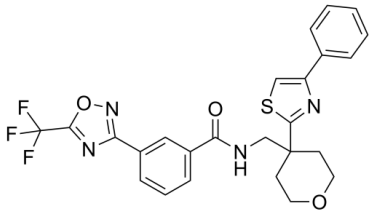
Data Sheet

Product Name:	TMP269
Cat. No.:	CS-2463
CAS No.:	1314890-29-3
Molecular Formula:	$C_{25}H_{21}F_3N_4O_3S$
Molecular Weight:	514.52
Target:	HDAC
Pathway:	Cell Cycle/DNA Damage; Epigenetics
Solubility:	DMSO : 100 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

TMP269 is a novel and selective class IIa **histone deacetylase (HDAC)** inhibitor with **IC_{50}**s of 157 nM, 97 nM, 43 nM and 23 nM for HDAC4, HDAC5, HDAC7 and HDAC9, respectively. IC50 & Target: IC50: 23 nM (HDAC9), 43 nM (HDAC7), 97 nM (HDAC5), 157 nM (HDAC4)[1] ***In Vitro:*** TMP269 has no impact on the mitochondrial activity and/or the viability of human $CD4^+$ T cells at 10 μM, and may be used as tools to identify the endogenous substrates of the class IIa HDAC enzymes[1]. In IEC-18 intestinal epithelial cells, TMP269 prevents cell cycle progression, DNA synthesis, and proliferation induced in response to G protein-coupled receptor/PKD1 activation [2]. As with HDAC4 knockdown, TMP269 significantly enhances cytotoxicity induced by CFZ in MM cell lines, upregulating ATF4 and CHOP and inducing apoptosis. TMP269 does not hyperacetylate histone H3K9 or α-tubulin in MM cell lines, confirming that it has no inhibitory effects on class I or IIb HDACs. In a dosedependent manner, TPM269-induced cytotoxicity is associated with cleavage of caspase-8, -9, -3 and PARP, consistent with apoptosis[3]. ***In Vivo:*** In ***vivo*** angiogenesis assay, MDA-MB-231 cells are mixed with growth factor-reduced Matrigel and implanted subcutaneously into the flanks of nude mice. TMP269 (subcutaneous injection; 15 mg/kg; every other day; 10 days) shows an obvious antiangiogenic effect with 76% inhibition of angiogenesis in mice[4].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]Dose-response studies are done with ten concentrations in a threefold dilution series from a maximum final compound concentration of 100 μM in the reaction mixture. All assays are based on the same principle as the HDAC9 assay described above: the deacetylation of acetylated or trifluoroacetylated lysine residues on fluorogenic peptide substrates by HDAC. HDAC1, HDAC2, HDAC3, HDAC6, HDAC10 and HDAC11 used a substrate based on residues 379-382 of p53 (Arg-His-Lys-Lys(Ac)). For HDAC8, the diacetylated peptide substrate, based on residues 379-382 of p53 (Arg-His-Lys(Ac)-Lys(Ac)), is used. HDAC4, HDAC5, HDAC7 and HDAC9 assays used the class IIa HDAC-specific fluorogenic substrate (Boc-Lys(trifluoroacetyl)-AMC). All reactions are done with 50 μM HDAC substrate in assay buffer (50 mM Tris-HCl, pH 8.0, 137 mM NaCl, 2.7 mM KCl, 1 mM $MgCl_2$, 1 mg/mL BSA) containing 1% DMSO final concentration; incubated for 2 h at 30°C; and developed with trichostatin A and trypsin.
Cell Assay: [1]Human $CD4^+$ T cells are isolated from whole blood via negative selection according to manufacturer's instructions (RosetteSep Human $CD4^+$ T cell enrichment kit), re-suspended in T-cell culture medium (10% FBS, 2 mM L-glutamine, 1 mM pyruvate, 10 mM HEPES, 10 U/10 mg penicillin/streptomycin, 0.5% DMSO in RPMI) and plated at 50,000 cells/well with IL-2 (10 BRMP units/mL) and 100,000 human T-expander Dynabeads for 72 h. Determination of mitochondrial function or cell viability is done according to manufacturer's instructions (Cell Proliferation Assay Kit I (MTT)) and is represented as a percent of control (no inhibitor) wells.

References:

[1]. Lobera M, et al. Selective class IIa histone deacetylase inhibition via a nonchelating zinc-binding group. Nat Chem Biol. 2013 May;9(5):319-25.

[2]. Sinnett-Smith J, et al. Protein kinase D1 mediates class IIa histone deacetylase phosphorylation and nuclear extrusion in intestinal epithelial cells: role in mitogenic signaling. Am J Physiol Cell Physiol. 2014 May 15;306(10):C961-71.

[3]. Kikuchi S, et al. Class IIa HDAC inhibition enhances ER stress-mediated cell death in multiple myeloma. Leukemia. 2015 Sep;29(9):1918-1927.

[4]. EricSalgado, et al. Volume 503 HDAC9 overexpression confers invasive and angiogenic potential to triple negative breast cancer cells via modulating microRNA-206. Biochemical and Biophysical Research Communications.

CAIndexNames:

Benzamide, N-[[tetrahydro-4-(4-phenyl-2-thiazolyl)-2H-pyran-4-yl]methyl]-3-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]-

SMILES:

O=C(NCC1(C2=NC(C3=CC=CC=C3)=CS2)CCOCC1)C4=CC=CC(C5=NOC(C(F)(F)F)=N5)=C4

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