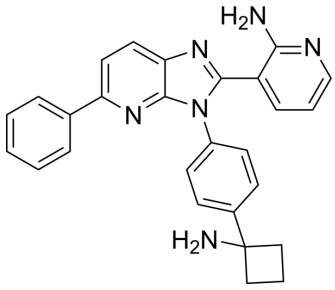
Miransertib

Cat. No.:	HY-19719
CAS No.:	1313881-70-7
Molecular Formula:	$C_{27}H_{24}N_6$
Molecular Weight:	432.52
Target:	Akt; Parasite
Pathway:	PI3K/Akt/mTOR; Anti-infection
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 1 year -20°C 6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 12.5 mg/mL (28.90 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3120 mL	11.5602 mL	23.1203 mL
	5 mM	0.4624 mL	2.3120 mL	4.6241 mL
	10 mM	0.2312 mL	1.1560 mL	2.3120 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: ≥ 1.25 mg/mL (2.89 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Miransertib (ARQ-092) is a potent, orally active, selective and allosteric Akt inhibitor with IC_{50}s of 2.7 nM, 14 nM and 8.1 nM for Akt1, Akt2, Akt3, respectively. Miransertib is also a potent the AKT1-E17K mutant protein inhibitor and has the potential for PI3K/AKT-driven tumors and Proteus syndrome research[1]. Miransertib is effective against ***Leishmania***[2].

IC_{50} & Target

Akt1 2.7 nM (IC_{50})	Leishmania	Akt3 8.1 nM (IC_{50})	Akt2 14 nM (IC_{50})
Akt1 E17K mutant			

In Vitro

In a large panel of cell lines derived from various tumor types, Miransertib (ARQ-092; Compound 21a) 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]. Miransertib is markedly effective against intracellular amastigotes of L. donovani or L. amazonensis-infected macrophages. Miransertib also enhances mTOR dependent autophagy in Leishmania-infected macrophages[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Miransertib (ARQ-092; Compound 21a) shows good absolute oral bioavailability in rats (5 mg/kg) and monkeys (10 mg/kg) with F values of 62% and 49%, respectively. The half-life is longer in rats compared to monkeys with $t_{1/2}$ values of 17 h in rats versus 7 h in monkeys. The C_{max} is 198 ng/mL and 258 ng/mL and the AUC_{inf} was 5496 h ng/mL and 2960 h ng/mL in rats and monkeys, respectively[1]. Miransertib (ARQ-092; Compound 21a) inhibits tumor growth in a human xenograft mouse model of endometrial adenocarcinoma[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [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. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Nat Commun. 2023 Sep 30;14(1):6117.
- Clin Pharmacol Ther. 2023 Jun 12.
- FASEB J. 2022 Aug;36(8):e22423.
- Biomedicines. 2022, 10(7), 1476.
- Hum Mol Genet. 2022 Aug 22;ddac201.

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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]. Devki Nandan, et al. Miransertib (ARQ 092), an orally-available, selective Akt inhibitor is effective against Leishmania. PLoS One. 2018 Nov 6;13(11):e0206920.

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