

产品名称: **GDC-0980 (RG7422)**

产品别名: **Apitolisib**

生物活性:

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	PI3Kβ	PI3Kδ	PI3Kγ	mTOR
	5 nM (IC ₅₀)	27 nM (IC ₅₀)	7 nM (IC ₅₀)	14 nM (IC ₅₀)	17 nM (K _i)
	TORC1	TORC2			
In Vitro	Apitolisib (GDC-0980) is remarkably selective for several other members of the closely related PIKK family kinases: C2alpha IC50=1300 nM; C2beta IC50=7 94 nM; VPS34 IC50=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 (IC50 < 200 nM 50%), <500 nM 100%), breast (IC50 <200 nM 37%, <500 nM 78%) and NSCLC lines (IC50 <200 nM 29%, <500 nM 88%) and less potency in pancreatic (IC50 <200 nM 13%, <500 nM 67%) and melanoma cell lines (IC50 <200 nM 0%, <500 nM 33%)[2].				
In Vivo	Apitolisib (GDC-0980) (1 mg/kg, p.o.) demonstrates 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].				
Solvent&Solubility	In Vitro: DMSO : 14.29 mg/mL (28.66 mM; Need ultrasonic)				
	Preparing Stock Solutions	<div>SolventMassConcentration</div>	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
	*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℃, 6 months; -20℃, 1 month。-80℃ 储存时，请在 6 个月内使用，-20℃ 储存时，请在 1 个月内使用。 In Vivo: 请根据您的实验动物和给药方式选择适当的溶解方案。以下溶解方案都请先按照 In Vitro 方式配制澄清的储备液，再依次添加助溶剂： ——为保证实验结果的可靠性，澄清的储备液可以根据储存条件，适当保存；体内实验的工作液，建议您现用现配，当天使用； 以下溶剂前显示的百分比是指该溶剂在您配制终溶液中的体积占比；如在配制过程中出现沉淀、析出现象，可以通过加热和/或超声的方式助溶 <div>1.请依序添加每种溶剂： 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</div> <div>Solubility: ≥ 1.43 mg/mL (2.87 mM); Clear solution</div>				

	<p>此方案可获得 ≥ 1.43 mg/mL (2.87 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 14.299999 mg/mL 的澄清 DMSO 储备液加到 400 μL PEG300 中, 混合均匀; 向上述体系中加入 50 μL Tween-80, 混合均匀; 然后继续加入 450 μL 生理盐水定容至 1 mL。</p> <p>2.请依序添加每种溶剂: 10% DMSO \rightarrow 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 1.43 mg/mL (2.87 mM); Clear solution</p> <p>此方案可获得 ≥ 1.43 mg/mL (2.87 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例, 取 100 μL 14.299999 mg/mL 的澄清 DMSO 储备液加到 900 μL 20% 的 SBE-β-CD 生理盐水水溶液中, 混合均匀。</p> <p>3.请依序添加每种溶剂: 10% DMSO \rightarrow 90% corn oil</p> <p>Solubility: ≥ 1.43 mg/mL (2.87 mM); Clear solution</p> <p>此方案可获得 ≥ 1.43 mg/mL (2.87 mM, 饱和度未知) 的澄清溶液, 此方案不适用于实验周期在半个月以上的实验。</p> <p>以 1 mL 工作液为例, 取 100 μL 14.299999 mg/mL 的澄清 DMSO 储备液加到 900 μL 玉米油中, 混合均匀。</p>
References	<p>[1]. Sutherlin DP, et al. <u>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.</u> J Med Chem. 2011, 54(21), 7579-7587.</p> <p>[2]. Wallin JJ, et al. <u>GDC-0980 is a novel class I PI3K/mTOR kinase inhibitor with robust activity in cancer models driven by the PI3K pathway.</u> Mol Cancer Ther. 2011, 10(12), 2426-2436.</p>
实验参考:	
Cell Assay	<p>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% CO₂ 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 (IC₅₀) or 50% maximal effective concentration (EC₅₀) is determined using Prism software. For cell lines that failed to achieve an IC₅₀ the highest concentration tested (20 μM) is listed. [2]</p>
Animal Administration	<p>Human prostate cancer PC3 cells are resuspended in Hank's Balanced Salt Solution and 3\times10⁶ 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 mm³ prior to the initiation of dosing.</p> <p>MCF7.1 cells resuspended in a 1:1 mixture of Hank's Buffered Salt Solution and Matrigel Basement Membrane Matrix are 5\times10⁶ 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 mm³ prior to initiating dosing.</p> <p>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. [1]</p>
	<p>Ten centimeter square dishes are seeded with 2 million cells in a volume of 10 mL followed by incubation at 37°C under 5% CO₂ overnight (appr 16 hours). Cells are treated with the indicated</p>

Kinase Assay	<p>concentration of GDC-0941, Apitolisib (GDC-0980), or mTOR1/2 inhibitor for the time indicated.</p> <p>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. [2]</p>
References	<p>[1]. <u>Sutherland 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.</u></p> <p>[2]. <u>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.</u></p>



源叶生物