AMG-3969

Cat. No.: HY-12411
CAS No.: 1361224-53-4
Molecular Formula: C₂₁H₂₀F₆N₄O₃S
Molecular Weight: 522.46
Target: Glucokinase
Pathway: 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 : ≥ 100 mg/mL (191.40 mM)
* "≥" means soluble, but saturation unknown.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Mass Concentration</th>
<th>1 mg</th>
<th>5 mg</th>
<th>10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>1.9140 mL</td>
<td>9.5701 mL</td>
<td>19.1402 mL</td>
<td></td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3828 mL</td>
<td>1.9140 mL</td>
<td>3.8280 mL</td>
<td></td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1914 mL</td>
<td>0.9570 mL</td>
<td>1.9140 mL</td>
<td></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 (4.79 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (4.79 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.79 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
AMG-3969 is a potent glucokinase-glucokinase regulatory protein interaction (GK-GKRP) disruptor with an IC₅₀ of 4 nM.

IC₅₀ & Target
IC₅₀: 4 nM (GK-GKRP)[3]
AMG-3969 exhibits potent cellular activity with an EC$_{50}$ of 0.202 μM and IC$_{50}$ of 4 nM$^{[1]}$, [2]. It potently reverses the inhibitory effect of GKR on GK activity and promotes GK translocation in vitro (isolated hepatocytes)$^{[3]}$. AMG-3969 has good in vivo pharmacokinetic (PK) properties in rats (75%) and significantly lowers blood glucose levels in a dose-dependent manner db/db mice$^{[1]}$. AMG-3969 (100 mg/kg) demonstrates significant reductions in blood glucose with robust efficacy (56% reduction) observed at the 8 h time point$^{[2]}$. AMG-3969 demonstrates dose-dependent efficacy in three models of diabetes: diet induced obese (DIO), ob/ob and db/db mice; however, AMG-3969 is ineffective in lowering blood glucose in normoglycaemic C57BL/6 (B6) mice. AMG-3969 is highly effective in promoting carbohydrate substrate. AMG-3969 exhibits extended changes to carbohydrate oxidation as observed by increased respiratory exchange ratio into the next night and day after a single dose$^{[3]}$. Mice: Diabetic db/db mice are used in the study. At 8:00 AM, mice are bled via retro-orbital sinus puncture and blood glucose values are determined and used to randomize the animals in which their averages are similar, and only mice with blood glucose ranges between 300 and 500 mg/dL are included. Vehicle (2% hydroxypropyl methylcellulose, 1% Tween 80, pH 2.2 adjusted with MSA) or AMG-3969 (10, 30, 100 mg/kg) are gavaged at 9:00 AM. Blood glucose is measured at 4, 6, or 8 h posttreatment. At each time point, a 15 μL sample of whole blood is analyzed for drug exposure$^{[2]}$. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

