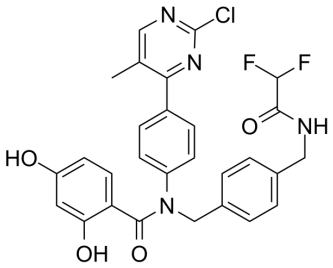
VER-246608

Cat. No.:	HY-12492
CAS No.:	1684386-71-7
Molecular Formula:	$C_{28}H_{23}ClF_2N_4O_4$
Molecular Weight:	553
Target:	PDHK
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (180.83 mM; Need ultrasonic)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	1.8083 mL	9.0416 mL	18.0832 mL
5 mM	0.3617 mL	1.8083 mL	3.6166 mL
10 mM	0.1808 mL	0.9042 mL	1.8083 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 (4.52 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (4.52 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

VER-246608 is a potent and ATP-competitive inhibitor of pyruvate dehydrogenase kinase (PDK) with IC_{50}s of 35 nM, 40 nM, 84 nM, and 91 nM for PDK-1, PDK-3, PDK-2, and PDK-4, respectively.

IC_{50} & Target

IC50: 35 nM (PDK-1), 40 nM (PDK-3), 84 nM (PDK-2), 91 nM (PDK-4)[1]

In Vitro

VER-246608 is a novel pan-isoform ATP competitive inhibitor of PDK. VER-246608 demonstrates similar potency across all four PDK isoforms in a DELFIA-based enzyme functional assay in the sub 100 nM range. In terms of cellular biomarker modulation, VER-246608 suppresses the phosphorylation of the Ser^{293} residue of E1α (phosphorylated by all four PDK isozymes) with IC_{50} values of 266 nM. Treatment of PC-3 cells with 9 μM and 27 μM VER-246608 results in a 21% and 42% reduction, respectively, in media L-lactate levels following a 1 h incubation. VER-246608 also decreases D-glucose

consumption at the same concentrations that result in reduced L-lactate production. An approximately 50% reduction in spheroid volume is achieved at concentrations of 10 μM and above, suggesting an increase in VER-246608 potency compared to monolayer growth[1].

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

PROTOCOL

Kinase Assay [1]

DELFIA assay reagents (assay buffer, wash buffer, enhancement solution and anti-rabbit IgG-Eu-N1 secondary antibody) and plates are used. Test compounds are subjected to a 10 point tripling dilution in DMSO, diluted in MOPS buffer (60 mM MOPS pH7.2, 15 mM Magnesium acetate, 60 mM KCl) and added to the enzyme mix (10 nM PDK-1, 2 and 3 or 20 nM PDK-4, 300 nM E1, 0.1 mg/mL BSA, 1 mM DTT) in 96-well V-bottom plates. The reaction is initiated by the addition of ATP to a final concentration of 5 μM followed by a 1 h incubation at 30°C. The reaction is then stopped by the addition of STOP solution (50 mM Carbonate-Bicarbonate Buffer, pH 9.6), and then transferred to 96 well DEFLIA yellow plates. The plates are then sealed and incubated o/n at 4°C. Detection and quantification of p(Ser^{293})E1α levels is then achieved through incubation with anti-p(Ser^{293})E1α primary antibody followed by anti-rabbit secondary IgG-Eu-N1 antibody and addition of enhancement solution. The time-resolved fluorescent signal is then measured using a Victor2 plate reader. The data is fitted by non-linear regression using XLFIT4 within a custom ABASE (IDBS) protocol in order to determine IC_{50} values[1].

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Cell Assay [1]

Compound cytotoxicity is determined using the Sulforhodamine B assay for cells cultured as a monolayer. For spheroid growth experiments, PC-3 cells are seeded (500 cells/well) into 96 well round bottom plates in RPMI-1640 media containing 2.5% (w/v) Matrigel. The resultant spheroids are treated with VER-246608 (2.5, 5, 10, 20, and 40 μM) 48 h post-seeding. Spheroid volumes are determined by obtaining diameter measurements from images taken on a Zeiss Axiovert 200 M inverted microscope using the axiovision software[1].

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

REFERENCES

[1]. Moore JD, et al. VER-246608, a novel pan-isoform ATP competitive inhibitor of pyruvate dehydrogenase kinase, disrupts Warburg metabolism and induces context-dependent cytostasis in cancer cells. Oncotarget. 2014 Dec 30;5(24):12862-76.

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