Pifusertib hydrochloride

Cat. No.: HY-19934A

CAS No.: 2930090-28-9

Molecular Formula: $C_{26}H_{25}ClN_4O_2$

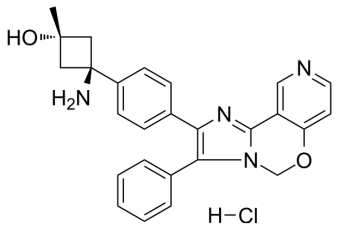
Molecular Weight: 460.96

Target: Akt; Apoptosis; Autophagy

Pathway: PI3K/Akt/mTOR; Apoptosis; Autophagy

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 : 62.5 mg/mL (135.59 mM; ultrasonic and warming and heat to 60°C)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.1694 mL	10.8469 mL	21.6939 mL
	5 mM	0.4339 mL	2.1694 mL	4.3388 mL
	10 mM	0.2169 mL	1.0847 mL	2.1694 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 (4.51 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.08 mg/mL (4.51 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (4.51 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Pifusertib (TAS-117) hydrochloride is a potent, selective, orally active allosteric Akt inhibitor (with IC_{50}s of 4.8, 1.6, and 44 nM for Akt1, 2, and 3, respectively). Pifusertib hydrochloride triggers anti-myeloma activities and enhances fatal endoplasmic reticulum (ER) stress induced by proteasome inhibition. Pifusertib hydrochloride induces apoptosis and autophagy[1].

IC_{50} & Target			
	Akt1	Akt2	Akt3
	4.8 nM (IC_{50})	1.6 nM (IC_{50})	44 nM (IC_{50})

In Vitro

Pifusertib (1 μM; 6 hours) blocks basal phosphorylation of Akt and downstream p-FKHR/FKHRL1 in MM cells with high baseline p-Akt[1].

Pifusertib (0-10 μM; 72 hours) selectively inhibits Akt and induces cytotoxicity in MM cells with high baseline phosphorylation of Akt[1].

Pifusertib abrogates the cytoprotective effect of the bone marrow microenvironment associated with Akt inhibition in both MM cells and BMSCs. Pifusertib enhances Carfilzomib-induced cytotoxicity and fatal ER stress in MM cells. Pifusertib (0.5, 1 μM) triggers G0/G1 arrest followed by apoptosis, associated with induction of autophagy and endoplasmic reticulum stress response[1].

Pifusertib enhances bortezomib-induced cytotoxicity, associated with increased CHOP (a fatal ER-stress marker) and PARP cleavage and blockade of bortezomib-induced p-Akt, suggesting that Pifusertib augments Bortezomib-induced ER stress and apoptotic signaling[1].

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

Cell Viability Assay[1]

Cell Line:	MM cell lines
Concentration:	0-10 μM
Incubation Time:	72 hours
Result:	Induced significant growth inhibition in MM cell lines with high baseline p-Akt, but not in cell lines with low baseline p-Akt.

Western Blot Analysis[1]

Cell Line:	MM.1S, MM.1R, H929, and KMS11 cells
Concentration:	1 μM
Incubation Time:	6 hours
Result:	Blocked basal phosphorylation of Akt and downstream p-FKHR/FKHRL1 in MM cells with high baseline p-Akt, but did not inhibit autophosphorylation of PDK1 which phosphorylates Akt at Thr308.

In Vivo

Pifusertib (12-16 mg/kg; p.o.; daily for 5 days a week, 21 days) inhibits tumor growth in murine xenograft models of human MM[1].

Pifusertib enhances bortezomib-induced MM cytotoxicity in vivo[1].

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

Animal Model:	SCID mice (xenograft models bearing MM.1S cells)[1]
Dosage:	12, 16 mg/kg
Administration:	P.o.; daily for 5 days a week, 21 days
Result:	Significantly reduced MM.1S tumor growth versus vehicle control.

REFERENCES

[1]. Mimura N, et al. Selective and potent Akt inhibition triggers anti-myeloma activities and enhances fatal endoplasmic reticulum stress induced by proteasome inhibition. Cancer Res. 2014;74(16):4458-4469.

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

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