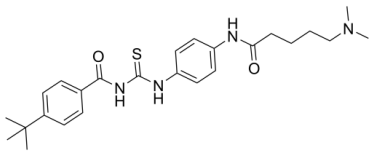
Data Sheet

Product Name:	Tenovin-6
Cat. No.:	CS-1976
CAS No.:	1011557-82-6
Molecular Formula:	$C_{25}H_{34}N_4O_2S$
Molecular Weight:	454.63
Target:	Autophagy; Dihydroorotate Dehydrogenase; MDM-2/p53; Sirtuin
Pathway:	Apoptosis; Autophagy; Cell Cycle/DNA Damage; Epigenetics; Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 31 mg/mL



BIOLOGICAL ACTIVITY:

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]. IC50 & Target: IC50: 21 μM (SirT1), 10 μM (SirT2), 67 μM (SirT3)[1] ***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]. ***In Vivo:*** Tenovin-6 (50 mg/kg, i.p.) inhibits the growth of tumor in mice[1].

PROTOCOL (Extracted from published papers and Only for reference)

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. **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. **Animal Administration:** Tenovin-6 is formulated in vehicle solution containing cyclodextrin 20% (w/v) and DMSO 10% (v/v).[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 $V=\pi 4/3[(d1 + d2)/4]^3$. 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.

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.

CAIndexNames:

Benzamide, N-[[[4-[[5-(dimethylamino)-1-oxopentyl]amino]phenyl]amino]thioxomethyl]-4-(1,1-dimethylethyl)-

SMILES:

O=C(NC(NC1=CC=C(NC(CCCCN(C)C)=O)C=C1)=S)C2=CC=C(C(C)(C)C)C=C2

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