Nedisertib

Cat. No.: HY-101570
CAS No.: 1637542-33-6
Molecular Formula: C₂₄H₂₁ClFN₅O₃
Molecular Weight: 481.91
Target: DNA-PK
Pathway: Cell Cycle/DNA Damage; PI3K/Akt/mTOR
Storage: -20°C, protect from light, stored under nitrogen
* In solvent: -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)

SOLVENT & SOLUBILITY

In Vitro
DMSO : 100 mg/mL (207.51 mM; Need ultrasonic)
H₂O : < 0.1 mg/mL (insoluble)

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Concentration</th>
<th>Mass</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td></td>
<td></td>
<td>2.0751 mL</td>
<td>10.3754 mL</td>
<td>20.7508 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td></td>
<td></td>
<td>0.4150 mL</td>
<td>2.0751 mL</td>
<td>4.1502 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td></td>
<td></td>
<td>0.2075 mL</td>
<td>1.0375 mL</td>
<td>2.0751 mL</td>
</tr>
</tbody>
</table>

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 (5.19 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
Nedisertib (M3814) is a potent, orally available and selective inhibitor of DNA-PK, with an IC₅₀ of <3 nM. Anti-tumor activity[1][2][3].

IC₅₀ & Target
DNA-PK
<3 nM (IC₅₀)

In Vitro
Nedisertib (Compound 136) is a potent and selective inhibitor of DNA-PK, with an IC₅₀ of <3 nM for DNA-PK and <0.5 μM for cellular pDNA-PK[3].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo
In combination with IR, Nedisertib shows efficacy in all of the 6 mouse models of human cancer. In all models, a dose of 2 Gy administered daily for 1 week in combination with Nedisertib induces statically significant tumor growth inhibition compared...
to IR alone. Nedisertib, alone or in combination with IR, does not induce significant weight loss or visual signs of toxicity in the mice in any study\textsuperscript{[1]}.

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**PROTOCOL**

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

The efficacy of Nedisertib in combination with IR is evaluated in 6 human xenograft models (HCT116, FaDu, NCI-H460, A549, Capan-1, BxPC3) in mice representing 4 different cancer types (colon, head and neck, lung, and pancreas). Tumor cells are injected s.c. into nude mice, and treatment starts when palpable tumors are established (~100 to 200 mm\textsuperscript{3}). Nedisertib is given orally at different doses (25 to 300 mg/kg) 10 min prior to IR. IR is applied using a radiation therapy device for small rodents calibrated to deliver 2 Gy. Autophosphorylation of DNA-PK (serine\textsuperscript{2056}) in FaDu tumor lysates is measured by immunoassay to assess pharmacological inhibition by Nedisertib\textsuperscript{[1]}.

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**REFERENCES**

\textsuperscript{[1]} L. Damstrup, et al. M3814, a DNA-dependent Protein Kinase Inhibitor (DNA-PKi), Potentiates the Effect of Ionizing Radiation (IR) in Xenotransplanted Tumors in Nude Mice. IJROBP. 2016; 94, 940-941.
