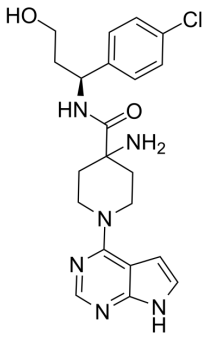
Capivasertib



Cat. No.:	HY-15431
CAS No.:	1143532-39-1
Molecular Formula:	$C_{21}H_{25}ClN_6O_2$
Molecular Weight:	428.92
Target:	Akt; Autophagy
Pathway:	PI3K/Akt/mTOR; Autophagy
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 : 125 mg/mL (291.43 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3314 mL	11.6572 mL	23.3144 mL
	5 mM	0.4663 mL	2.3314 mL	4.6629 mL
	10 mM	0.2331 mL	1.1657 mL	2.3314 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: ≥ 2.08 mg/mL (4.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.85 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Capivasertib (AZD5363) is an orally active and potent pan-AKT kinase inhibitor with IC_{50} of 3, 7 and 7 nM for Akt1,Akt2 and Akt3, respectively.

IC_{50} & Target

Akt1 3 nM (IC_{50})	Akt2 7 nM (IC_{50})	Akt3 7 nM (IC_{50})	P70S6K 6 nM (IC_{50})
PKA 7 nM (IC_{50})	ROCK2 60 nM (IC_{50})	ROCK1 470 nM (IC_{50})	Autophagy

In Vitro	Capivasertib, a novel pyrrolopyrimidine-derived compound, inhibits all AKT isoforms with a potency of 10 nM or less. Capivasertib inhibits phosphorylation of these substrates with an IC_{50} value of 0.06 to 0.76 μM in the 3 cell lines. Capivasertib effectively inhibits phosphorylation of S6 and 4E-BP1 in these cell lines, whereas it increases phosphorylation of AKT at both ser^{473} and thr^{308}. In BT474c cells, Capivasertib induces FOXO3a nuclear translocation with EC_{50} value of 0.69 μM; a concentration of 3 μM is sufficient to almost completely localize FOXO3a to the nucleus. AZD5363Capivasertibhibitor MK-2206 is much less active (IC_{50}>30 μM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Oral dosing of Capivasertib (AZD5363) to nude mice causes dose- and time-dependent reduction of PRAS40, GSK3β, and S6 phosphorylation in BT474c xenografts (PRAS40 phosphorylation EC_{50} ~0.1 μM total plasma exposure), reversible increases in blood glucose concentrations, and dose-dependent decreases in 2[^{18}F]fluoro-2-deoxy-D-glucose (^{18}F-FDG) uptake in U87-MG xenografts. Chronic oral dosing of Capivasertib caused dose-dependent growth inhibition of xenografts derived from various tumor types, including $HER2^+$ breast cancer models. Capivasertib also significantly enhances the antitumor activity of RP-56976 and GW572016 in breast cancer xenografts[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	Cell proliferation assay is determined by 2 methods, MTS and Sytox Green. Briefly, cells are seeded in 96-well plates (at a density to allow for logarithmic growth during the 72-hour assay) and incubated overnight at 37°C, 5% CO_2. Cells are then exposed to concentrations of Capivasertib ranging from 30 to 0.003 μM for 72 hours. For the MTS endpoint, cell proliferation is measured by the CellTiter AQueous Non-Radioactive Cell Proliferation Assay reagent. Absorbance is measured with a Tecan Ultra instrument. For the Sytox Green endpoint, Sytox Green nucleic acid dye diluted in TBS-EDTA buffer is added to cells (final concentration of 0.13 μM) and the number of dead cells detected using an Acumen Explorer. Cells are then permeabilized by the addition of saponin (0.03% final concentration, diluted in TBS-EDTA buffer), incubated overnight and a total cell count measured. Predose measurements are made for both MTS and Sytox Green endpoints, and concentration needed to reduce the growth of treated cells to half that of untreated cells (GI_{50}) values are determined using absorbance readings (MTS) or live cell counts[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Mice[1] Specific, pathogen-free, female nude mice (nu/nu: Alpk) and male SCID mice (SCID/CB17; 786-0 xenograft studies) are used. When mean tumor sizes reach approximately 0.2 cm3, the mice are randomized into control and treatment groups. The treatment groups received varying dose schedules of Capivasertib (AZD5363) solubilized in a 10% DMSO 25% w/v Kleptose HPB (Roquette) buffer by oral gavage, RP-56976 solubilized in 2.6% ethanol in injectable water by intravenous injection once on day 1 at 15 or 5 mg/kg once weekly. When administered in combination, RP-56976 is administered 1 hour before the oral dose of Capivasertib (AZD5363). The control group received the DMSO/Kleptose buffer alone, twice daily by oral gavage. Tumor volumes (measured by caliper), animal body weight, and tumor condition are recorded twice weekly for the duration of the study. Mice are sacrificed by CO2 euthanasia. The tumor volume is calculated (taking length to be the longest diameter across the tumor and width to be the corresponding perpendicular diameter) using the formula: (length×width)×√(length×width)×(π/6). Growth inhibition from the start of treatment is assessed by comparison of the differences in tumor volume between control and treated groups. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2018 Jul 18;10(450):eaaq1093.
- Nat Commun. 2021 Aug 25;12(1):5112.

- Nat Commun. 2020 Aug 13;11(1):4053.
- Autophagy. 2021 Jun;17(6):1349-1366.
- Engineering. 28 October 2022.

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REFERENCES

[1]. Davies BR, et al. Preclinical pharmacology of AZD5363, an inhibitor of AKT: pharmacodynamics, antitumor activity, and correlation of monotherapy activity with genetic background. Mol Cancer Ther. 2012 Apr;11(4):873-87.

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