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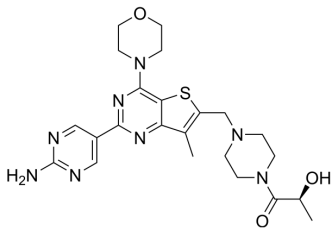
Apitolisib

Cat. No.:	HY-13246
CAS No.:	1032754-93-0
Molecular Formula:	$C_{23}H_{30}N_8O_3S$
Molecular Weight:	498.6
Target:	PI3K; mTOR; Apoptosis
Pathway:	PI3K/Akt/mTOR; Apoptosis
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 : 14.29 mg/mL (28.66 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0056 mL	10.0281 mL	20.0562 mL
	5 mM	0.4011 mL	2.0056 mL	4.0112 mL
	10 mM	0.2006 mL	1.0028 mL	2.0056 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: ≥ 1.43 mg/mL (2.87 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1.43 mg/mL (2.87 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1.43 mg/mL (2.87 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Apitolisib (GDC-0980; GNE 390; RG 7422) is a selective, potent, orally bioavailable Class I PI3 kinase and mTOR kinase (TORC1/2) inhibitor with IC_{50}s of 5 nM/27 nM/7 nM/14 nM for PI3Kα/PI3Kβ/PI3Kδ/PI3Kγ, and with a K_i of 17 nM for mTOR.

IC_{50} & Target

PI3Kα 5 nM (IC_{50})	PI3Kδ 7 nM (IC_{50})	PI3Kγ 14 nM (IC_{50})	PI3Kβ 27 nM (IC_{50})
mTOR 17 nM (Ki)	TORC1	TORC2	

In Vitro	Apitolisib (GDC-0980) is remarkably selective for several other members of the closely related PIKK family kinases: C2alpha IC_{50}=1300 nM; C2beta IC_{50}=7 94 nM; VPS34 IC_{50}=2000 nM; PI4Kalpha >10 μM; PI4Kbeta >10 μM; DNA-PK Kiapp=623 nM, respectively[1]. A recent study shows that Apitolisib (GDC-0980) reduces cancer cell viability by inhibiting cell-cycle procession and inducing apoptosis with most potency in prostate (IC_{50} < 200 nM 50%), <500 nM 100%), breast (IC_{50} <200 nM 37%, <500 nM 78%) and NSCLC lines (IC_{50} <200 nM 29%, <500 nM 88%) and less potency in pancreatic (IC_{50} <200 nM 13%, <500 nM 67%) and melanoma cell lines (IC_{50} <200 nM 0%, <500 nM 33%)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Apitolisib (GDC-0980) (1 mg/kg, p.o.) demonstrats significant efficacy in mouse xenografts and is currently in phase I clinical trials for cancer. Clearance and PPB are low, and Apitolisib (GDC-0980) shows dose-proportional exposure from 5 mg/kg dosed in PEG to 50 mg/kg dosed in suspension in MCT, a finding attributed partially to the compound's good solubility[1]. Apitolisib (GDC-0980) (5 mg/kg, p.o.) results in greater than 50% TGI in 15 of the 20 xenograft models. The difference in tumor response to Apitolisib (GDC-0980) treatment correlates with the duration of knockdown of pAkt/tAkt[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Ten centimeter square dishes are seeded with 2 million cells in a volume of 10 mL followed by incubation at 37°C under 5% CO_2 overnight (appr 16 hours). Cells are treated with the indicated concentration of GDC-0941, Apitolisib (GDC-0980), or mTOR1/2 inhibitor for the time indicated. Following treatment, cells are washed with cold PBS and lysed in 1X Cell Extraction Buffer, 1 mM PMSF, and Phosphatase Inhibitor Cocktails 1 and 2 are all needed. Protein concentration is determined using the Pierce BCA Protein Assay Kit. For immunoblots, equal protein amounts are separated by electrophoresis through NuPage Bis-Tris 10% gradient gels; proteins are transferred onto polyvinylidene difluoride membranes using the Criterion system and protocol. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Cell Assay [2]	Three hundred and eighty-four-well plates are seeded with 2,000 cells/well in a volume of 54 μL per well followed by incubation at 37°C under 5% CO_2 overnight (appr 16 hours). Compounds are diluted in dimethyl sulfoxide to generate the desired stock concentrations then added in a volume of 6 μL per well. All treatments are tested in quadruplicate. After 4 days incubation, relative numbers of viable cells are estimated using CellTiter-Glo and total luminescence is measured on a Wallac Multilabel Reader. The concentration of drug resulting in 50% inhibition of cell viability (IC_{50}) or 50% maximal effective concentration (EC_{50}) is determined using Prism software. For cell lines that failed to achieve an IC_{50} the highest concentration tested (20 μM) is listed. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [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 are monitored until they reach 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 are 5×10^6 subcutaneously implanted into the right hind flank of athymic nu/nu (nude) mice. Prior to cell inoculation, 17β-estradiol (0.36 mg/pellet, 60-day release, no. SE-121) are implanted into the dorsal shoulder blade area of each nude mouse. After implantation of cells, tumors are monitored until they reach a mean tumor volume of 250-350 mm^3 prior to initiating dosing. Compound 2 is dissolved in 0.5% methylcellulose with 0.2% Tween-80 (MCT). Female nude (nu/nu) mice that are 6-8 weeks old and weighed 20-30 g are obtained from Charles River Laboratories. Tumor bearing mice are dosed daily for 14-21 days depending on the xenograft model with 100 μL of vehicle (MCT) or test agent orally. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nature. 2018 Aug;560(7719):499-503.
- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Clin Cancer Res. 2020 Apr 15;26(8):2011-2021.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.
- Cell Syst. 2020 Jan 22;10(1):66-81.e11.

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REFERENCES

[1]. Sutherlin DP, et al. Discovery of a potent, selective, and orally available class I phosphatidylinositol 3-kinase (PI3K)/mammalian target of rapamycin (mTOR) kinase inhibitor (GDC-0980) for the treatment of cancer. J Med Chem, 2011, 54(21), 7579-7587.

[2]. Wallin JJ, et al. GDC-0980 is a novel class I PI3K/mTOR kinase inhibitor with robust activity in cancer models driven by the PI3K pathway. Mol Cancer Ther, 2011, 10(12), 2426-2436.

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