GNE-9815

Cat. No.: HY-142160

CAS No.: 2729996-45-4

Molecular Formula: $C_{26}H_{22}FN_5O_2$

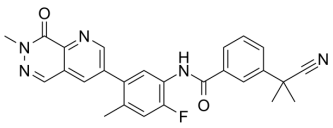
Molecular Weight: 455.48

Target: Raf

Pathway: MAPK/ERK Pathway

Storage:

Powder	-20°C	3 years
In solvent	-80°C	6 months
	-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 50 mg/mL (109.77 mM; ultrasonic and warming and heat to 80°C)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1955 mL	10.9774 mL	21.9549 mL
	5 mM	0.4391 mL	2.1955 mL	4.3910 mL
	10 mM	0.2195 mL	1.0977 mL	2.1955 mL

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 (5.49 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.5 mg/mL (5.49 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.49 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

GNE-9815 (compound 7) is a highly selective, pan-RAF inhibitor with good oral bioavailability. GNE-9815 exhibits K_i values of 0.062 and 0.19 nM for CRAF and BRAF, respectively. GNE-9815 combines with MEK inhibitor Cobimetinib (HY-13064) shows synergistic modulation of MAPK pathway. GNE-9815 can be used in studies of KRAS mutant cancers[1].

IC_{50} & Target

CRAF	Braf
0.062 nM (Ki)	0.19 nM (Ki)

In Vitro

GNE-9815 shows synergistic activity in KRAS mutant A549 and HCT116 cancer cells in combination with the MEK inhibitor

Cobimetinib[1].

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

In Vivo

GNE-9815 (15 mg/kg; p.o.; single) demonstrates synergistic MAPK pathway modulation when combines with the MEK inhibitor Cobimetinib in an HCT116 xenograft mouse model[1].

GNE-9815 (5 mg/kg; p.o.; single) shows good oral bioavailability and (1 mg/kg; i.v.; single) exhibits low blood clearance, moderate volume of distribution, and short half-life[1].

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

Animal Model:	Female NCR nude mice (6 to 8-week-old; 24-26 g; HCT116 xenograft mice model)[1].
Dosage:	15 mg/kg
Administration:	Intravenous injection or oral administration; single.
Result:	Resulted in pathway inhibition as demonstrated by partial inhibition of pRSK between 2 and 24 h, but more robust, albeit transient, inhibition of the downstream MAPK target genes, DUSP6 and SPRY4. Led to deeper inhibition of the downstream MAPK target genes DUSP6 and SPRY4, when combined with the MEK inhibitor Cobimetinib, with maximal inhibition at 8 h and with a more modest rebound in levels at 24 h, post final dose.

Animal Model:	Female NCR nude mice (6 to 8-week-old; 24-26 g)[1].
Dosage:	1 mg/kg (for i.v.); 5 mg/kg (for p.o.).
Administration:	Intravenous injection or oral administration; single.
Result:	Exhibited CL_b, V_{dss} and $t_{1/2}$ values of 17 mL/min·kg, 1.7 L/kg and 1.9 h, respectively. Showed good oral bioavailability with F% of 37%. (methylcellulose/Tween formulation).

REFERENCES

[1]. Huestis MP, et al. Targeting KRAS Mutant Cancers via Combination Treatment: Discovery of a Pyridopyridazinone pan-RAF Kinase Inhibitor. ACS Med Chem Lett. 2021 Apr 21;12(5):791-797.

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

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