myelin basic protein (MBP) is coated onto an ELISA plate, and the active form of B-Raf/c-Raf is mixed with unphosphorylated MEK1/MEK2 and ERK2 in 10 μM ATP and 12.5 mM $MgCl_2$ containing MOPS buffer in the presence of various concentrations of Trametinib (JTP-74057). The phosphorylation of MBP is detected by the anti-phosphoMBP antibody. Kinase inhibitory activities against a total of 99 kinases are tested at 10 μM ATP[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Cells are treated with various concentrations of Trametinib (JTP-74057) in 100 mm dishes for 3 or 4 days. Both floating and adherent cells are collected and fixed with 70% ethanol. After washing with PBS, the cells are suspended in 100 μL/mL RNase and 25 μL/mL Propidium iodide (PI) and incubated at 37°C for 30 min in the dark. The DNA content of each single cell is determined using the flow cytometer Cytomics FC500 or Guava EasyCyte plus[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	Mice[2] Female BALB/c-nu/nu mice are used. On day 0, HT-29 cells or COLO205 cells suspended in ice-cold HBSS (-) are inoculated subcutaneously into the right flank of the mice at 5×10^6 cells/100 μL/site or 1×10^6 cells/100 μL/site, respectively. The acetic acid-solvated form of Trametinib (JTP-74057, 0.3 mg/kg, 1 mg/kg) is dissolved in 10% Cremophor EL-10% PEG400 and is administered orally once daily for 14 days from the day when the mean tumor volume reached 100 mm^3. The tumor length [L(mm)] and width [W(mm)] are measured using a microgauge twice a week after commencement of dosing, and the tumor volume is calculated using the following formula: tumor volume (mm^3)=L×W×W/2. 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 Discov. 2020 Aug;10(8):1226-1239.
- Cancer Discov. 2018 Mar;8(3):354-369.
- Cancer Discov. 2015 Sep;5(9):960-71.
- Cancer Discov. 2012 Oct;2(10):934-47.

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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]. Yamaguchi T, et al. Antitumor activities of JTP-74057 (GSK1120212), a novel MEK1/2 inhibitor, on colorectal cancer cell lines in vitro and in vivo. Int J Oncol, 2011, 39(1),

23-31.

[3]. 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.

[4]. Liu H, et al. Identifying and Targeting Sporadic Oncogenic Genetic Aberrations in Mouse Models of Triple Negative Breast Cancer. Cancer Discov. 2018 Mar;8(3):354-369.

[5]. Lai J, et al. Elimination of melanoma by sortase A-generated TCR-like antibody-drug conjugates (TL-ADCs) targeting intracellular melanoma antigen MART-1. Biomaterials. 2018 Sep;178:158-169.

India Contact:
Life Technologies (India) Pvt. Ltd.
306, Aggarwal City Mall, Opposite M2K Pitampura, Delhi – 110034 (INDIA). Ph: +91-11-42208000, 42208111, 42208222, Mobile: +91-9810521400, Fax: +91-11-42208444
Email: customerservice@lifetechindia.com Website: www.lifetechindia.com