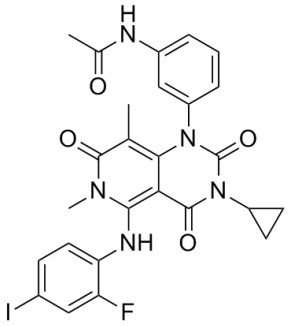
Data Sheet

Product Name:	Trametinib
Cat. No.:	CS-0060
CAS No.:	871700-17-3
Molecular Formula:	$C_{26}H_{23}FIN_5O_4$
Molecular Weight:	615.39
Target:	MEK
Pathway:	MAPK/ERK Pathway
Solubility:	DMSO: ≥ 69 mg/mL (Heating Trametinib at 80°C in DMSO for 10 min-30 min to get a clear solution and then cool to room temperature)[3]



BIOLOGICAL ACTIVITY:

Trametinib is a potent **MEK** inhibitor that specifically inhibits MEK1/2, with an **IC_{50}** value of about 2 nM. Due to the poor solubility of Trametinib, **Trametinib DMSO solvate (Cat. No.: HY-10999A)** is the more commonly used form.
IC50 & Target: IC50: 2 nM (MEK1/2)[1]
In Vitro: Trametinib (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].
In Vivo: Adjuvant-induced arthritis (AIA) and type II collageninduced arthritis (CIA) development are suppressed almost completely by 0.1 mg/kg of Trametinib (JTP-74057) or 10 mg/kg of Leflunomide[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].

PROTOCOL (Extracted from published papers and Only for reference)

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]. **Cell Assay:** Heating Trametinib at 80°C in DMSO for 10 min-30 min to get a clear solution and then cool to room temperature[3].[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].
Animal Administration: Trametinib is dissolved in 10% Cremophor EL-10% PEG400 (Mice)[2].[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.

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 leflunomide. 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.

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