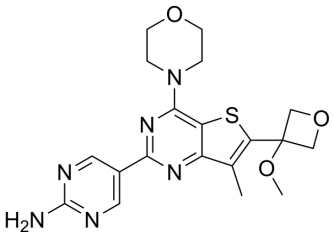
GNE-317

Cat. No.:	HY-12763
CAS No.:	1394076-92-6
Molecular Formula:	$C_{19}H_{22}N_6O_3S$
Molecular Weight:	414.48
Target:	PI3K; mTOR
Pathway:	PI3K/Akt/mTOR
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 20 mg/mL (48.25 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.4127 mL	12.0633 mL	24.1266 mL
	5 mM	0.4825 mL	2.4127 mL	4.8253 mL
	10 mM	0.2413 mL	1.2063 mL	2.4127 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description	GNE-317 is a PI3K/mTOR inhibitor, is able to cross the blood-brain barrier (BBB).
IC_{50} & Target	PI3K mTOR
In Vitro	GNE-317 is an oxetane derivative of GDC-0980 synthesized with the goal of reducing substrate affinity for efflux transporters. In vitro, GDC-0980 and GNE-317 demonstrate similar profiles in MTS cytotoxicity experiments using the GL261 cell line[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Seven days after i.c. inoculation with GL261-GFP-Luc cells, mice are treated once daily with the maximum tolerated dose of GDC-0980 (7.5 mg/kg), GNE-317 (30 mg/kg), or vehicle. For GL261, tumor growth is tracked through bioluminescence imaging on a weekly basis. There are no significant changes in GL261 tumor growth among the 3 groups. In assessing survival benefits in GL261, neither GDC-0980 nor GNE-317 provides survival benefit over the vehicle-treated animals. The fact that these drugs are not effective in vivo is suggested by the in vitro cytotoxicity data showing that the drugs have limited efficacy in inducing cell death in the GL261 cell line. Neither drug is effective in the GL261 tumor in spite of greater delivery and enhanced therapeutic targeting efficacy of GNE-317[1].

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PROTOCOL

Cell Assay [1]

GL261 is an aggressive C57BL/6J-derived glioma line. This cell line is transfected with both green fluorescent protein (GFP) and luciferase (Luc) from separate plasmids. The resultant monoclonal GL261-GFP-Luc cells are maintained in Dulbecco's modified Eagle's medium supplemented with 10% FBS and Penicillin/Streptomycin (100 U/mL) and cultured at 5% oxygen. Cell selection used 4 mg/mL Puromycin and 4 mg/mL G418. Cellular viability assays are set up in a 96-well format with 2000 cells plated per well in the culture conditions. Cells are incubated in the presence of drug or vehicle for 48 hours, and viability was assessed by MTS assay. Absorbance at 490 nm is used to determine viability and at 650 nm to account for background using a Synergy Mx automated plate reader. Numerical values from drug-treated wells are normalized to the values of vehicle-treated wells to yield percent survival[1].

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Animal Administration [1]

Mice[1]

GL261-GFP-Luc cells are implanted into 7-week-old C57BL/6J mice. When tumors reach 5e7 photons/s/cm^2/sr (radiance), animals are orally administered the maximum tolerated dose of GDC-0980 (7.5 mg/kg), GNE-317 (30 mg/kg) or vehicle once a day for 3 days. The maximum tolerated doses are defined as the greatest dose that could be administered to mice with <10% drop in bodyweight. Even at these different doses, both doses provide similar plasma concentrations and thus the same overall systemic exposure. At 1 or 6 hours after the third dose, mice are euthanized with carbon dioxide and perfused with 30 mL PBS. With the aid of GFP goggles, brains are dissected into tumor core, tumor rim, and normal brain tissue. Tissue samples and blood are processed, and tissue specimens from each group are analyzed for drug concentrations using LC-MS/MS.

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

CUSTOMER VALIDATION

- Front Pharmacol. 2020 Nov 11;11:580407.

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REFERENCES

[1]. Salphati L, et al. Distribution of the phosphatidylinositol 3-kinase inhibitors Pictilisib (GDC-0941) and GNE-317 in U87 and GS2 intracranial glioblastoma models-assessment by matrix-assisted laser desorption ionization imaging. Drug Metab Dispos. 2014 Jul;42(7):1110-6.

[2]. Becker CM, et al. Decreased affinity for efflux transporters increases brain penetrance and molecular targeting of a PI3K/mTOR inhibitor in a mouse model of glioblastoma. Neuro Oncol. 2015 Sep;17(9):1210-9.

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