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产品名称：GNE-493
产品别名：GNE-493

生物活性：

Description

GNE-493 is a potent, selective, and orally available dual pan-PI3-kinase/mTOR inhibitor with IC_{50}s of 3.4 nM, 12 nM, 16 nM, 16 nM and 32 nM for PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ and mTOR.

IC_{50} & Target

PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ	mTOR
3.4 nM (IC_{50})	12 nM (IC_{50})	16 nM (IC_{50})	16 nM (IC_{50})	30 nM (IC_{50})

In Vitro

GNE-493 is a low molecular weight, potent dual inhibitor of pan-PI3 kinases and mTOR. GNE-493 displays approximately equipotent inhibition of Class I PI3K isoforms, is submitted for screening in a 142 kinase panel provided by Invitrogen's SelectScreen service. Of these kinases, only three are subject to greater than 50% inhibition by GNE-493, and none are inhibited greater than 80% when tested at 1 μM. Subsequently measured IC50s demonstrated that GNE-493 is more than 100-fold selective for PI3Kα over these three unrelated kinases (Aurora A IC50>10 μM, MLK1 IC50=591 nM and SYK IC50=371 nM)[1].

In Vivo

To confirm and compare in vivo efficacy, GNE-493 is examined in the human MCF7.1 breast cancer xenograft model that harbors a PI3Kα activating mutation. Mice bearing xenografts are dosed orally once daily with 10 mg/kg of GNE-493 for 21 continuous days. Similar to observations made in the PC3 prostate cancer xenograft model, 10 mg/kg of GNE-493 results in 73% tumor growth inhibition at day 21 when compared to vehicle control animals. When achieving comparable levels of drug exposure, GNE-493 shows a similar suppression of the PI3K pathway and consequently, a similar efficacy profile against MCF7.1 breast tumors[1].

Solvent&Solubility

In Vitro:

DMSO : ≥ 45 mg/mL (120.82 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.6850 mL	13.4250 mL	26.8500 mL
	5 mM	0.5370 mL	2.6850 mL	5.3700 mL
	10 mM	0.2685 mL	1.3425 mL	2.6850 mL

*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液；一旦配成溶液，请分装保存，避免反复冻融造成的产品失效。

储备液的保存方式和期限：-80°C, 6 months; -20°C, 1 month。-80°C 储存时，请在 6 个月内使用，-20°C 储存时，请在 1 个月内使用。

References

[1]. Sutherlin DP, et al. Discovery of (thienopyrimidin-2-yl)aminopyrimidines as potent, selective, and orally available pan-PI3-kinase and dual pan-PI3-kinase/mTOR inhibitors for the treatment of cancer. J Med Chem. 2010 Feb 11;53(3):1086-97.

实验参考：

Mice[1]

Human prostate cancer PC3 cells are resuspended in Hank's Balanced Salt Solution and 3×10^6 cells implanted subcutaneously into the right hind flank of athymic nu/nu (nude) mice. Tumors

Animal Administration	are monitored until they reached a mean tumor volume of 150-200 mm^3 prior to the initiation of dosing. MCF7.1 cells resuspended in a 1:1 mixture of Hank's Buffered Salt Solution and Matrigel Basement Membrane Matrix, were 5×10^6 subcutaneously implanted into the right hind flank of athymic nu/nu (nude) mice. Prior to cell inoculation, 17 β-estradiol (0.36 mg/pellet, 60-day release) are implanted into the dorsal shoulder blade area of each nude mouse. After implantation of cells, tumors are monitored until they reached a mean tumor volume of 250-350 mm^3 prior to initiating dosing. Female nude (nu/nu) mice that are 6-8 weeks old and weighed 20-30 g are used. Tumor bearing mice are dosed orally daily with 10 mg/kg of GNE-493 for 14 continuous days. Tumor volume is measured in two dimensions (length and width) and is analyzed using Excel version 11.2. Animal body weights are measured. Tumor sizes are recorded twice weekly over the course of the study (14-21 days)
Kinase Assay	Enzymatic activity of the Class I PI3K isoforms is measured using a fluorescence polarization assay that monitors formation of the product 3,4,5-inositoltriphosphate molecule as it competes with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidyl inositide-3-phosphate product results in a decrease in fluorescence polarization signal as the labeled fluorophore is displaced from the GRP-1 protein binding site. Class I PI3K isoforms are expressed and purified as heterodimeric recombinant proteins. Tetramethylrhodamine-labeled PIP3 (TAMRA-PIP3), di-C8-PIP2, and PIP3 detection reagents are used. PI3K isoforms are assayed under initial rate conditions in the presence of 10 mM Tris (pH 7.5), 25 μM ATP, 9.75 μM PIP2, 5% glycerol, 4 mM $MgCl_2$, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, 2% (v/v) DMSO at the following concentrations for each isoform: PI3Kα, PI3β at 60 ng/mL; PI3Kγ at 8 ng/mL; PI3Kδ at 45 ng/mL. After assay for 30 min at 25°C, reactions are terminated with a final concentration of 9 mM EDTA, 4.5 nM TAMRA-PIP3, and 4.2 μg/mL GRP-1 detector protein before reading fluorescence polarization on an Envision plate reader. IC_{50}s are calculated from the fit of the dose−response curves to a 4-parameter equation[1].
References	[1]. Sutherlin DP, et al. Discovery of (thienopyrimidin-2-yl)aminopyrimidines as potent, selective, and orally available pan-PI3-kinase and dual pan-PI3-kinase/mTOR inhibitors for the treatment of cancer. J Med Chem. 2010 Feb 11;53(3):1086-97.