Pifusertib

Cat. No.: HY-19934

CAS No.: 1402602-94-1

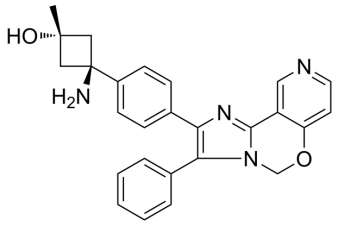
Molecular Formula: $C_{26}H_{24}N_4O_2$

Molecular Weight: 424.49

Target: Akt; Apoptosis; Autophagy

Pathway: PI3K/Akt/mTOR; Apoptosis; Autophagy

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description

Pifusertib (TAS-117) 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 triggers anti-myeloma activities and enhances fatal endoplasmic reticulum (ER) stress induced by proteasome inhibition. Pifusertib 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 cell lines

Concentration:	0-10 μM
Incubation Time:	72 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.

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