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Tubastatin A

Cat. No.: HY-13271A

CAS No.: 1252003-15-8

Molecular Formula: $C_{20}H_{21}N_3O_2$

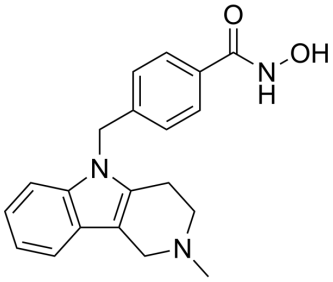
Molecular Weight: 335.4

Target: HDAC; Autophagy; Apoptosis; Beta-lactamase

Pathway: Cell Cycle/DNA Damage; Epigenetics; Autophagy; Apoptosis; Anti-infection

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 : 12.5 mg/mL (37.27 mM; Need ultrasonic)

H_2O : < 0.1 mg/mL (insoluble)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.9815 mL	14.9076 mL	29.8151 mL
5 mM	0.5963 mL	2.9815 mL	5.9630 mL
10 mM	0.2982 mL	1.4908 mL	2.9815 mL

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

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 25 mg/mL (74.54 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1.25 mg/mL (3.73 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.25 mg/mL (3.73 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.25 mg/mL (3.73 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tubastatin A is a potent and selective HDAC6 inhibitor with an IC_{50} of 15 nM in a cell-free assay, and is selective (1000-fold more) against all other isozymes except HDAC8 (57-fold more). Tubastatin A also inhibits HDAC10 and metallo-β-lactamase domain-containing protein 2 (MBLAC2).

IC_{50} & Target	HDAC6 15 nM (IC_{50})	HDAC8 854 nM (IC_{50})	HDAC1 16400 nM (IC_{50})

In Vitro

Tubastatin A is substantially selective for all 11 HDAC isoforms and maintains over 1000-fold selectivity against all isoforms excluding HDAC8, where it has approximately 57-fold selectivity. In homocysteic acid (HCA) induced neurodegeneration assays, Tubastatin A displays dose-dependent protection against HCA-induced neuronal cell death starting at 5 μM with near complete protection at 10 μM[1]. At 100 ng/mL Tubastatin A increases $Foxp^{3+}$ T-regulatory cells (Tregs) suppression of T cell proliferation in vitro[2]. Tubastatin A treatment in CC12 cells would lead to myotube formation impairment when alpha-tubulin is hyperacetylated early in the myogenic process; however, myotube elongation occurs when alpha-tubulin is hyeperacetylated in myotubes[3]. A recent study indicates that Tubastatin A treatment increases cell elasticity as revealed by atomic force microscopy (AFM) tests without exerting drastic changes to the actin microfilament or microtubule networks in mouse ovarian cancer cell lines, MOSE-E and MOSE-L[4].

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

In Vivo

Daily treatment of Tubastatin A at 0.5 mg/kg inhibits HDAC6 to promote Tregs suppressive activity in mouse models of inflammation and autoimmunity, including multiple forms of experimental colitis and fully major histocompatibility complex (MHC)-incompatible cardiac allograft rejection[2].

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

PROTOCOL

Cell Assay [1]

Primary cortical neuron cultures are obtained from the cerebral cortex of fetal Sprague-Dawley rats (embryonic day 17) as described previously. All experiments are initiated 24 hours after plating. Under these conditions, the cells are not susceptible to glutamate-mediated excitotoxicity. For cytotoxicity studies, cells are rinsed with warm PBS and then placed in minimum essential medium containing 5.5 g/L glucose, 10% fetal calf serum, 2 mM L-glutamine, and 100 μM cystine. Oxidative stress is induced by the addition of the glutamate analogue homocysteate (HCA; 5 mM) to the media. HCA is diluted from 100-fold concentrated solutions that are adjusted to pH 7.5. In combination with HCA, neurons are treated with Tubastatin A at the indicated concentrations. Viability is assessed after 24 hours by MTT assay.

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

Animal Administration [2]

The effects of HDAC6 targeting in dextran sodium sulfate (DSS) and adoptive transfer models of colitis are evaluated, using 10 mice per group. Freshly prepared 4% (wt/vol) DSS (MP Biomedicals) is added daily for 5 days to the pH-balanced tap water of WT B6 mice. Mice are treated daily for 7 days with tubacin or niltubacin (0.5 mg/kg of body weight/day, i.p.), and colitis is assessed by daily monitoring of body weight, stool consistency, and fecal blood. Stool consistency is scored as 0 (hard), 2 (soft), or 4 (diarrhea), and fecal blood (Hemoccult) is scored as 0 (absent), 2 (occult), or 4 (gross). To assess prevention of colitis in a T cell-dependent model, CD^{4+} CD45RBhi T cells (1×10^6) isolated from WT mice using magnetic beads (>95% cell purity, flow cytometry) are injected i.p. into B6/$Rag1^{-/-}$ mice plus CD^{4+} CD^{25+} Tregs (1.25×10^5) isolated using magnetic beads from $HDAC6^{-/-}$ or WT mice (>90% Treg purity, flow cytometry) and mice are monitored biweekly for clinical evidence of colitis. To assess therapy of established T cell-dependent colitis, B6/$Rag1^{-/-}$ mice are injected i.p. with CD^{4+} CD45RBhi cells (1×10^6). Once colitis has developed, mice also receive CD^{4+} CD^{25+} Tregs (5×10^5 cells) isolated as described above from $HDAC6^{-/-}$ or WT mice or treatment with HDAC6i (tubastatin A) or HSP90i (17-AAG). Mice are monitored for continued weight loss and stool consistency. At the cessation of the study, paraffin sections of colons stained with Alcian Blue or hematoxylin and eosin are graded histologically or evaluated by immunoperoxidase staining for $Foxp^{3+}$ Treg infiltration.

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

CUSTOMER VALIDATION

- Acta Pharm Sin B. 20 May 2022.

- Cell Death Dis. 2022 Oct 21;13(10):888.
- NPJ Precis Oncol. 2024 Mar 7;8(1):66.
- J Med Chem. 2023 Nov 16.
- Antioxidants (Basel). 2022 Apr 7;11(4):732.

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[2]. Géraldy M, Morgen M, Sehr P, et al. Selective Inhibition of Histone Deacetylase 10: Hydrogen Bonding to the Gatekeeper Residue is Implicated. J Med Chem. 2019;62(9):4426-4443.

[3]. Severin Lechner, et al. Target deconvolution of HDAC pharmacopoeia reveals MBLAC2 as common off-target. Nat Chem Biol. 2022 Apr 28.

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