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Tenovin-6

Cat. No.: HY-15510

CAS No.: 1011557-82-6

Molecular Formula: $C_{25}H_{34}N_4O_2S$

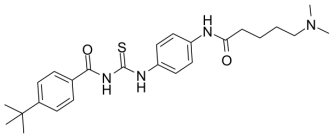
Molecular Weight: 454.63

Target: Sirtuin; MDM-2/p53; Autophagy; Dihydroorotate Dehydrogenase

Pathway: Cell Cycle/DNA Damage; Epigenetics; Apoptosis; Autophagy; Metabolic Enzyme/Protease

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 : ≥ 31 mg/mL (68.19 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Concentration \ Solvent \ Mass	1 mg	5 mg	10 mg
1 mM	2.1996 mL	10.9980 mL	21.9959 mL
5 mM	0.4399 mL	2.1996 mL	4.3992 mL
10 mM	0.2200 mL	1.0998 mL	2.1996 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 (5.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Tenovin-6, an analog of Tenovin-1 (HY-13423), is an activator of p53 transcriptional activity. Tenovin-6 inhibits the protein deacetylase activities of purified human SIRT1, SIRT2, and SIRT3 with IC_{50}s of 21 μM, 10 μM, and 67 μM, respectively. Tenovin-6 also inhibits dihydroorotate dehydrogenase (DHODH)[1][2].

IC_{50} & Target

SIRT2 10 μM (IC_{50})	SIRT1 21 μM (IC_{50})	SIRT3 67 μM (IC_{50})	HDAC8
MDM-2/p53			

In Vitro	Tenovin-6 inhibits the growth of S. cerevisiae cultures with an IC_{50} of 30 μM and is more toxic to yeast than the less water-soluble tenovin-1. Tenovin-6 rapidly increases the levels of endogenous K382-Ac p53 in MCF-7 cells[1]. Tenovin-6 (0 to 15 μM) dose dependently increases the level of LC3-II in diverse cell types, and the increase is ATG5/7 dependent. Tenovin-6 treatment also increases the number and intensity of autophagic vesicles with or without the presence of Torin 1, and prevents Torin 1-induced SQSTM1/p62 degradation. Tenovin-6 affects the acidification of autolysosomes and impairs the hydrolytic activity of lysosomes but does not affect the fusion between autophagosomes and lysosomes. That tenovin-6 inhibits autophagy does not correlate with p53 activation and SIRT1/2 inhibition by knockdown or knockout cannot mimic the effect of tenovin-6 on LC3B accumulation[3]. Tenovin-6 (0, 1, 2.5, 5 or 10 μM) potently inhibits cell proliferation in a dose- and time-dependent manner in all OCI-Ly1, DHL-10, U2932, RIVA, HBL1 and OCI-Ly10 cell lines. Tenovin-6 consistently increases LC3B-II level in DLBCL cell lines by inhibiting the classical autophagy pathway, without activating p53, and the increase is independent of SIRT1/2/3 and p53. Tenovin-6 induces apoptosis through the extrinsic cell-death pathway[4]. Tenovin-6 suppresses the growth of UM cells with IC50 of 12.8 μM, 11.0 μM, 14.58 μM and 9.62 μM for 92.1, Mel 270, Omm 1 and Omm 2.3 cells, respectively[5]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Tenovin-6 (50 mg/kg, i.p.) inhibits the growth of tumor in mice[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	Assays are carried out using purified components in the Fluor de Lys Fluorescent Assay Systems. Relevant FdL substrates are used at 7 μM and NAD^+ at 1 mM. Tenovins are solubilized in DMSO with the final DSMO concentration in the reaction being less than 0.25%. For SirT1 and HDAC8, one unit of enzyme is used per reaction, and for SirT2 and SirT3, five units is used per reaction. Reactions are carried out at 37°C for 1 hr. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [4]	The MTS assay is used to evaluate cell viability. UM cells are seeded into each well of 96-well plates (5,000 cells/well) and treated the next day with control or Tenovin-6 in an increasing concentrations from 0 to 20 μM for 68 h, and then MTS is added at 20 μL/well to be read at a wave length of 490 nm, the IC_{50} is determined by curve fitting of the sigmoidal dose-response curve. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Female SCID mice are injected subcutaneously with 1×10^6 ARN8 cells suspended in matrigel. Tumors are allowed to reach a size of approximately 10 mm^3. Tenovin-6 is administered daily at 50 mg/kg by intraperitoneal injection. Control animals are treated with vehicle solution containing cyclodextrin 20% (w/v) and DMSO 10% (v/v). Tumor diameters are measured using calipers, and volumes are calculated using the equation $V=\pi4/3[(d1 + d2)/4]^3$. Median values of tumor size are calculated for each time point as well as the corresponding 95% confidence intervals. Comparison of control and drug-treated tumor size distributions are made by Mann-Whitney U-test. An alpha-level of 0.05 is considered appropriate for determination of statistical significance. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharmacol Sin. 2021 Apr 13.
- Lipids Health Dis. 2021 Apr 26;20(1):40.
- J Nutr. 2020 Jul 1;150(7):1731-1737.
- Exp Cell Res. 2020 Mar 1;388(1):111810.

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REFERENCES

[1]. Lain S, et al. Discovery, in vivo activity, and mechanism of action of a small-molecule p53 activator. Cancer Cell. 2008 May;13(5):454-63.

[2]. Yuan H, et al. Tenovin-6 impairs autophagy by inhibiting autophagic flux. Cell Death Dis. 2017 Feb 9;8(2):e2608.

[3]. Yuan H, et al. Tenovin-6 inhibits proliferation and survival of diffuse large B-cell lymphoma cells by blocking autophagy. Oncotarget. 2017 Feb 28;8(9):14912-14924.

[4]. Dai W, et al. Class III-specific HDAC inhibitor Tenovin-6 induces apoptosis, suppresses migration and eliminates cancer stem cells in uveal melanoma. Sci Rep. 2016 Mar 4;6:22622.

[5]. Ladds MJGW, et al. Exploitation of DHODH and p53 activation as therapeutic targets - a case study in polypharmacology [published online ahead of print, 2020 Sep 8]. J Biol Chem. 2020;jbc.RA119.012056.

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