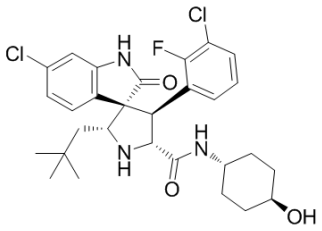
MI-773

Cat. No.:	HY-17493
CAS No.:	1303607-07-9
Molecular Formula:	$C_{29}H_{34}Cl_2FN_3O_3$
Molecular Weight:	562.5
Target:	MDM-2/p53
Pathway:	Apoptosis
Storage:	4°C, stored under argon * In solvent : -80°C, 6 months; -20°C, 1 month (stored under argon)



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 53 mg/mL (94.22 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7778 mL	8.8889 mL	17.7778 mL
	5 mM	0.3556 mL	1.7778 mL	3.5556 mL
	10 mM	0.1778 mL	0.8889 mL	1.7778 mL

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

BIOLOGICAL ACTIVITY

Description	MI-773 is a new small molecule inhibitor of the **MDM2-p53** interaction, binds to **MDM2** with high affinity (K_i=0.88 nM) and blocks the p53-MDM2 interaction.
IC_{50} & Target	Ki: 0.88 nM (MDM2)[1]
In Vitro	MI-773 potently induces expression of p53 and its downstream targets p21, MDM2, and induces phosphorylation of p53 (serine 392) in low passage primary human ACC cells. Notably, MI-773 induces a dose-dependent increase in the fraction of apoptotic ACC cells and in the fraction of cells in the G1 phase of cell cycle ($P<0.05$). Consequently, MI-773 causes apoptotic cell death[1]. MI-773 is an advanced synthetic small molecule inhibitor, displays high binding affinity against MDM2 (K_d=8.2 nM)[2].
In Vivo	MI-773 at 10 mg/kg modestly reduces the rate of tumor growth, whereas 100 mg/kg causes significant tumor regression. Control tumors reach an average of 1,000 mm^3 at 20 days of treatment, compare to an average volume of 600 mm^3 for the 10 mg/kg group and 30 mm^3 for the 100 mg/kg group. Kaplan-Meier analysis shows an increase in tumor failure, define as two times increase in tumor volume as compared to pretreatment volume ($P=0.044$), for

	vehicle-treated mice when compare to mice treated with 100 mg/kg MI-773[1].

PROTOCOL

Cell Assay [1]	Sulforhodamine B or the WST-1 cytotoxicity assay are performed to determine the effect of MI-773 on ACC cell viability. Briefly, 1 to 3×10^3 UM-HACC cells are plated per well, and treated with 0 to 40 μM MI-773 for 24 to 96 hours. To assess apoptosis, 2×10^5 cells are plated in 60 mm^3 dishes, attached overnight, and treated with 0 to 20 μM MI-773 for 72 hours. Cells are lysed with a hypotonic buffer and stained with propidium iodide. Primary low passage ACC cells (UM-HACC-5) are stably transduced with lentiviral vectors expressing shRNA-p53 or scrambled sequence control shRNA-C and selected with 1.0 μg/mL puromycin[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] To establish a patient-derived xenograft (PDX) model of ACC, human tumor fragments from the UM-HACC-5 patient are transplanted subcutaneously into the dorsal region of male severe combined immunodeficient (SCID) mice (CB.17.SCID). Two of six initial patient tumor fragments transplant, grow, and are retransplanted in vivo into new male or female mice for up to 12 passages. When tumors reach an average of 250 mm^3, mice are randomized into groups and received either vehicle (polyethylene glycol-200 + D-α-tocopherol polyethylene glycol 1000 succinate), or treatment with 10, 50, or 100 mg/kg MI-773 daily by oral gavage. The ACCx6 and ACCx9 models are treated with vehicle or 100 mg/kg MI-773. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- **Nat Chem Biol**. 2018 Feb;14(2):118-125.
- **BMC Biol**. 2017 Nov 9;15(1):108.

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REFERENCES

[1]. Warner KA, et al. Targeting MDM2 for Treatment of Adenoid Cystic Carcinoma. Clin Cancer Res. 2016 Jul 15;22(14):3550-9.

[2]. Zhang Q, et al. Targeting p53-MDM2-MDMX loop for cancer therapy. Subcell Biochem. 2014;85:281-319.

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