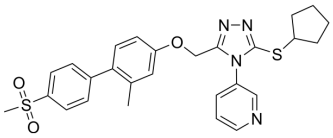
NMS-873

Cat. No.:	HY-15713
CAS No.:	1418013-75-8
Molecular Formula:	$C_{27}H_{28}N_4O_3S_2$
Molecular Weight:	520.67
Target:	p97
Pathway:	Cell Cycle/DNA Damage
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20.5 mg/mL (39.37 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.9206 mL	9.6030 mL	19.2060 mL
	5 mM	0.3841 mL	1.9206 mL	3.8412 mL
	10 mM	0.1921 mL	0.9603 mL	1.9206 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (4.80 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.80 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.80 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	NMS-873 is a potent, selective allosteric VCP/p97 inhibitor with an IC_{50} value of 30 nM.
IC_{50} & Target	IC50: 30 nM[1]
In Vitro	NMS-873 has antiproliferative effect on a panel of tumor cell lines with IC_{50} values in the range of 0.08 μM to 2 μM. For HCT116 and HeLa cells, the IC_{50} values are 0.4 μM and 0.7 μM, respectively. NMS-873 reduces VCP?sensitivity to trypsin digestion, preventing degradation of the linker-D2 domain. NMS-873 induces clear, dose-dependent accumulation of poly-

Ub proteins and stabilization of cyclin E and Mcl-1 at doses consistent with its antiproliferative IC_{50} value[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]

The ATPase activity and the kinetic parameters of recombinant wild-type VCP and its mutants are evaluated by monitoring ADP formation in the reaction, using a modified NADH-coupled assay46. As ADP and NADH are ATP-competitive inhibitors of VCP ATPase activity, the standard protocol for the NADH-coupled assay is modified into a two-step procedure. In the first part, an ATP-regenerating system (40 U/mL pyruvate kinase and 3 mM phosphoenolpyruvate) recycles the ADP produced by VCP activity, keeps the substrate concentration constant (thus preventing product inhibition) and accumulates a stoichiometric amount of pyruvate. In the second part, the VCP enzymatic reaction is quenched with 30 mM EDTA and 250 μM NADH and stoichiometrically oxidized by 40 U/mL lactic dehydrogenase to reduce accumulated pyruvate. The decrease of NADH concentration is measured at 340 nm using a Tecan Safire 2 reader plate. The assay is performed in 96- or 384-well UV platesin a reaction buffer with 50 mM Hepes, pH 7.5, 0.2 mg/mL BSA, 10 mM $MgCl_2$ and 2 mM DTT.

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Cell Assay [1]

Cells are seeded at 1,600 cells per well in 384-well white clear-bottom plates. Twenty-four hours after seeding, cells are treated with the compounds (eight dilution points, in duplicate, for each compound) and incubated for an additional 72 h at 37°C under a 5% CO_2 atmosphere. Cells are then lysed, and the ATP content in each well is determined using a thermostable firefly luciferase-based assay from Promega as a measure of cell viability. IC_{50} values are calculated using the percentage of growth of treated cells versus the untreated control.

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Mol Cell. 2020 Jul 16;79(2):320-331.e9.
- EMBO Mol Med. 2022 May 25;e15373.
- Cell Chem Biol. 2019 Sep 19;26(9):1306-1314.e5.
- J Cell Mol Med. 2016 Jan;20(1):58-70.
- J Biol Chem. 2022 Apr 14;298(6):101936.

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REFERENCES

[1]. Paola Magnaghi, et al. Covalent and allosteric inhibitors of the ATPATP ase VCP/p97 induce cancer cell death. Nat Chem Biol. 2013 Jul 28. doi: 10.1038/nchembio.1313.

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