Siremadlin

Cat. No.: HY-18658
CAS No.: 1448867-41-1
Molecular Formula: C₂₆H₂₄Cl₂N₆O₄
Molecular Weight: 555.41
Target: MDM-2/p53; E1/E2/E3 Enzyme
Pathway: Apoptosis; Metabolic Enzyme/Protease
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 : ≥ 56.75 mg/mL (102.18 mM)
* “≥” means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Preparing Stock Solutions</th>
<th>Solvent Concentration</th>
<th>Mass (1 mg)</th>
<th>Mass (5 mg)</th>
<th>Mass (10 mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 mM</td>
<td>1.8005 mL</td>
<td>9.0024 mL</td>
<td>18.0047 mL</td>
</tr>
<tr>
<td></td>
<td>5 mM</td>
<td>0.3601 mL</td>
<td>1.8005 mL</td>
<td>3.6009 mL</td>
</tr>
<tr>
<td></td>
<td>10 mM</td>
<td>0.1800 mL</td>
<td>0.9002 mL</td>
<td>1.8005 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 (4.50 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.50 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
Siremadlin (NVP-HDM201) is a potent, orally bioavailable and highly specific p53-MDM2 interaction inhibitor.

In Vitro
Siremadlin (NVP-HDM201) disrupts both human and murine TP53- MDM2 interactions, with nanomolar cellular IC₅₀ values, blocking TP53 degradation[1].

In Vivo
Siremadlin (NVP-HDM201) is an imidazolpyrrolidinone analogue, showing a very advantageous in vivo profile. NVP-HDM201 has recently entered Phase 1 clinical trials in cancer patients[2]. Constitutive PB mutagenesis in Arf⁻/⁻ mice provides a collection of spontaneous tumors with characterized insertional genetic landscapes. Tumors are
allografted in large cohorts of mice to assess the pharmacologic effects of Siremadlin (NVP-HDM201). Sixteen out of 21 allograft models are sensitive to Siremadlin (NVP-HDM201) but ultimately relapse under treatment. A comparison of tumors with acquired resistance to Siremadlin (NVP-HDM201) and untreated tumors identified 87 genes that are differentially and significantly targeted by the PB transposon[1]. Siremadlin (NVP-HDM201) administered either daily at a low dose or once at a high dose revealed a differentiated engagement of the p53 molecular response. In contrast to the daily low dose treatment regimen, the single high dose Siremadlin (NVP-HDM201) regimen results in a rapid and dramatic induction of p53-dependent PUMA expression and apoptosis. This is consistent with the finding that a single high dose Siremadlin (NVP-HDM201) treatment, administered orally or intravenously, results in a robust and sustained tumor regression. Overall, both daily and once every 3 weeks dosing regimen shows comparable long term efficacy in preclinical studies. The ongoing clinical trial is currently designed to compare both dosing regimens with regard to efficacy and tolerability[3].

REFERENCES

