NVP-HSP990

Cat. No.: HY-15190

CAS No.: 934343-74-5

Molecular Formula: $C_{20}H_{18}FN_5O_2$

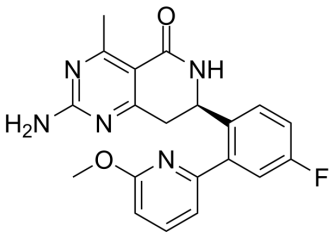
Molecular Weight: 379.39

Target: HSP; Apoptosis

Pathway: Cell Cycle/DNA Damage; Metabolic Enzyme/Protease; 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 : ≥ 33 mg/mL (86.98 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.6358 mL	13.1791 mL	26.3581 mL
5 mM	0.5272 mL	2.6358 mL	5.2716 mL
10 mM	0.2636 mL	1.3179 mL	2.6358 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: ≥ 2.08 mg/mL (5.48 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (5.48 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

NVP-HSP990 is a potent, selective and orally active Hsp90 inhibitor, with IC_{50} values of 0.6, 0.8, and 8.5 nM for Hsp90α, Hsp90β, and Grp94, respectively.

IC_{50} & Target

HSP90α	HSP90β	GRP94	TRAP1 ATPase
0.6 nM (IC_{50})	0.8 nM (IC_{50})	8.5 nM (IC_{50})	320 nM (IC_{50})

In Vitro

NVP-HSP990 is a potent and selective Hsp90 inhibitor, with IC_{50} values of 0.6, 0.8, and 8.5 nM for Hsp90α, Hsp90β, and Grp94, respectively. NVP-HSP990 (10 μM) shows no affect the ATPase activity of topoisomerase II, a GHKL (Gyrase, Hsp90, Histidine Kinase, MutL) family ATPase, closely related to Hsp90. NVP-HSP990 also exerts efficient effects on c-Met, Hsp70, p-ERK and

	p-AKT in CTL-16 cells, with EC_{50}s of 37 ± 4, 20 ± 2, 11 ± 1, and 6 ± 1 nM, respectively. NVP-HSP990 suppresses the proliferation of BT474, A549, H1975 and MV4;11 cells, with GI_{50}s of 7 ± 2, 28 ± 5, 35 ± 4, and 4 ± 1 nM, respectively[1]. NVP-HSP990 inhibits cellular proliferation of GTL-16, with an EC_{50} of 14 nM[2]. NVP-HSP990 (5-500 nM) inhibits the multiple myeloma cell lines, with IC_{50}s of 27-49 nM after treatment for 72 h. NVP-HSP990 induces apoptosis in multiple myeloma cell lines (0-100 nM), leads to cell cycle arrest in the G2/M phase (25-200 nM), and induces apoptosis via caspase-8 followed by caspase-3 activation (100 nM). NVP-HSP990 increases HSP70 expression and interacts with Akt and ERK signaling. Moreover, NVP-HSP990 (100 nM) in combination with melphalan, causes synergistic effects on growth inhibition in multiple myeloma cells and increases cleavage of caspase-3, caspase-8, and caspase-9 and activates caspase-2[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	NVP-HSP990 (2.5 to 5 mg/kg twice weekly, or 5 to 15 mg/kg weekly, p.o.) causes dose proportional antitumor efficacy, without obvious loss or overt signs of toxicity in a GTL-16 tumor bearing mice. NVP-HSP990 (5 or 10 mg/kg weekly, p.o.) also results in significant inhibition of tumor growth in BT-474 breast cancer model. NVP-HSP990 (5 mg/kg twice weekly or 15 mg/kg weekly, p.o.) inhibits the growth of tumor in the MV4;11 xenograft model. Furthermore, NVP-HSP990 (0.5 mg/kg every day, 14, 5 mg/kg twice weekly, or 15 mg/kg weekly, p.o.) displays antitumor efficacy in H1975 and A549 tumor models[1]. NVP-HSP990 (5, 15 mg/kg, p.o.) shows prolonged suppression of c-Met levels with 30% and 50% reduction and exhibits antitumor activities in GTL-16 tumor xenograft[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	His-tagged Hsp90α N-terminal domain protein (N-Hsp90α-His) is diluted to 2× the final concentration in the assay buffer consisting of 50 mM Hepes, pH 7, 6 mM $MgCl_2$, 20 mM KCl and 0.1% BSA. The Hsp90 is dispensed into 96 well polypropylene plates at 50 µL per well. In a separate polypropylene plate, test compounds (NVP-HSP990) are diluted to 40× their final concentration in 100% DMSO. Serial dilutions in DMSO are made in 3-fold increments. 2.5 µL of diluted compounds are transferred to the 50 µL of Hsp90 and mixed. Background wells receive 25 µM (final concentration) radicicol. Biotin-radicicol is diluted into assay buffer at 2× the final concentration and 50 µL are added to the Hsp90/compound plate. DMSO is at a final concentration of 2.5%. Samples are incubated at room temperature for 2 hours before 50 µL are transferred to NeutrAvidin-coated plates. Plates are incubated 1 hour, washed 3× with DELFIA wash buffer (5 mM Tris, pH 7.5, 0.1% Tween 20, 0.1% sodium azide, 0.9% NaCl), and then 50 µL per well of 3 nM Eu-anti-His diluted into DELFIA assay buffer are added. The plates are next incubated 2 hours at room temperature, washed 4×, and then 50 µL enhancement solution are added. Plates are gently shaken for 7-10 minutes before reading in a VICTOR2 instrument[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	GTL-16 Cells (1×10^3) are plated into 96 well tissue culture plates and cultured at 37°C, 5% CO_2. Serially diluted compounds (NVP-HSP990) are added to the cells and are incubated for 72 hrs. at 37°C, 5% CO_2. Cell proliferation is determined using Cell Viability assay[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Human tumor xenograft models GTL-16, NCI-H1975, BT474, and MV4;11 are implanted subcutaneously with 50% Matrigel in nude or severe combined immunodeficient mice. Mice are randomized into cohorts (10 mice/group for efficacy) when tumors reach 200 to 500 mm^3. NVP-HSP990 is administered orally in a vehicle of 100% polyethylene glycol (PEG400). Tumor caliper measurements are converted into tumor volumes using the formula: [length × $(width)^2$]/2. Relative tumor inhibition is calculated as %T/C = 100 × dT/dC, where, dT or dC = difference of mean tumor volume of drug treatment (T) or vehicle (C) on the final day of the study and the randomization volume. Statistical comparisons are conducted using a one-way ANOVA, followed by the Dunn or Tukey post hoc test. Differences are statistically significant at $P < 0.05$[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Theranostics. 2019 Aug 12;9(20):5769-5783.
- Viruses. 2021, 13(4), 610.

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REFERENCES

[1]. Menezes DL, et al. The novel oral Hsp90 inhibitor NVP-HSP990 exhibits potent and broad-spectrum antitumor activities in vitro and in vivo. Mol Cancer Ther. 2012 Mar;11(3):730-9.

[2]. McBride CM, et al. Design, structure-activity relationship, and in vivo characterization of the development candidate NVP-HSP990. J Med Chem. 2014 Nov 13;57(21):9124-9.

[3]. Lamottke B, et al. The novel, orally bioavailable HSP90 inhibitor NVP-HSP990 induces cell cycle arrest and apoptosis in multiple myeloma cells and acts synergistically with melphalan by increased cleavage of caspases. Eur J Haematol. 2012 May;88(5):406-15.

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