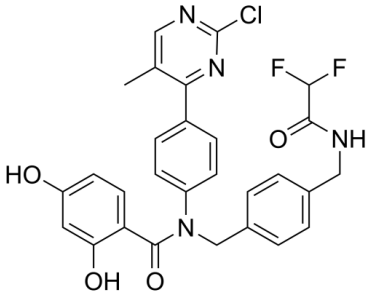
Data Sheet

Product Name:	VER-246608
Cat. No.:	CS-0011787
CAS No.:	1684386-71-7
Molecular Formula:	$C_{28}H_{23}ClF_2N_4O_4$
Molecular Weight:	552.96
Target:	PDHK
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : 100 mg/mL (ultrasonic)



BIOLOGICAL ACTIVITY:

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. IC50 & 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].

PROTOCOL (Extracted from published papers and Only for reference)

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].

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].

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.

CAIndexNames:

Benzamide, N-[4-(2-chloro-5-methyl-4-pyrimidinyl)phenyl]-N-[[4-[[(2,2-difluoroacetyl)amino]methyl]phenyl]methyl]-2,4-dihydroxy-

SMILES:

O=C(C1=CC=C(O)C=C1O)N(CC2=CC=C(CNC(C(F)F)=O)C=C2)C(C=C3)=CC=C3C4=NC(Cl)=NC=C4C

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