GNE-477

Cat. No.: HY-11042
CAS No.: 1032754-81-6
Molecular Formula: \( \text{C}_{21}\text{H}_{28}\text{N}_{8}\text{O}_{3}\text{S}_{2} \)
Molecular Weight: 504.63
Target: PI3K; mTOR
Pathway: PI3K/Akt/mTOR

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: 16.67 mg/mL (33.03 mM; Need ultrasonic)

Preparing Stock Solutions

<table>
<thead>
<tr>
<th>Solvent Mass</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 mM</td>
<td>1.9816 mL</td>
<td>9.9082 mL</td>
<td>19.8165 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3963 mL</td>
<td>1.9816 mL</td>
<td>3.9633 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1982 mL</td>
<td>0.9908 mL</td>
<td>1.9816 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: ≥ 1.67 mg/mL (3.31 mM); Clear solution

2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.67 mg/mL (3.31 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
GNE-477 is a potent and efficacious dual PI3K (IC\(_{50}=4\) nM)/mTOR (K\(_{i}=21\) nM) inhibitor.

IC\(_{50}\) & Target

- PI3K\(_{\alpha}\)
  - 4 nM (IC\(_{50}\))
- mTOR
  - 21 nM (K\(_{i}\))

In Vitro
GNE-477 (Compound 8) has improved potency in the MCF7.1 cell proliferation assay with an EC\(_{50}\) of 143 nM\(^{[1]}\).
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo
GNE-477 also exhibits stasis in a PC3 tumor growth inhibition study. In an experiment evaluating the tumor growth inhibition of a PC3 tumor xenograft over 14 days, stasis is achieved at a 20 mg/kg QD dose and significant inhibition is
observed with doses as low as 1 mg/kg QD. GNE-477 is generally well tolerated during this study as demonstrated by acceptable levels of weight loss comparable to that observed with the animals in the vehicle cohort[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**PROTOCOL**

**Animal Administration[1]**

Female nu/nu mice are dosed with the GNE-477 HCl salt as a solution intravenously (1 mg/kg) in 5% DMSO/5% cremophor and dosed orally as a solution in 80% PEG (5 mg/kg). Male rats are dosed with the GNE-477 TFA salt as a solution intravenously (1 mg/kg) in 5% DMSO/5% cremophor and dosed orally as a solution in 80% PEG (5 mg/kg). Male beagle dogs are dosed with the GNE-477 HCl salt as a solution intravenously (1 mg/kg) in 10% HP-β-CD and dosed orally as a suspension in MCT (2 mg/kg). Efficacy study of GNE-477 in the PC3-NCI tumor xenograft model is performed. The percent of tumor growth inhibition (TGI) at the end of study (day 14) is measured and compared with the vehicle control group. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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**REFERENCES**