Miltefosine

Cat. No.: HY-13685

CAS No.: 58066-85-6

Molecular Formula: $C_{21}H_{46}NO_4P$

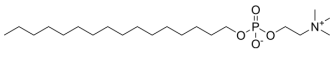
Molecular Weight: 407.57

Target: Akt; HIV; Parasite

Pathway: PI3K/Akt/mTOR; Anti-infection

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

H_2O : 33.33 mg/mL (81.78 mM; ultrasonic and warming and heat to 60°C)
DMSO : 3.33 mg/mL (8.17 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4536 mL	12.2678 mL	24.5357 mL
5 mM	0.4907 mL	2.4536 mL	4.9071 mL
10 mM	0.2454 mL	1.2268 mL	2.4536 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: PBS
Solubility: 100 mg/mL (245.36 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Miltefosine is a broad spectrum antimicrobial, anti-leishmanial, phospholipid agent acting by inhibiting the PI3K/Akt activity [1][2][3][4]. Miltefosine is an inhibitor of CTP-phosphocholine cytidyltransferase (CCT)[5].

IC_{50} & Target

HIV-1

In Vitro

Treatment of HIV-1 infected macrophages with Miltefosine inhibits the recruitment of PH-AktGFP to the plasma membrane. Since Miltefosine inhibits Akt through mimicry of the PH domain, it is likely that Miltefosine binds to PIP3, blocking the recruitment of PH-Akt to the membrane[1]. Miltefosine (HePC) inhibits protein kinase C (PKC) from NIH3T3 cells in cell-free extracts with a IC_{50} of about 7 μM. Inhibition is competitive with regard to phosphatidylserine with a K_i of 0.59 μM[2]. Miltefosine is an alkylphospholipid that inhibit activation of Akt. Miltefosine is a direct inhibitor of Akt, and induces dose-dependent inhibition of primary effusion lymphoma (PEL) in culture and also inhibits the downstream targets of Akt, such as

mTOR, leading to reduced phosphorylation and activation of S6K and S6. Importantly, Miltefosine also inhibits Akt targets that are not part of the mTOR pathway, eg, FOXO1, and are therefore expected to have a greater therapeutic impact than mTORC1 inhibitors alone[3].

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

In Vivo

Mice are randomized into groups of 5 and injected intraperitoneally 5 days a week with 50 mg/kg of either Miltefosine or Perifosine dissolved in PBS, or equivalent volume of vehicle (PBS). Both Miltefosine and Perifosine inhibit the growth rate of tumors compared with vehicle-treated mice. By day 14 after treatment, there is an approximately 50% decrease in average tumor volume in Perifosine- and Miltefosine-treated mice, compared with vehicle-treated mice ($P<0.04$). Tumor growth is also significantly retarded ($P<0.04$ for Perifosine and $P\leq0.055$ for Miltefosine by linear mixed-effects model analysis). Immunohistochemical analyses display an overall reduction in staining for phosphorylated ribosomal S6 protein in tumor sections from Miltefosine- and Perifosine-treated mice compared with the PBS-treated mice. This reduced phosphorylation correlated with the delay in tumor progression in drug-treated animals[3].

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

PROTOCOL

Kinase Assay [3]

Levels of enzymatically active caspase-3 are quantified using the ApoAlert Caspase Fluorescent assay kit. Briefly, 1×10^6 BC-1 PEL cells are treated with 50 μM Miltefosine, 50 μM Perifosine, or 20 nM NVP-BEZ235, as well as the respective vehicle controls. Cells are harvested and lysed 12 hours later. Equivalent micrograms of cell lysate for all samples are incubated with a fluorogenic caspase-3 substrate (DEVD-AFC). Cleavage of DEVD by caspase-3 releases AFC, the fluorescence of which is measured using a FLUOstar OPTIMA fluorometer, with excitation and emission filter wavelengths set to 400 and 505 nm, respectively[3].

