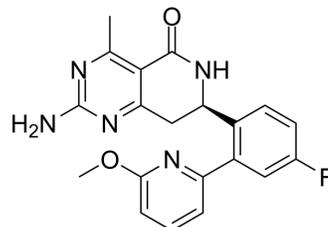


## NVP-HSP990

<b>Cat. No.:</b>	HY-15190		
<b>CAS No.:</b>	934343-74-5		
<b>Molecular Formula:</b>	C <sub>20</sub> H <sub>18</sub> FN <sub>5</sub> O <sub>2</sub>		
<b>Molecular Weight:</b>	379.39		
<b>Target:</b>	HSP; Apoptosis		
<b>Pathway:</b>	Cell Cycle/DNA Damage; Metabolic Enzyme/Protease; Apoptosis		
<b>Storage:</b>	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 Concentration	Mass		
		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

- 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
- 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<sub>50</sub> values of 0.6, 0.8, and 8.5 nM for Hsp90α, Hsp90β, and Grp94, respectively.

#### IC<sub>50</sub> & Target

HSP90α 0.6 nM (IC <sub>50</sub> )	HSP90β 0.8 nM (IC <sub>50</sub> )	GRP94 8.5 nM (IC <sub>50</sub> )	TRAP1 ATPase 320 nM (IC <sub>50</sub> )
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#### In Vitro

NVP-HSP990 is a potent and selective Hsp90 inhibitor, with IC<sub>50</sub> 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<sub>50</sub>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<sub>50</sub>s of 7 ± 2, 28 ± 5, 35 ± 4, and 4 ± 1 nM, respectively<sup>[1]</sup>. NVP-HSP990 inhibits cellular proliferation of GTL-16, with an EC<sub>50</sub> of 14 nM<sup>[2]</sup>. NVP-HSP990 (5-500 nM) inhibits the multiple myeloma cell lines, with IC<sub>50</sub>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<sup>[3]</sup>.

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<sup>[1]</sup>. 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<sup>[2]</sup>.

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## PROTOCOL

#### Kinase Assay <sup>[2]</sup>

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<sub>2</sub>, 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<sup>[2]</sup>.

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

#### Cell Assay <sup>[2]</sup>

GTL-16 Cells (1 × 10<sup>3</sup>) are plated into 96 well tissue culture plates and cultured at 37°C, 5% CO<sub>2</sub>. Serially diluted compounds (NVP-HSP990) are added to the cells and are incubated for 72 hrs. at 37°C, 5% CO<sub>2</sub>. Cell proliferation is determined using Cell Viability assay<sup>[2]</sup>.

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#### Animal Administration <sup>[1]</sup>

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<sup>3</sup>. 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)<sup>2</sup>]/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<sup>[1]</sup>.

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## CUSTOMER VALIDATION

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

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## REFERENCES

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- [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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**Caution: Product has not been fully validated for medical applications. For research use only.**

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