Fimepinostat

Cat. No.: HY-13522

CAS No.: 1339928-25-4

Molecular Formula: $C_{23}H_{24}N_8O_4S$

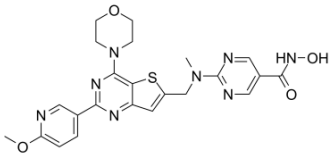
Molecular Weight: 508.55

Target: PI3K; HDAC; Apoptosis

Pathway: PI3K/Akt/mTOR; Cell Cycle/DNA Damage; Epigenetics; 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 : 62.5 mg/mL (122.90 mM; Need ultrasonic)
DMF : 5 mg/mL (9.83 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.9664 mL	9.8319 mL	19.6637 mL
5 mM	0.3933 mL	1.9664 mL	3.9328 mL
10 mM	0.1966 mL	0.9832 mL	1.9664 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 (4.09 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.09 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.09 mM); Clear solution
4. Add each solvent one by one: 30 % SBE-β-CD
   Solubility: 10 mg/mL (19.66 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Fimepinostat (CUDC-907) potently inhibits class I PI3Ks as well as classes I and II HDAC enzymes with an IC_{50} of 19/54/39 nM and 1.7/5.0/1.8/2.8 nM for PI3Kα/PI3Kβ/PI3Kδ and HDAC1/HDAC2/HDAC3/HDAC10 , respectively.

IC_{50} & Target	PI3Kα	PI3Kδ	PI3Kβ	PI3Kγ

	19 nM (IC_{50})	39 nM (IC_{50})	54 nM (IC_{50})	311 nM (IC_{50})
	HDAC1 1.7 nM (IC_{50})	HDAC3 1.8 nM (IC_{50})	HDAC10 2.8 nM (IC_{50})	HDAC2 5 nM (IC_{50})
	HDAC11 5.4 nM (IC_{50})	HDAC6 27 nM (IC_{50})	HDAC8 191 nM (IC_{50})	HDAC4 409 nM (IC_{50})
	HDAC7 426 nM (IC_{50})	HDAC9 554 nM (IC_{50})	HDAC5 674 nM (IC_{50})	

In Vitro

Fimepinostat is a potent pan-inhibitor of HDAC classes I and II enzymes and observed that its potency against class I HDACs is similar to that of LBH589 and greater than that of SAHA. Fimepinostat is also a potent inhibitor of class I PI3K kinases with an IC_{50} of 19, 54, and 39 nM for PI3Kα, PI3Kβ, and PI3Kδ, respectively. Fimepinostat markedly induces p21 protein in H460, a non-small cell lung cancer (NSCLC) cell line. Fimepinostat causes the reduction of both p-STAT3 (Y-705) and p-SRC in RPMI-8226 multiple myeloma cells and reduces both phosphorylated and total protein levels of MET and EGFR as well as HER2 and HER3 in H1975 NSCLC cells and BT-474 breast cancer cells, respectively. Fimepinostat induces caspase-3 and -7 activation in HCT-116 colon cancer cells in a dose-dependent manner. Fimepinostat potently inhibits the growth of cancer cells derived from both hematologic and solid tumors. Fimepinostat potently inhibits the proliferation of cells expressing either mutant or wild-type PI3K[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Oral administration of Fimepinostat inhibits growth of the Daudi cancer cell xenografts in a dose-dependent manner. Tumor stasis is observed at 100 mg/kg in this model without obvious toxicity. Importantly, in the same model, Fimepinostat achieves better efficacy than GDC-0941, SAHA, or a combination of these 2 compounds given at their maximal tolerated doses (MTD). Furthermore, Fimepinostat causes tumor regression or stasis after intravenous (50 mg/kg) or oral administration (100 mg/kg) in a xenograft tumor model of SU-DHL4 diffuse large B-cell lymphoma (DLBCL) and causes tumor stasis in KRAS-mutant A549 NSCLC cell xenografts[1].

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PROTOCOL

Kinase Assay [1]

The activities of classes I and II HDACs are measured using the Color-de-Lys assay system. The activity of PI3K is measured using the ADP-Glo luminescent kinase assay. Recombinant PI3K protein, a complex of N-terminal GST-tagged recombinant full-length human p110 and untagged recombinant full-length human p85, is coexpressed in a baculovirus-infected Sf9 cell expression system[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Assay [1]

Human cancer cell lines are plated at densities of 5,000 to 10,000 per well in 96-well flat-bottomed plates with the recommended culture medium. The cells are then incubated with compounds (e.g.,Fimepinostat) at various concentrations for 72 hours in culture medium supplemented with 0.5% (v/v) FBS. Growth inhibition is assessed by assay of cellular ATP content using the Perkin-Elmer ATPlite kit[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Administration [1]

Mice[1]

Six- to 8-week-old female athymic (nude nu/nu CD-1) or severe combined immunodeficient (SCID) mice obtained from Charles River Laboratories are injected subcutaneously with 3 to 20×10^6 cells in a medium suspension of 100 to 200 µL into the right hind flank region. Varying doses of Fimepinostat, standard anticancer agents, or vehicle are administered orally or via tail vein injection as indicated.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- J Clin Endocrinol Metab. 2020 Sep 30;dgaa699.
- Acta Pharmacol Sin. 2019 May;40(5):677-688
- ACS Med Chem Lett. 2015 Jun 22;6(8):948-52.
- Research Square Preprint. 2020 Aug.
- Harvard Medical School LINCS LIBRARY

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REFERENCES

[1]. Qian C, et al. Cancer network disruption by a single molecule inhibitor targeting both histone deacetylase activity and phosphatidylinositol 3-kinase signaling. Clin Cancer Res. 2012 Aug 1;18(15):4104-13.

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