Zebularine

Cat. No.: HY-13420

CAS No.: 3690-10-6

Molecular Formula: $C_9H_{12}N_2O_5$

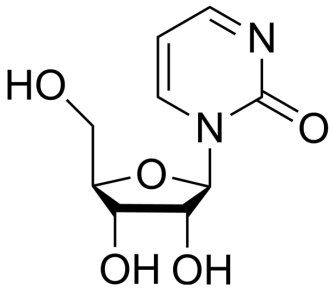
Molecular Weight: 228.2

Target: DNA Methyltransferase; Autophagy

Pathway: Epigenetics; Autophagy

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 (438.21 mM)

H_2O : 50 mg/mL (219.11 mM; Need ultrasonic)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	4.3821 mL	21.9106 mL	43.8212 mL
	5 mM	0.8764 mL	4.3821 mL	8.7642 mL
	10 mM	0.4382 mL	2.1911 mL	4.3821 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 (438.21 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (10.96 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (10.96 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (10.96 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Zebularine (NSC309132; 4-Deoxyuridine) is a DNA methyltransferase inhibitor. Zebularine also inhibits cytidine deaminase with a K_i of 0.95 μM.

IC_{50} & Target	DNMT1	DNMT3a/3L	Cytidine deaminase 0.95 μM (Ki)	Autophagy

In Vitro	Zebularine exerts its demethylation activity by stabilizing the binding of DNMTs to DNA, hindering the methylation and decreasing the dissociation, thereby trapping the enzyme and preventing turnover even at other sites. zebularine enhances tumor cell chemo- and radiosensitivity? and has antimitogenic and angiostatic activities[1]. Zebularine inhibits DNA methylation and reactivates a gene previously silenced by methylation. Zebularine induces the myogenic phenotype in 10T1/2 cells, which is a phenomenon unique to DNA methylation inhibitors. Zebularine reactivates a silenced p16 gene and demethylated its promoter region in T24 bladder carcinoma cells[2]. Zebularine treatment inhibits cell growth in a dose and time dependent manner with an IC_{50} of ⊠100 μM and 150 μM in MDA-MB-231 and MCF-7 cells, respectively, on 96 h exposure. At high doses zebularine induced changes in apoptotic proteins in a cell line specific manner manifested by alteration in caspase-3, Bax, Bcl2 and PARP cleavage[3]. Zebularine is also a potent competitive inhibitor of the enzyme CR deaminase. The K_i for zebularine is 0.95μM[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Zebularine is only slightly cytotoxic to tumor-bearing mice. Compared with those in control mice, tumor volumes are statistically significantly reduced in mice treated with high-dose zebularine administered by intraperitoneal injection or by oral gavage[2]. Zebularine also enhances the survival time of mice with L1210 leukemia treated with 5-AZA-CdR. About 27% of the mice treated with this drug combination has a survival time longer than the mice treated with only 5-AZA-CdR[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	For methylation analysis, 10T1/2 cells and T24 cells are treated with the various concentrations of zebularine. For 10T1/2 cells, the medium is changed 24 hours after the initial drug treatment, whereas for T24 cells, the medium is changed 24 hours or 48 hours after the initial drug treatment. DNA and RNA are harvested from 10T1/2 cells 72 hours after initial drug treatment and from T24 cells 96 hours after initial drug treatment. The methylation status of the indicated DNA regions is measured in two separate and independent experiments, both of which are done in duplicate[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	EJ6 cells (5×10^5/injection) suspended in PBS are inoculated subcutaneously into the right and left flanks (along the midaxillary lines) of 4- to 6-week-old male BALB/c nu/nu mice. Mice (n=30) are randomLy divided into six groups (intraperitoneal control, oral control, intraperitoneal zebularine at 500 mg/kg, oral zebularine at 500 mg/kg, intraperitoneal zebularine at 1000 mg/kg, and oral zebularine at 1000 mg/kg). Each group consisted of five mice (at least six tumors per group; one or two mice per group are randomLy killed at earlier time points to establish a time course of expression). After 2–3 weeks and after macroscopic tumors (50–200 mm^3) had formed, zebularine or control treatments are initiated. Zebularine, at doses of 500 mg/kg or 1000 mg/kg, is administered daily by intraperitoneal injection or oral gavage in a solution of 0.45% saline over a period of 18 days[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Proc Natl Acad Sci U S A. 2019 Feb 19;116(8):2961-2966.
- Oncogene. 2021 Apr;40(15):2711-2724.
- BMC Genomics. 2019 Oct 15;20(1):736.
- Patent. US20180263995A1.

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REFERENCES

[1]. Champion C, et al. Mechanistic insights on the inhibition of c5 DNA methyltransferases by zebularine. PLoS One. 2010 Aug 24;5(8):e12388.

[2]. Cheng JC, et al. Inhibition of DNA methylation and reactivation of silenced genes by zebularine. J Natl Cancer Inst. 2003 Mar 5;95(5):399-409.

[3]. Billam M, et al. Effects of a novel DNA methyltransferase inhibitor zebularine on human breast cancer cells. Breast Cancer Res Treat. 2010 Apr;120(3):581-92.

[4]. Lemaire M, et al. Inhibition of cytidine deaminase by zebularine enhances the antineoplastic action of 5-aza-2'-deoxycytidine. Cancer Chemother Pharmacol. 2009 Feb;63(3):411-6.

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