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Cell Assay [2]

NIH3T3 cells are grown in DMEM supplemented with 10% FCS in a humidified atmosphere of 95% air with 5% CO_2. Cells are plated on 35-mm culture dishes (6-well plates) at $0.5\text{-}0.8\times10^5$ cells/well. Growth is established for 18-24 h and the cell number of representative wells is determined (time 0). The experiments are started by addition of fresh prepared solution of Miltefosine at given concentrations to the cells or equal volumes of Tris-HCI to control cells. After incubation for 60 h, cells are counted with an electronic counter. Cellular multiplication is calculated[2].

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Animal Administration [3][4]

Mice[3]

PEL cells are washed in ice-cold phosphate buffered saline, counted, and diluted in 100 μL of PBS mixed with 100 μL of growth factor-depleted Matrigel. A total of 1×10^5 to 7.5×10^5 BC-1 cells are injected subcutaneously into the right flank of NOD.CB17-Prkdc^{scid}/J or CB17-Prkdc^{scid}/J mice. The mice are monitored on alternate days for development of palpable tumors (2 mm^3), at which point drug or vehicle treatments are initiated, and are administered either intraperitoneally (Perifosine) or by oral gavage (Rosiglitazone, NVP-BEZ235) 5 days a week. Groups of 5 to 7 mice are used to generate PEL tumors and treated with either vehicle or drug cocktail. Each biologic experiment is repeated multiple times. For Rosiglitazone, 0.25% methylcellulose is used as vehicle, and 30 mg/kg or 60 mg/kg Rosiglitazone is suspended in methylcellulose. For Perifosine and Miltefosine, PBS is used as a vehicle and 50 mg/kg Perifosine or Miltefosine is dissolved in PBS. For NVP-BEZ235, the compound is dissolved in a 1:9 vol/vol mixture of 1-methyl-2-pyrrolidone and polyethylene glycol 300. A dose of 40 mg/kg NVP-BEZ235 or equal volume of the vehicle is administered. Tumor diameters are measured using digital calipers, and tumor volume is calculated. The tumors are excised and fixed in formalin. Statistical analyses are performed using linear model fit by maximum likelihood with individual animals treated as random effect.

Rats[4]

Male Sprague-Dawley rats (weight 270-290 g) are divided into five groups (n=5). Rats in the treatment groups are administered a single 10 mg/kg oral dose of Miltefosine (MFS) either as an aqueous solution or MFS-LNCs dispersion by gastric gavage. This dose is equivalent to the 20 mg/kg Miltefosine dose administered to mice in the preclinical study after correction for rats. Following administration, blood samples are collected via the orbital plexus under anesthesia at time intervals of 0.5, 1, 2, 4, 7, 10, 24, 48, 72 and 216 h in Eppendorf tubes containing EDTA. Blood samples are then centrifuged immediately at 4000 rpm for 10 min. Plasma samples are frozen and maintained at -80°C pending analysis.

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CUSTOMER VALIDATION

- Leukemia. 2021 Mar 8.
- J Cell Mol Med. 2019 Aug;23(8):5349-5359.
- Chem Biol Interact. 2019 Sep 1;310:108731.
- Molecules. 2020 Apr 23;25(8):1980.
- J Cell Biochem. 2023 Aug 11.

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[1]. Chugh P, et al. Akt inhibitors as an HIV-1 infected macrophage-specific anti-viral therapy. Retrovirology. 2008 Jan 31;5:11

[2]. Uberall F, et al. Hexadecylphosphocholine inhibits inositol phosphate formation and protein kinase C activity. Cancer Res. 1991 Feb 1;51(3):807-12.

[3]. Bhatt AP, et al. Dual inhibition of PI3K and mTOR inhibits autocrine and paracrine proliferative loops in PI3K/Akt/mTOR-addicted lymphomas. Blood. 2010 Jun 3;115(22):4455-63.

[4]. Eissa MM, et al. Miltefosine Lipid Nanocapsules for Single Dose Oral Treatment of Schistosomiasis Mansoni: A Preclinical Study. PLoS One. 2015 Nov 17;10(11):e0141788

[5]. de Freitas-Junior PR, et al. Effects of miltefosine on the proliferation, ultrastructure, and phospholipid composition of Angomonas deanei, a trypanosomatid protozoan that harbors a symbiotic bacterium. FEMS Microbiol Lett. 2012 Aug;333(2):129-37.

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