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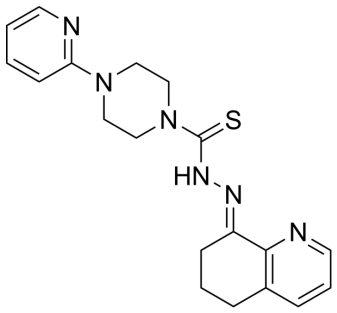
COTI-2

Cat. No.:	HY-19896
CAS No.:	1039455-84-9
Molecular Formula:	$C_{19}H_{22}N_6S$
Molecular Weight:	366.48
Target:	MDM-2/p53; Apoptosis
Pathway:	Apoptosis
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 : 5 mg/mL (13.64 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7287 mL	13.6433 mL	27.2866 mL
	5 mM	0.5457 mL	2.7287 mL	5.4573 mL
	10 mM	0.2729 mL	1.3643 mL	2.7287 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 0.67 mg/mL (1.83 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

COTI-2, an anti-cancer agent with low toxicity, is an orally available third generation activator of p53 mutant forms. COTI-2 acts both by reactivating mutant p53 and inhibiting the PI3K/AKT/mTOR pathway. COTI-2 induces apoptosis in multiple human tumor cell lines. COTI-2 exhibits antitumor activity in HNSCC through p53-dependent and -independent mechanisms. COTI-2 converts mutant p53 to wild-type conformation[1][2][3].

IC_{50} & Target

p53[1]

In Vitro

COTI-2 efficiently inhibits the proliferation rate of all the tested cell lines following 72 h of treatment. COTI-2 is significantly effective at inhibiting tumor cell proliferation in all three cell lines (COLO-205, HCT-15, and SW620). Relatively low concentrations of COTI-2 are active against all human glioblastoma cell lines tested (U87-MG, SNB-19, SF-268, and SF-295). COTI-2 treatment of SHP-77 cells with approximate IC_{50} concentrations results in the induction of early apoptosis among 40 to 47% of total cells[2].

	MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	COTI-2 significantly inhibits tumor growth in the HT-29 human colorectal tumor xenografts at a dose of 10 mg/kg. In addition to reducing tumor volumes at specific times post-treatment, COTI-2 also delays the time required for tumors to reach specified volumes. COTI-2 also significantly inhibits tumor growth in the SHP-77 SCLC xenograft model at a dose as low as 3 mg/kg. COTI-2 treatment both reduces U87-MG tumor volumes at specific times post-treatment and lengthens the time required for U87-MG xenografts to grow in nude mice. Control tumors in mice treated with vehicle alone take only 5 days to reach an average volume of 828 mm^3 while tumors in animals treated with COTI-2 take double that time (10 days) to reach a similar mean volume (857 mm^3). COTI-2 treatment effectively inhibits OVCAR-3 xenograft growth regardless of the route of administration[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	The interaction of COTI-2 with 227 kinases is tested using the AMBIT BIOSCIENCES KINOMESCAN assay. In brief, streptavidin-coated magnetic beads are treated with biotinylated small molecule ligands for 30 min at 25°C to generate affinity resins for kinase assays. The liganded beads are blocked with excess biotin and washed with blocking buffer (1% BSA, 0.05% Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific binding. Binding reactions are assembled by combining phage lysates, liganded affinity beads, and COTI-2 in 1× binding buffer (20% SeaBlock, 0.17× PBS, 0.05% Tween 20, 6 mM DTT). All reactions are carried out in polystyrene 96-well plates that have been pre-treated with blocking buffer in a final volume of 0.1 mL[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	SHP-77 cells are cultured with various concentrations of COTI-2 for 48 h. Cells are then washed twice with 1× cold PBS and stained with Annexin V and 7AAD according to the manufacturer's instructions. Briefly, 5 μL of Annexin V and 7AAD are added to 1×10^5 cells and incubated for 15 min at room temperature in the dark. Then 400 μL of the 1× binding buffer (100 mM HEPES, pH 7.4, 140 mM NaCl, 2.5 mM $CaCl_2$) is added to the cells. Finally, cells are analyzed using a flow cytometer[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [2]	SHP-77 and HT-29 cells are injected in 50% matrigel into flanks of NCr-nu mice (2×10^6 cells per injection site) (n=5 mice per group). In the case of SHP-77 xenografts, treatment with COTI-2 begins prior to the appearance of palpable tumors. One day after injection of SHP-77 cells, animals receive 3 mg/kg of COTI-2 (once every two days, up to 38 days). Tumor sizes are estimated at 5, 10, 17, 24, and 38 days, by standard caliper measurements. In the case of HT-29 xenografts, the capacity of COTI-2 to suppress growth of established tumors is assessed. HT-29 xenografts are allowed to grow to 200 mm^3 before starting IP treatment with COTI-2 (10 mg/kg, 5 days a week for 7 weeks) or saline IP. Tumor growth is measured every 4 days by caliper measurement[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Dis. 2023 Dec 14;14(12):831.
- Cell Rep. 2022 Apr 12;39(2):110622.

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REFERENCES

[1]. Duffy MJ, et al. Mutant p53 as a target for cancer treatment. Eur J Cancer. 2017 Sep;83:258-265.

[2]. Salim KY, et al. COTI-2, a novel small molecule that is active against multiple human cancer cell lines in vitro and in vivo. Oncotarget. 2016 Jul 5;7(27):41363-41379.

[3]. Lindemann A, et al. COTI-2, A Novel Thiosemicarbazone Derivative, Exhibits Antitumor Activity in HNSCC through p53-dependent and -independent Mechanisms. Clin Cancer Res. 2019 Sep 15;25(18):5650-5662.

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