

Product Data Sheet

Product Name: EMD-1214063

Cat. No.: GC10466

Chemical Properties

Cas. No. 1100598-32-0

Chemical Name 3-[1-[[3-[5-[(1-methylpiperidin-4-yl)methoxy]pyrimidin-2-yl]phenyl]methyl]-6-oxopyridazin-3-yl]benzonitrile

SMILES CN1CCC(CC1)COC2=CN=C(N=C2)C3=CC(=CC=C3)CN4C(=O)C=CC(=N4)C5=CC=C(C(=C5)C#N)

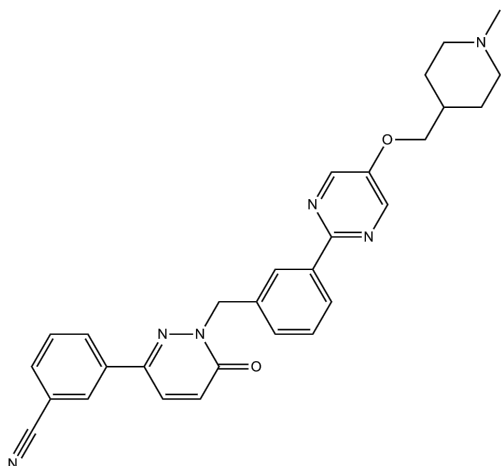
Formula $C_{29}H_{28}N_6O_2$ M.Wt 492.57

Solubility ≥ 4.93 mg/mL in DMSO, <2.52 mg/mL in EtOH, <2.56 mg/mL in Water Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Protocol

Cell experiment [1]:

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Cell lines	Triple-negative breast cancer cell lines (MDA-MB-468, HCC-1395, and MDA-MB-231) and hormone receptor positive cell line (T47D)
Preparation Method	Cells were seeded in 96-well microplates in medium supplemented with 5% FBS and penicillin/streptavidin. The optimal cell number for each cell line was determined to ensure that each was in growth phase at the end of the assay (~70% confluency). Cells were allowed to attach for 24 hours. The media was changed to low FBS (2%) and drugs with different combinations were added (cetuximab 200ug/mL, gefitinib 0.25-8 umol/L and EMD-1214063 2-10 µM). Cells were incubated at 37°C for 72 hours.
Reaction Conditions	2-10 µM for 72 hours
Applications	These cell lines were essentially resistant to both gefitinib and EMD-1214063 as single agents. The inhibitory effect of combined treatment with gefitinib and EMD-1214063 was significantly enhanced compared with single agent therapy in MDA-MB-468 cells but not in the other cell lines (MDA-MB-231, HCC1395, and T47D)
Animal experiment [2]:	
Animal models	BALB/c nude male mice

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Preparation Method	The patient-derived hepatocellular carcinoma (HCC) cells were subcutaneously inoculated in male BALB/c nude mice. When the tumors reached approximately 1 cm in diameter, subcutaneous tumors were collected and cut into pieces of about 2–3 mm³ and inoculated into the left lobe of the liver of male BALB/c nude mice. Mice were treated orally five days on/two days off with either vehicle combination (n = 10; 20% Solutol/80% 100 mM Na-acetate buffer, pH 5.5), EMD-1214063 (n = 10; 10, 30, or 100 mg/kg), sorafenib (n = 10; 50 mg/kg), or rapamycin (n = 10; 3 mg/kg) as single-agent treatment. In addition, EMD-1214063 (10 mg/kg) was given as a combination treatment with sorafenib (n = 10, 50 mg/kg) or rapamycin (n = 10; 3 mg/kg). Treatment was started seven days after orthotopic implantation of tumor fragments and terminated after five weeks.
Dosage form	10, 30, or 100 mg/kg/d, five days on/two days off, oral
Applications	The intrahepatic tumor size and weight were significantly lower in EMD-1214063 treated mice compared to the control group. EMD-1214063 treatment reduced the number of metastatic foci in the lungs of mice bearing orthotopic MHCC97H tumors, compared to the control group.

References:

- [1] : Sohn J, Liu S, Parinyanitikul N, et al. cMET activation and EGFR-directed therapy resistance in triple-negative breast cancer[J]. Journal of Cancer, 2014, 5(9): 745.
- [2] :Bladt F, Friese-Hamim M, Ihling C, et al. The c-Met inhibitor MSC2156119J effectively inhibits tumor growth in liver cancer models[J]. Cancers, 2014, 6(3): 1736-1752.

Background

EMD-1214063 (Tepotinib, MSC2156119J) is a novel potent and highly selective reversible, ATP-competitive small molecule c-Met inhibitor ^[1]. EMD-1214063 inhibited recombinant human c-Met

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kinase with an average IC₅₀ of 3 nmol/L [2].

EMD-1214063 treated A549 cells resulted in inhibition of HGF-induced c-Met phosphorylation, with an average IC₅₀ of 6 nmol/L [2]. The inhibitory effect of combined treatment with gefitinib (0.25-8 μ M) and EMD-1214063 (2-10 μ M) was significantly enhanced compared with single agent therapy in MDA-MB-468 cells [3].

EMD-1214063(5, 15 mg/kg) treated EBC-1 non-small cell lung cancer tumor cells bearing mice resulted in effective inhibition or complete tumor regression [1]. EMD-1214063 induced dose-dependent tumor growth inhibition in mice bearing human pancreatic carcinoma KP-4 tumors . Daily administration of EMD 1214063 at 200 mg/kg resulted in partial tumor regressions in 60% of tumor bearing mice [1].The combination of EMD-1214063 (100 mg/kg) with rociletinib (100 mg/kg) caused complete tumor regression over the treatment period of 21 d , with no regrowth during the observation period following withdrawal of treatment, in the model of EGFR TKI-resistant tumors with high HGF/c-Met expression [4].EMD-1214063 (100 mg/kg) in combination with afatinib (5 mg/kg) caused complete tumor regression with no regrowth during the period of observation in PC-9 xenografts [4].

References:

- [1]. Naing A, Falchook G S, Fu S, et al. A Phase I Dose-Escalation Study of emd 1214063, an Oral Selective CMET Inhibitor, in Patients with Advanced Solid Tumors[J]. Annals of Oncology, 2012, 23: xi21.
- [2]. Bladt F, Faden B, Friese-Hamim M, et al. EMD 1214063 and EMD 1204831 Constitute a New Class of Potent and Highly Selective c-Met InhibitorsEMD 1214063 and EMD 1204831, a New Class of c-Met Inhibitors[J]. Clinical Cancer Research, 2013, 19(11): 2941-2951.
- [3]. Sohn J, Liu S, Parinyanitikul N, et al. cMET activation and EGFR-directed therapy resistance in triple-negative breast cancer[J]. Journal of Cancer, 2014, 5(9): 745.
- [4]. Friese-Hamim M, Bladt F, Locatelli G, et al. The selective c-Met inhibitor tepotinib can overcome epidermal growth factor receptor inhibitor resistance mediated by aberrant c-Met activation in NSCLC models[J]. American journal of cancer research, 2017, 7(4): 962.

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