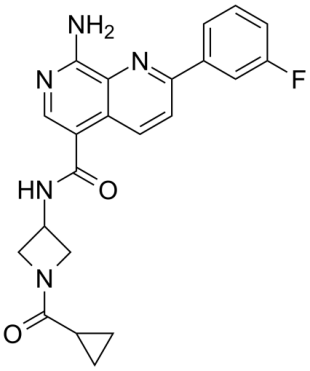
Data Sheet

Product Name:	GNE-495
Cat. No.:	CS-5957
CAS No.:	1449277-10-4
Molecular Formula:	C22H20FN5O2
Molecular Weight:	405.42
Target:	MAP4K
Pathway:	MAPK/ERK Pathway
Solubility:	DMSO : 2.17 mg/mL (5.35 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

GNE-495 is a potent and selective **MAP4K4** inhibitor with an **IC_{50}** of 3.7 nM. IC50 & Target: IC50: 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].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: GNE-495 is prepared in 10%/60%/30% DMSO/PEG400/sterile water (Rats, IV) [1].
GNE-495 is prepared in 40% PEG400/60% 50 mM Citrate pH 5 buffer or 10% DMSO/35% PEG400/55% water (Mice, IV)[1].
GNE-495 is prepared in 0.5% (w/v) methylcellulose/0.2% (w/v) Tween 80 in sterile water (Mice, oral gavage)[1].
[1]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.

References:

[1]. Ndubaku CO et al. Structure-Based Design of GNE-495, a Potent and Selective MAP4K4 Inhibitor with Efficacy in Retinal Angiogenesis. ACS Med Chem Lett. 2015 Jun 29;6(8):913-8.

CAIndexNames:

1,7-Naphthyridine-5-carboxamide, 8-amino-N-[1-(cyclopropylcarbonyl)-3-azetidinyl]-2-(3-fluorophenyl)-

SMILES:

O=C(C1=C2C=CC(C3=CC=CC(F)=C3)=NC2=C(N)N=C1)NC4CN(C(C5CC5)=O)C4

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

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