GNE-781

Cat. No.: HY-108696
CAS No.: 1936422-33-1
Molecular Formula: C₂₇H₃₃F₂N₇O₂
Molecular Weight: 525.59
Target: Epigenetic Reader Domain; Histone Acetyltransferase
Pathway: Epigenetics
Storage: -20°C, stored under nitrogen

* In solvent: -80°C, 6 months; -20°C, 1 month (stored under nitrogen)

SOLVENT & SOLUBILITY

In Vitro
DMSO : 100 mg/mL (190.26 mM; Need ultrasonic)

<table>
<thead>
<tr>
<th>Solvent Concentration</th>
<th>Mass 1 mg</th>
<th>Mass 5 mg</th>
<th>Mass 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>1.9026 mL</td>
<td>9.5131 mL</td>
<td>19.0262 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.3805 mL</td>
<td>1.9026 mL</td>
<td>3.8052 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.1903 mL</td>
<td>0.9513 mL</td>
<td>1.9026 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: ≥ 1.67 mg/mL (3.18 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.67 mg/mL (3.18 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.67 mg/mL (3.18 mM); Clear solution

BIOLOGICAL ACTIVITY

Description
GNE-781 is a highly potent and selective CBP inhibitor with an IC₅₀ of 0.94 nM in TR-FRET assay. GNE-781 also inhibits BRET and BRD4(1) with IC₅₀s of 6.2 nM and 5100 nM, respectively.

IC₅₀ & Target
IC₅₀: 0.94 nM (CBP), 6.2 nM (BRET), 5100 nM (BRD4(1))

In Vitro
GNE-781 is a highly advanced potent and selective bromodomain inhibitor of cyclic adenosine monophosphate response element binding protein, binding protein (CBP). GNE-781 reduces FOXP3 (forkhead box P3) transcript levels. Examination of a subset of bromodomains reveals that GNE-781 is exquisitely selective for CBP/P300 and is
remarkably selective for CBP (5425-fold) and P300 (4250-fold). GNE-781 demonstrates an appropriate balance of cell potency, selectivity (5425-fold over BRD4(1)) [1].

**In Vivo**

GNE-781 is a highly potent and selective CBP inhibitor that is efficacious in a MOLM-16 AML xenograft model. GNE-781 displays antitumor activity in an AML tumor model and is also shown to decrease Foxp3 transcript levels in a dose dependent manner. GNE-781 shows moderate to low clearance in vivo in all species evaluated, with acceptable oral bioavailability. The effect of GNE-781 is determined in an in vivo PK/PD experiment using a MOLM-16 (adult AML cell line) xenograft mouse model. Single doses of GNE-781 are given at dose levels between 3 and 30 mg/kg in MOLM-16 tumor-bearing animals, and samples are collected at time points covering 2-24 h. Tumor RNA is generated and used to assess MYC transcript by quantitative RT-PCR relative to vehicle-treated animals. Suppression of MYC is observed at doses as low as 3 mg/kg at 2 and 8 h, with maximal suppression observed at 10 and 30 mg/kg at 2 h (87% and 88% inhibition, respectively). To evaluate the in vivo efficacy of GNE-781, MOLM-16 AML xenografts are established in SCID beige mice. Upon tumor establishment, dosing of GNE-781 is initiated with po doses of 3-30 mg/kg, twice daily (BID). Single-agent efficacy is observed at all doses, as evidenced by inhibition of MOLM-16 tumor growth. Tumor growth inhibition (%TGI) is 73%, 71%, and 89% at 3, 10, and 30 mg/kg, respectively. All doses of GNE-781 are well tolerated over the 21-day dosing window, with a maximal body weight loss of 3.7% [1].

**PROTOCOL**

**Animal Administration** [1]

**Mice** [1]

Twelve female CD-1 mice are used. All animals are 6-9 weeks old at the time of study and weighed between 20 and 35 g. Animals (n=3 per dosing route) are dosed with 10 or GNE-781 at 1 mg/kg iv (in propyl ethylene glycol 400 (35% v/v) and water (65% v/v)) or 5 mg/kg po (suspended in 0.5% w/v methylcellulose, 0.2% w/v Tween 80). Food and water are available ad libitum to all animals. Serial blood samples (15 μL) are collected by tail nick at 0.033, 0.083, 0.25, 0.5, 1, 3, 8, and 24 h after the intravenous administration and 0.083, 0.25, 0.5, 1, 3, 8, and 24 h after the oral administration. All blood samples are diluted with 60 μL of water containing 1.7 mg/mL EDTA and kept at -80 °C until analysis [1].

**Rats** [1]

Twelve male Sprague-Dawley rats are used. All animals are 6-9 weeks old at the time of study and weighed between 200 and 300 g. Animals (n=3 per dosing route) are dosed with 10 or GNE-781 at 1 mg/kg iv (in propyl ethylene glycol 400 (35% v/v) and water (65% v/v)) or 5 mg/kg po (suspended in 0.5% w/v methylcellulose, 0.2% w/v Tween 80). Food and water are available ad libitum to animals in the iv groups. Animals in po groups are fasted overnight and food withheld until 4 h postdose. Approximately 250 μL of blood are collected via the catheter at 0.033, 0.083, 0.25, 0.5, 1, 2, 4, 8, and 24 h after the intravenous or oral administration. All blood samples are collected into tubes containing 5 μL of 0.5 M K2EDTA and processed for plasma. Samples are centrifuged (2500g for 15 min at 4°C) within 1 h of collection, and plasma samples are kept at -80 °C until analysis [1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

**REFERENCES**


Caution: Product has not been fully validated for medical applications. For research use only.

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