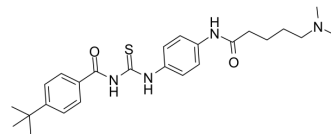


Tenovin-6

Cat. No.:	HY-15510		
CAS No.:	1011557-82-6		
Molecular Formula:	C ₂₅ H ₃₄ N ₄ O ₂ S		
Molecular Weight:	454.63		
Target:	MDM-2/p53; Dihydroorotate Dehydrogenase; Sirtuin; Autophagy		
Pathway:	Apoptosis; Metabolic Enzyme/Protease; Cell Cycle/DNA Damage; Epigenetics; Autophagy		
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 : ≥ 31 mg/mL (68.19 mM)
 * "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent Concentration	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

- 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
- 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 IC₅₀s of 21 μM, 10 μM, and 67 μM, respectively. Tenovin-6 also inhibits dihydroorotate dehydrogenase (DHODH)^{[1][2]}.

IC₅₀ & Target

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

In Vitro	<p>Tenovin-6 inhibits the growth of <i>S. cerevisiae</i> cultures with an IC₅₀ 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].</p> <p>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].</p> <p>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].</p> <p>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].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
In Vivo	<p>Tenovin-6 (50 mg/kg, i.p.) inhibits the growth of tumor in mice^[1].</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

PROTOCOL

Kinase Assay ^[1]	<p>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 DMSO 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.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Cell Assay ^[4]	<p>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 IC₅₀ is determined by curve fitting of the sigmoidal dose-response curve.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>
Animal Administration ^[1]	<p>Female SCID mice are injected subcutaneously with 1×10⁶ ARN8 cells suspended in matrigel. Tumors are allowed to reach a size of approximately 10 mm³. 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 $V = \pi/3[(d1 + d2)/4]^3$. 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.</p> <p>MCE has not independently confirmed the accuracy of these methods. They are for reference only.</p>

CUSTOMER VALIDATION

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

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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