**GNE-495**

**Cat. No.:** HY-100343  
**CAS No.:** 1449277-10-4  
**Molecular Formula:** C_{22}H_{20}FN_{5}O_{2}  
**Molecular Weight:** 405.42  
**Target:** MAP4K  
**Pathway:** MAPK/ERK Pathway  
**Storage:**  
- Powder: -20°C, 3 years; 4°C, 2 years  
- In solvent: -80°C, 6 months; -20°C, 1 month

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### Solvent & Solubility

**In Vitro**  
DMSO: 10 mg/mL (24.67 mM; Need ultrasonic and warming)

<table>
<thead>
<tr>
<th>Preparing Concentration</th>
<th>Mass (mL) 1 mg</th>
<th>Mass (mL) 5 mg</th>
<th>Mass (mL) 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mM</td>
<td>2.4666 mL</td>
<td>12.3329 mL</td>
<td>24.6658 mL</td>
</tr>
<tr>
<td>5 mM</td>
<td>0.4933 mL</td>
<td>2.4666 mL</td>
<td>4.9332 mL</td>
</tr>
<tr>
<td>10 mM</td>
<td>0.2467 mL</td>
<td>1.2333 mL</td>
<td>2.4666 mL</td>
</tr>
</tbody>
</table>

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### BIOLOGICAL ACTIVITY

**Description**  
GNE-495 is a potent and selective MAP4K4 inhibitor with an IC_{50} of 3.7 nM.

**IC_{50} & Target**  
IC_{50}: 3.7 nM (MAP4K4)\(^1\)

**In Vitro**  
GNE-495 is a potent and selective MAP4K4 inhibitor with efficacy in retinal angiogenesis. GNE-495 shows the best balance of MAP4K4 inhibition, permeability, microsomal stability, and cellular potency\(^1\).

**In Vivo**  
GNE-495 is administered intraperitoneally to neonatal mouse pups at high doses: 25 and 50 mg/kg. GNE-495 shows good in vivo profile in all species tested, with low clearances, moderate terminal half-lives, and reasonable oral exposure levels \(F=37-47\%)\(^1\).

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### PROTOCOL

**Product Data Sheet**

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Rats, Mice and Pups [1]

For the brain cassette study, three male Sprague-Dawley (SD) rats are dosed with intravenous (IV) bolus of six test compounds (e.g., GNE-495; 0.5 mg/kg). For the mouse PK study, female CD-1 mice are administered IV bolus doses of GNE-495 (1 mg/kg). In addition, female CD-1 mice are administered GNE-495 (5 mg/kg) via oral (PO) gavage. A dosing volume of 2 mL/kg is used for the rat brain cassette PK and 5 mL/kg is used for all other dosing. Animals are not fasted prior to dose administration, and water and food are available ad libitum. Following administration of the compound of interest, three blood samples (~60 μL) are collected at each time point from individual mice up to either 9 or 24 hours post-dose using a serial sampling approach. Immediately upon collection, the blood is mixed with K2EDTA and stored on ice or in a chilled Kryorack prior to centrifugation to obtain plasma. Within 1 hr of collection, blood samples are centrifuged at approximately 1000-2000× g for 10-15 min at 4°C, and plasma is harvested. The plasma samples are stored at -70 to -80°C until analysis. For neonate PK, 3-day old CD1 pups are injected with 25 mg/kg and 50 mg/kg GNE-495 intraperitoneally, blood samples are collected at the time points indicated, retinas are collected one hour post-dose and snap frozen in liquid nitrogen and stored at -80°C until analysis. Plasma and retinal lysate concentrations are determined by LC/MS/MS.

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

REFERENCES