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产品名称: **PQR309**
产品别名: **Bimiralisib**

生物活性:					
Description	Bimiralisib (PQR309) is a potent, brain-penetrant, orally bioavailable, pan-class I PI3K/mTOR inhibitor with IC50s of 33 nM, 451 nM, 661 nM, 708 nM and 89 nM for PI3Kα, PI3Kδ, PI3Kβ, PI3Kγ and mTOR, respectively. Bimiralisib is an mTORC1 and mTORC2 inhibitor.				
IC50 & Target	PI3Kα	PI3Kβ	PI3Kδ	PI3Kγ	PI3Kα-H1047R
	33 nM (IC50)	661 nM (IC50)	451 nM (IC50)	708 nM (IC50)	36 nM (IC50)
	PI3Kα-E545K	PI3Kα-E542K	Vps34	mTOR	mTORC1
	136 nM (IC50)	63 nM (IC50)	6486 nM (IC50)	89 nM (IC50)	
	mTORC2	DNA-PK			
		8567 nM (IC50)			
In Vitro	Bimiralisib is a highly selective pan-PI3K inhibitor with a balanced targeting of mTOR kinase. Bimiralisib also inhibits PI3Kα-H1047R, PI3Kα-E542K and PI3Kα-E545K with IC50s of 36 nM, 63 nM and 136 nM, respectively[1].				
In Vivo	Oral administration yields similar concentrations of Bimiralisib in brain and plasma samples illustrates that Bimiralisib readily passes the blood–brain barrier. In mice, both po and iv application routes show a rapid drop below 200 ng/mL (~0.5 μM) of PQR309 within <1 h (iv) to <2 h (po) after administration, which reflects the time point when the drug reaches the median GI50 determined in tumor cell lines. In female rats a single oral dose (10 mg/kg) achieves similar drug levels as a single intravenous injection (5 mg/kg) with regard to Cmax. The half-life of 5-8 h and an AUC0.25-12 of around 14 000 h•ng/mL contributed to an excellent oral bioavailability of PQR309 (>50%). Twenty-four hours after po administration, plasma levels of PQR309 are still >2 μM (800-1000 ng/mL). Moreover, after 1-2 h exposure to PQR309 , drug levels in rat brain samples are comparable to plasma levels, confirming rapid access of PQR309 to the brain[1].				
Solvent&Solubility	In Vitro: DMSO : ≥ 50 mg/mL (121.54 mM) * "≥" means soluble, but saturation unknown.				
	Preparing Stock Solutions	<div>Solvent / Mass / Concentration</div>	1 mg	5 mg	10 mg
		1 mM	2.4308 mL	12.1542 mL	24.3084 mL
		5 mM	0.4862 mL	2.4308 mL	4.8617 mL
		10 mM	0.2431 mL	1.2154 mL	2.4308 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：				



	<p>——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</p> <p>1.请依序添加每种溶剂: 10% DMSO→40% PEG300 →5% Tween-80 → 45% saline</p> <p>Solubility: ≥ 2.5 mg/mL (6.08 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.08 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例,取 100 μL 25.0 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→ 90% (20% SBE-β-CD in saline)</p> <p>Solubility: ≥ 2.5 mg/mL (6.08 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.08 mM, 饱和度未知) 的澄清溶液。</p> <p>以 1 mL 工作液为例,取 100 μL 25.0 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 →90% corn oil</p> <p>Solubility: ≥ 2.5 mg/mL (6.08 mM); Clear solution</p> <p>此方案可获得 ≥ 2.5 mg/mL (6.08 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 25.0 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]. Beaufils F, et al. 5-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a Potent, Brain-Penetrant, Orally Bioavailable, Pan-Class I PI3K/mTOR Inhibitor as Clinical Candidate in Oncology. J Med Chem. 2017 Sep 14;60(17):7524-7538.</p> <p>[2]. Wicki A, et al. First-in human, phase 1, dose-escalation pharmacokinetic and pharmacodynamic study of the oral dual PI3K and mTORC1/2 inhibitor PQR309 in patients with advanced solid tumors (SAKK 67/13). Eur J Cancer. 2018 Jun;96:6-16.</p>
实验参考:	
Cell Assay	<p>Human tumor cell lines are seeded into 96-well microtiter plates and exposed to five (1/2 log serial) drug dilutions plus control, followed by 48 h (except for two controls of each cell line which are fixed with TCA (cell population at $t = 0$ h [Tz]). The assay is terminated by fixation with TCA (10% final). Cell density is determined using a sulforhodamine B staining protocol and the absorbance measured at 515 nm. Using seven absorbance measurements, the percentage growth is calculated at each of the drug concentrations levels. Percentage growth inhibition is calculated. The NTRC Oncolines 44 cell lines are exposed for 72 h to 9-point 3-fold serial dilutions of Bimiralisib. The concentration of 50% growth inhibition is associated with the signal $((\text{luminescence}_{\text{untreated}, t=72\text{h}} - \text{luminescence}_{t=0})/2) + \text{luminescence}_{t=0}$. The data set integrated here is used for IC₅₀ calculations. IC₅₀ values of A2058 or SKOV3 cell proliferation given are determined and calculated^[1].</p>
	<p>Mice^[1]</p> <p>Healthy male nude NIH rats are used. 2×10^7 PC-3 cells are injected subcutaneously at day 0 (D0) in</p>



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Animal Administration	<p>200 μL of RPMI1640 into the right flank of male nude rats, 24 h after a whole-body irradiation with a γ-source (5 Gy, ^{60}Co). Tumor-bearing rats are randomized on day 16 (mean volume of $330 \pm 70 \text{ mm}^3$ according to their individual tumor volume into five groups of each eight animals using Vivo manager software. Analysis of variance is performed to test for homogeneity between groups. Daily administration on D17-D44 and from D51 to D57: group 1, vehicle; group 2, compound 1 at 5 mg/kg; group 3, Bimiralisib at 10 mg/kg. Group 4: Bimiralisib at 15 mg/kg from D17 to D21, from D24 to D28, from D34 to D38, from D41 to D44, and from D51 to D56. Group 5: one iv injection of Vinorelbine at 2.5 mg/kg on D17, D24, D31, and D38. Final termination of rats is performed on D87. Body weight is measured at least twice a week. Length and width of tumors are measured and recorded twice a week with calipers, and the tumor volume is estimated.</p>
References	<p>[1]. Beaufils F, et al. 5-(4,6-Dimorpholino-1,3,5-triazin-2-yl)-4-(trifluoromethyl)pyridin-2-amine (PQR309), a Potent, Brain-Penetrant, Orally Bioavailable, Pan-Class I PI3K/mTOR Inhibitor as Clinical Candidate in Oncology. J Med Chem. 2017 Sep 14;60(17):7524-7538.</p> <p>[2]. Wicki A, et al. First-in human, phase 1, dose-escalation pharmacokinetic and pharmacodynamic study of the oral dual PI3K and mTORC1/2 inhibitor PQR309 in patients with advanced solid tumors (SAKK 67/13). Eur J Cancer. 2018 Jun;96:6-16.</p>

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