Afuresertib

Cat. No.: HY-15727

CAS No.: 1047644-62-1

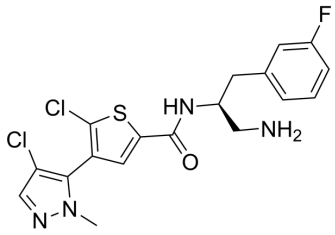
Molecular Formula: $C_{18}H_{17}Cl_2FN_4OS$

Molecular Weight: 427.32

Target: Akt; PKC; ROCK

Pathway: PI3K/Akt/mTOR; Epigenetics; TGF-beta/Smad; Cell Cycle/DNA Damage; Cytoskeleton; Stem Cell/Wnt

Storage: -20°C, protect from light, stored under nitrogen
* In solvent : -80°C, 6 months; -20°C, 1 month (protect from light, stored under nitrogen)



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (234.02 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3402 mL	11.7008 mL	23.4017 mL
	5 mM	0.4680 mL	2.3402 mL	4.6803 mL
	10 mM	0.2340 mL	1.1701 mL	2.3402 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: ≥ 2.5 mg/mL (5.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (5.85 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (5.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Afuresertib (GSK2110183) is an orally bioavailable, selective, ATP-competitive and potent pan-Akt kinase inhibitor with K_is of 0.08/2/2.6 nM for Akt1/Akt2/Akt3, respectively[1][2].

IC_{50} & Target

Akt2 2 nM (Ki)	Akt3 2.6 nM (Ki)	Akt1 E17K mutant 0.2 nM (IC_{50})	PKCη 210 nM (IC_{50})
PKC-βI 430 nM (IC_{50})	PKCθ 510 nM (IC_{50})	ROCK 100 nM (IC_{50})	

In Vitro	Afuresertib (GSK2110183) exhibits favorable tumor-suppressive effects on malignant pleural mesothelioma (MPM) cells. Afuresertib significantly increases caspase-3 and caspase-7 activities and apoptotic cell number among ACC-MESO-4 and MSTO-211H cells. Afuresertib strongly arrests the cell cycle in the G_1 phase. Western blotting analysis shows that Afuresertib increases the expression of $p21^{WAF1/CIP1}$ and decreases the phosphorylation of Akt substrates, including GSK-3β and FOXO family proteins. Afuresertib-induced p21 expression promotes G_1 phase arrest by inducing FOXO activity. Afuresertib significantly enhances cisplatin-induced cytotoxicity. Afuresertib modulates the expression E2F1 and MYC, which are associated with fibroblast core serum response[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Mice bearing BT474 breast tumor xenografts are dosed orally with either vehicle or GSK2110183 at 10, 30 or 100 mg/kg daily for 21 days which result in 8, 37 and 61% TGI, respectively. Mice tolerated GSK2110183 well, with 1-3% body weight loss reported after 5 days of dosing which recover over the course of the study. Other tumor xenograft models which possess an activation of the Akt pathway are explored to further demonstrate compound efficacy. Mice treated with GSK2110183 at 10, 30 and 100 mg/kg result in 23, 37 and 97% TGI, respectively, of SKOV3 xenografts[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	MPM cells are seeded in 96-well plates (cell density, 2.5×10^3 cells/well) and are incubated for 24 h at 37°C. Next, the cells are incubated in a medium containing indicated concentrations of Akt inhibitors (e.g., Afuresertib ; 50, 20, 10, 5, 2, 1, 0.5, 0.2, 0.1, and 0.01 μM) for 72 h. Next, MTT solution is added to each well, and the cells are incubated for 4 h. Finally, the cells are incubated overnight with lysis buffer (10% SDS in 0.01 mol/L hydrogen chloride). Absorbance is measured at 550 nm using SpectraMAX M5 spectrophotometer[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Sci Transl Med. 2021 Jan 27;13(578):eaba7308.
- Theranostics. 2019 Jan 30;9(4):1096-1114.
- Cell Syst. 2018 Apr 25;6(4):424-443.e7.
- Genes Dis. 2021 Aug 17;9(2):562-575.
- Int J Cancer. 2020 Apr 1;146(7):1963-1978.

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REFERENCES

[1]. Yamaji M, et al. Novel ATP-competitive Akt inhibitor Afuresertib suppresses the proliferation of malignant pleural mesothelioma cells. Cancer Med. 2017 Nov;6(11):2646-2659.

[2]. Dumble M, et al. Discovery of novel AKT inhibitors with enhanced anti-tumor effects in combination with the MEK inhibitor. PLoS One. 2014 Jun 30;9(6):e100880

Caution: Product has not been fully validated for medical applications. For research use only.

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