Tinostamustine

Cat. No.: HY-101780

CAS No.: 1236199-60-2

Molecular Formula: $C_{19}H_{28}Cl_2N_4O_2$

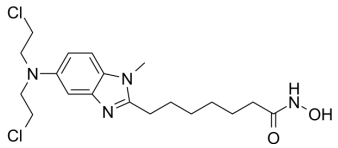
Molecular Weight: 415.36

Target: HDAC

Pathway: Cell Cycle/DNA Damage; Epigenetics

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (240.76 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4076 mL	12.0378 mL	24.0755 mL
	5 mM	0.4815 mL	2.4076 mL	4.8151 mL
	10 mM	0.2408 mL	1.2038 mL	2.4076 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 (6.02 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

Tinostamustine (EDO-S101) is a pan HDAC inhibitor; inhibits HDAC6, HDAC1, HDAC2 and HDAC3 with IC_{50} values of 6 nM, 9 nM, 9 nM and 25 nM, respectively[1].

IC_{50} & Target

HDAC6 6 nM (IC_{50})	HDAC1 9 nM (IC_{50})	HDAC2 9 nM (IC_{50})	HDAC3 25 nM (IC_{50})
HDAC10 72 nM (IC_{50})	HDAC8 107 nM (IC_{50})		

In Vitro

Tinostamustine inhibits HDAC activity in rat peripheral blood mononuclear cells (PBMCs) in a cellular assay by approximately 90% one hour after dosing with 10mg/kg i.v. HDAC inhibition in PBMCs could not be increased with higher doses up to 50mg/kg. Tinostamustine triggers apoptosis and shows strong antitumor activity in HL60 and Daudi cells. Initial

	in vitro experiments in HL60 cells shows an activation of the intrinsic pathway of apoptosis with cleavage of caspases 3, 9 and PARP and a marked reduction of anti-apoptotic proteins XIAP and Mcl-1[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Intracellular HDAC inhibition of Tinostamustine, which occurs rapidly after dosing is at maximum activity already at the lowest dose of 10mg/kg and lasts for about 12-16 hours. Exposure to Tinostamustine causes a strong DNA repair response evidenced by activation of pH2AX and p53 in tumors taken from mice bearing subcutaneous human Burkitt's lymphoma. Tumors of BL rapidly shrink or are completely eradicated after i.v. administration of Tinostamustine[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Tinostamustine is dissolved in DMSO and added to the assay buffer solution. Tinostamustine dilutions of 5 µL of each dilution is added to 50 µL of the reaction mixture including the Fluor de Lys substrate and all of the enzymatic reactions are conducted in duplicate at 37°C for 30 minutes. After enzymatic reactions, 50 µL of 2xHDAC developer is added to each well and fluorescence intensity is measured[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats: The duration of HDAC inhibition is assessed in 12 female rats after receiving a single dose of either vehicle or Tinostamustine (25mg/kg). Blood samples from EDO-S101 treated rats are collected 1hr, 3hr, 6hr, 16hr and 24hr post dosing (n=2 per time point). Blood sample from vehicle treated rats (n=2) are collected 24hr post dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharmacol Sin. 2021 Apr 13.
- Nutrients. 2023 Jun 15, 15(12), 2760.
- Int J Mol Sci. 2022 Apr 2;23(7):3980.

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REFERENCES

[1]. Mehrling T, et al. The Alkylating-HDAC Inhibition Fusion Principle: Taking Chemotherapy to the Next Level with the First in Class Molecule EDO-S101. Anticancer Agents Med Chem. 2016;16(1):20-8.

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