Vevorisertib trihydrochloride

Cat. No.: HY-137458A

CAS No.: 1416775-08-0

Molecular Formula: $C_{35}H_{41}Cl_3N_8O$

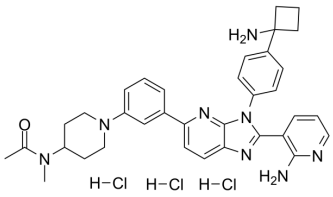
Molecular Weight: 696.11

Target: Akt

Pathway: PI3K/Akt/mTOR

Storage: 4°C, sealed storage, away from moisture

* In solvent : -80°C, 6 months; -20°C, 1 month (sealed storage, away from moisture)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 150 mg/mL (215.48 mM; Need ultrasonic)

H_2O : 25 mg/mL (35.91 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.4366 mL	7.1828 mL	14.3655 mL
5 mM	0.2873 mL	1.4366 mL	2.8731 mL
10 mM	0.1437 mL	0.7183 mL	1.4366 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: ≥ 5.25 mg/mL (7.54 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 5.25 mg/mL (7.54 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Vevorisertib (ARQ 751) trihydrochloride is a selective, allosteric, pan-AKT and AKT1-E17K mutant inhibitors. Vevorisertib trihydrochloride potently inhibit phosphorylation of AKT. Vevorisertib trihydrochloride has ***Kd*** values of 1.2 nM and 8.6 nM for AKT1 and AKT1-E17K, respectively. Vevorisertib trihydrochloride has IC_{50} values of 0.55, 0.81, and 1.3 nM for AKT1, AKT2, and AKT3, respectively. Vevorisertib trihydrochloride can be used for the research of cancer[1].

IC_{50} & Target

Akt1 0.55 nM (IC_{50})	Akt2 0.81 nM (IC_{50})	Akt3 1.31 nM (IC_{50})	Akt1 1.2 nM (Kd)
$Akt1^{E17K}$ 8.6 nM (Kd)			

In Vitro

Vevorisertib trihydrochloride (0, 12, 33, 111, 333, 1000 nM, 2 hours) inhibits phosphorylation of AKT1-E17K[1].
Vevorisertib trihydrochloride (1 μM for 2 hours; NIH 3T3 cells are transfected with either pcDNAAKT-WT-GFP or pcDNA-E17K-GFP) inhibits plasma membrane translocation of AKT-WT and AKT1-E17K irrespective of the presence of growth factors[1].
Vevorisertib trihydrochloride (5 μM) exhibites 57% inhibition of full-length AKT1[1].
Vevorisertib trihydrochloride (0, 0.012, 0.037, 0.11, 0.33, 1 μM; 2 hours) shows a dose-dependent effect on mTORC1 and AKT direct substrates including PRAS40, GSK3β, FOXO, BAD, and AS160 in cancer cell lines[1].
Vevorisertib trihydrochloride has anti-proliferative effect on esophageal, breast, and head and neck cancer cells (GI_{50} < 1 μM)[1].
Vevorisertib trihydrochloride exhibits strong anti-proliferative activity in PIK3CA mutant cell lines[1].
Vevorisertib trihydrochloride (MK-4440)/imatinib mesylate (IM) combination shows cell cycle arrest, and increases cell death of gastrointestinal stromal tumor (GIST) cells[2].
Vevorisertib trihydrochloride exhibits strong anti-proliferative activity in PIK3CA mutant cell lines[1]:

Breast Cancer Cell Lines	GI_{50} (nM)	PIK3CA	ER	PR
T47D	1.05	H1047R	+	+
EFM-19	1.54	H1047R	+	+
MCF-7	2.20	E545K	+	+
BT474	3.25	K111N	+	+
MDA-MB-453	6.05	H1047R	-	-

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

Western Blot Analysis[1]

Cell Line:	293T cells (transiently transfected with pcDNA-E17K-GFP)
Concentration:	0, 12, 33, 111, 333, 1000 nM
Incubation Time:	2 hours
Result:	Inhibited phosphorylation of AKT1-E17K.

Western Blot Analysis[1]

Cell Line:	Cancer cell lines: MDA-MB 453 (PIK3CAH1047R; Her2 amp), NCI-H1650 (PTEN null), KU-19-19 (AKT1-E17K&E49K; NRas Q61R)
Concentration:	0, 0.012, 0.037, 0.11, 0.33, 1 μM
Incubation Time:	2 hours
Result:	Showed a dose-dependent effect on mTORC1 and AKT direct substrates including PRAS40, GSK3β, FOXO, BAD, and AS160.

In Vivo

Vevorisertib trihydrochloride (25, 50 and 75 mg/kg; p.o.; 5 days dosing followed by a 4 day dosing holiday for 20 days) shows potent tumor growth inhibition of 68, 78 and 98%, respectively[1].
Vevorisertib trihydrochloride (5, 10, 20, 40, 80, and 120 mg/kg; p.o. daily for ten days) shows tumor growth inhibition of 29, 33, 50, 73, 83, and 92%, respectively[1].
Vevorisertib trihydrochloride reachs C_{max} plasma concentrations of ≥2 μM[1].
Vevorisertib trihydrochloride is generally well-tolerated at dose levels up to 120 mg/kg[1].

Vevorisertib trihydrochloride (MK-4440)/IM combination shows superior efficacy in an IM-sensitive preclinical model of GIST compared with either single agent[2].

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

Animal Model:	Endometrial PDX mouse xenograft models (AKT1-E17K mutation tumor fragments subcutaneously implanted in athymic nude mice; tumor volume of approximately 200 mm^3)[1]
Dosage:	25, 50 and 75 mg/kg
Administration:	p.o.; 5 days dosing followed by a 4 day dosing holiday for 20 days
Result:	Showed potent tumor growth inhibition of 68, 78 and 98%, respectively.

Animal Model:	AN3CA mouse xenograft models (female NCr nu/nu mice with 250 mm^3 tumors size)[1]
Dosage:	5, 10, 20, 40, 80, and 120 mg/kg
Administration:	p.o.; daily for ten days
Result:	Showed tumor growth inhibition of 29, 33, 50, 73, 83, and 92%, respectively.

REFERENCES

[1]. Yu Y, et al. Targeting AKT1-E17K and the PI3K/AKT Pathway with an Allosteric AKT Inhibitor, ARQ 092. PLoS One. 2015 Oct 15;10(10):e0140479.

[2]. Kozinova M, et al. Combined Inhibition of AKT and KIT Restores Expression of Programmed Cell Death 4 (PDCD4) in Gastrointestinal Stromal Tumor. Cancers (Basel). 2021 Jul 23;13(15):3699.

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