NVP-HSP990

Cat. No.: HY-15190
CAS No.: 934343-74-5
Molecular Formula: C₂₀H₁₈FN₅O₂
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 6 months
-20°C 1 month

SOLVENT & SOLUBILITY

In Vitro
DMSO : ≥ 33 mg/mL (86.98 mM)
* "≥" means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.6358 mL</td>
<td>13.1791 mL</td>
<td>26.3581 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.5272 mL</td>
<td>2.6358 mL</td>
<td>5.2716 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2636 mL</td>
<td>1.3179 mL</td>
<td>2.6358 mL</td>
</tr>
</tbody>
</table>

Preparing Stock Solutions

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 (6.59 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.59 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
NVP-HSP990 is a potent and selective Hsp90 inhibitor, with IC₅₀ values of 0.6, 0.8, and 8.5 nM for Hsp90α, Hsp90β, and Grp94, respectively.

IC₅₀ & Target

<table>
<thead>
<tr>
<th>Target</th>
<th>IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HSP90α</td>
<td>0.6 (IC₅₀)</td>
</tr>
<tr>
<td>HSP90β</td>
<td>0.8 (IC₅₀)</td>
</tr>
<tr>
<td>GRP94</td>
<td>8.5 (IC₅₀)</td>
</tr>
<tr>
<td>TRAP1 ATPase</td>
<td>320 (IC₅₀)</td>
</tr>
</tbody>
</table>

In Vitro
NVP-HSP990 is a potent and selective Hsp90 inhibitor, with IC₅₀ 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.

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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\textsubscript{50} 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\textsubscript{50} of 7 ± 2, 28 ± 5, 35 ± 4, and 4 ± 1 nM, respectively\textsuperscript{[1]}. NVP-HSP990 inhibits cellular proliferation of G1T-16, with an EC\textsubscript{50} of 14 nM\textsuperscript{[2]}. NVP-HSP990 (5-500 nM) inhibits the multiple myeloma cell lines, with IC\textsubscript{50} 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\textsuperscript{[3]}.

**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 G1T-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\textsuperscript{[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 G1T-16 tumor xenograft\textsuperscript{[2]}.

**PROTOCOL**

**Kinase Assay**\textsuperscript{[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\textsubscript{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\textsuperscript{[2]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**Cell Assay**\textsuperscript{[2]}

G1T-16 Cells (1 × 10\textsuperscript{3}) are plated into 96 well tissue culture plates and cultured at 37°C, 5% CO\textsubscript{2}. Serially diluted compounds (NVP-HSP990) are added to the cells and are incubated for 72 hrs at 37°C, 5% CO\textsubscript{2}. Cell proliferation is determined using Cell Viability assay\textsuperscript{[2]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**Animal Administration**\textsuperscript{[1]}

Human tumor xenograft models G1T-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\textsuperscript{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: \(V = \frac{\text{length} \times \text{width}^2}{2}\). Relative tumor inhibition is calculated as \(\%T/C = 100 \times \frac{dT/dC}{dC}\), 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 \(P < 0.05\)\textsuperscript{[1]}. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
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REFERENCES

