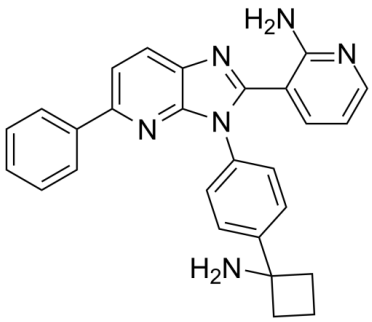
Data Sheet

Product Name:	Miransertib
Cat. No.:	CS-5377
CAS No.:	1313881-70-7
Molecular Formula:	C27H24N6
Molecular Weight:	432.52
Target:	Akt
Pathway:	PI3K/Akt/mTOR
Solubility:	DMSO : 12.5 mg/mL (28.90 mM; Need ultrasonic)



BIOLOGICAL ACTIVITY:

Miransertib (ARQ-092) is an orally bioavailable, selective, and potent allosteric **Akt** inhibitor with **IC_{50}**s of 2.7 nM, 14 nM and 8.1 nM for **Akt1**, **Akt2**, **Akt3**, respectively. IC50 & Target: IC50: 2.7 nM (Akt1), 14 nM (Akt2), 8.1 nM (Akt3)[1] **In Vitro:** Miransertib (ARQ-092; Compound 21a) demonstrates high enzymatic potency against Akt1, Akt2 and Akt3, as well as potent cellular inhibition of Akt activation and the phosphorylation of the downstream target PRAS40. Miransertib shows strong affinity for un-phosphorylated fulllength Akt1 and potently inhibited the phosphorylated form of full-length Akt isoforms. In a large panel of cell lines derived from various tumor types, Miransertib shows potent anti-proliferative activity in cell lines containing PIK3CA/PIK3R1 mutations compared to those with wild-type (wt) PIK3CA/PIK3R1 or PTEN loss. Miransertib shows excellent inhibition of p-Akt (S473) and p-Akt (T308) in both AN3CA and A2780 cells. The inhibition of the downstream protein p-PRAS40 (T246) is observed with Miransertib (IC_{50}=0.31 μM)[1]. **In Vivo:** In a mouse pharmacokinetic study, (po at 100 mg/kg, iv at 5 mg/kg), Miransertib (ARQ-092; Compound 21a) shows an oral bioavailability of 23%. Miransertib results in 99%, 95% and 58% reductions in p-Akt (S473), p-Akt (T306) and p-PRAS40 (T246), respectively, after tumor-bearing mice are treated with 100 mg/kg po. The inhibition of phosphorylation is sustained at eight hours. The plasma concentration of Miransertib at one hour is 2.1 μM and decreased to 0.26 μM at 8 hours, while in the tumor, the concentration is 21.0 μM at one hour and 9.6 μM at 8 hours[1]. To determine the effects of Miransertib (ARQ-092) on cardiac function, echocardiographic analysis of $SHP2^{+/+}$ and $SHP2^{Y279C/+}$ littermates is conducted, either in the presence of orally administered vehicle or Miransertib (100 mg/kg/day), at 12, 14, and 16 weeks of age. By 12 weeks of age, $SHP2^{Y279C/+}$ mice show significant left ventricular hypertrophy, as indicated by decreased chamber dimension and increased posterior wall thickness compared with those of littermate controls; hypertrophy in these mice continued to progress over the 4 week time period. Treatment of the $SHP2^{Y279C/+}$ mice with Miransertib normalizes the hypertrophic cardiomyopathy (HCM) phenotype as early as 2 weeks following treatment, with levels comparable to those in $SHP2^{+/+}$ at this time point[2].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: [1]Anti-proliferative cellular assays are conducted using the CellTiter Non-Radioactive Cell Proliferation Assay, which utilizes the production of formazan from a tetrazolium compound by live cells. AN3CA and A2780 cells are obtained from the ATCC. AN3CA cells are cultured in DMEM, and A2780 cells are cultured in RPMI. Cells are plated in 96-well plates at 2,000-10,000 cells/well, cultured for 24 h, and treated with the test compound for 72 h at a final DMSO concentration no greater than 0.5% v/v. PMS stock reagent (0.92 mg/mL in DPBS) is diluted 20-fold in MTS stock reagent (2 mg/mL in DPBS), and this MTS/PMS mixture is diluted 5-fold into each well of the 96-well plate. The plates are incubated for 3-4 h, and the absorbance of formazan is measured at 490 nm. The data are normalized to the untreated controls, the dose-response curves are fit to a four-parameter logistic equation, and the IC_{50} values are determined. All IC_{50} values reported are the geometric mean of at least two independent determinations[1].

Animal Administration: ARQ-092 is dissolved in 0.01 M phosphoric acid (vehicle) at a concentration of 20 mg/mL and filter sterilized [2].[2]Mice[2]

$SHP2^{Y279C/+}$ mice are used. Only male progeny are used for the experiments herein and all mice are maintained on outbred C57BL6/J backgrounds, backcrossed for more than 10 generations. Either vehicle or Miransertib (100 mg/kg body weight) is then daily administered by oral gavage for 4 weeks. Administration began at 12 weeks of age (after established hypertrophy is indicated), and continued for 4 weeks, until the mice reach 16 weeks of age. As controls, $SHP2^{+/+}$ and $SHP2^{Y279C/+}$ mice are treated with vehicle alone.

References:

[1]. Lapierre JM, et al. Discovery of 3-(3-(4-(1-Aminocyclobutyl)phenyl)-5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl)pyridin-2-amine (ARQ 092): An Orally Bioavailable, Selective, and Potent Allosteric AKT Inhibitor. J Med Chem. 2016 Jul 14;59(13):6455-69.

[2]. Wang J, et al. In vivo efficacy of the AKT inhibitor ARQ 092 in Noonan Syndrome with multiple lentigines-associated hypertrophic cardiomyopathy. PLoS One. 2017 Jun 5;12(6):e0178905.

CAIndexNames:

2-Pyridinamine, 3-[3-[4-(1-aminocyclobutyl)phenyl]-5-phenyl-3H-imidazo[4,5-b]pyridin-2-yl]-

SMILES:

NC1=NC=CC=C1C2=NC3=CC=C(C4=CC=CC=C4)N=C3N2C5=CC=C(C6(N)CCC6)C=C5

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