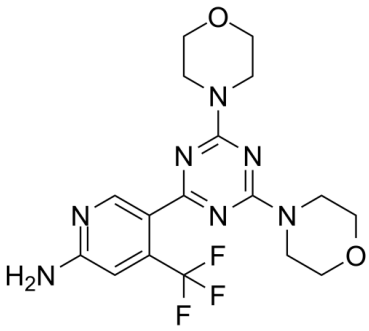
Data Sheet

Product Name:	Bimiralisib
Cat. No.:	CS-4672
CAS No.:	1225037-39-7
Molecular Formula:	C17H20F3N7O2
Molecular Weight:	411.38
Target:	mTOR; PI3K
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO : ≥ 50 mg/mL (121.54 mM)



BIOLOGICAL ACTIVITY:

Bimiralisib (PQR309) is a potent, brain-penetrant, orally bioavailable, pan-class I **PI3K/mTOR** inhibitor with **IC_{50}**s 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: IC50: 33 nM (PI3Kα), 451 nM (PI3Kδ), 661 nM (PI3Kβ), 708 nM (PI3Kγ), 36 nM (PI3Kα-H1047R), 63 nM (PI3Kα-E542K), 136 nM (PI3Kα-E545K), 89 nM (mTOR), 8486 nM (VPS34), 8567 nM (DNAPK)[1] Kd: 1.5 nM (PI3Kα), 11 nM (PI3Kβ), 25 nM (PI3Kδ), 25 nM (PI3Kγ), 12 nM (mTOR), 230 nM (VPS34), 850 nM (PI3KC2β), 40000 nM (PI4KCβ), 1600 nM (DNAPK)[1] mTORC1, mTORC2[2] **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 IC_{50}s 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 GI_{50} 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 C_{max}. The half-life of 5-8 h and an $AUC_{0.25-12}$ 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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]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 $((luminescence_{untreated,t=72h}-luminescence_{t=0})/2)+luminescence_{t=0}$. The data set integrated here is used for IC_{50} calculations. IC_{50} values of A2058 or SKOV3 cell proliferation given are determined and calculated[1].

Animal Administration: PQR309 is dissolved in DMSO to 40 mg/mL. This solution is diluted with 20% HPBCD [(2-hydroxypropyl)-β-cyclodextrin] in water[1].[1]Mice[1]

Healthy male nude NIH rats are used. 2×10^7 PC-3 cells are injected subcutaneously at day 0 (D0) in 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±70 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 D4, 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.

References:

[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.

[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.

CAIndexNames:

2-Pyridinamine, 5-(4,6-di-4-morpholinyl-1,3,5-triazin-2-yl)-4-(trifluoromethyl)-

SMILES:

NC1=NC=C(C2=NC(N3CCOCC3)=NC(N4CCOCC4)=N2)C(C(F)(F)F)=C1

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