

Product Data Sheet

Product Name: PDK1 inhibitor

Cat. No.: GC12866

Chemical Properties

Cas. No. 1001409-50-2

Chemical Name 1-[(3,4-difluorophenyl)methyl]-2-oxo-N-[(1R)-2-[(2-oxo-1,3-dihydrobenzimidazol-5-yl)oxy]-1-phenylethyl]pyridine-3-carboxamide

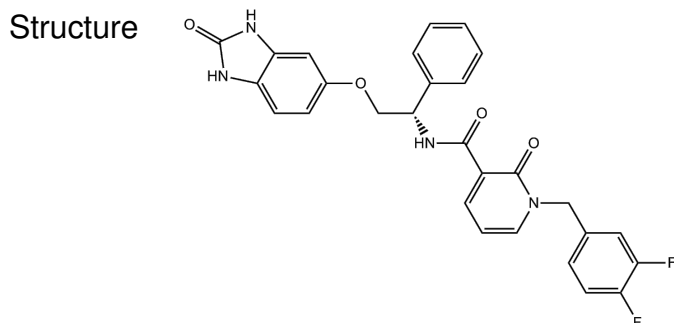
SMILES C1=CC=C(C=C1)C(COC2=CC3=C(C=C2)NC(=O)N3)NC(=O)C4=CC=CN(C4=O)CC5=CC(=C(C=C5)F)F

Formula $C_{28}H_{22}F_2N_4O_4$ M.Wt 516.5

Solubility Soluble in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution: ship with blue ice All other available size: ship with RT, or blue ice upon request.



Protocol

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

Cell experiment: The human GBM cells (i.e., U87MG, U343MG, or ANGM-CSS) or the respective GSCs are seeded and incubated for the indicated times with the indicated concentrations of SA16 (1 nM to 100 μ M), MP7 (2.5 nM, 25 nM, 250 nM and 2.5 μ M), or Alisertib. When indicated, cells are treated with MP7 and Alisertib in combination. To verify GSC chemoresistance, U87MG or GSCs are incubated with 50 μ M TMZ for 72 h. For the long-term treatment of cells, NSC or complete medium containing drugs is replaced every 3 days. Cell proliferation is determined using the MTS assay: the dehydrogenase activity in active mitochondria reduces MTS to the soluble formazan product, whose absorbance at 490 nm is measured with an automated plate reader. The mean background from each test condition is subtracted, and the data are expressed as the percentage of untreated cells (control). IC₅₀ values are derived from the sigmoid dose-response curve. The percentage of inhibition is calculated as 100% minus the percentage of cell proliferation[1].

References:

[1]. Daniele S, et al. Dual Inhibition of PDK1 and Aurora Kinase A: An Effective Strategy to Induce Differentiation and Apoptosis of Human Glioblastoma Multiforme Stem Cells. ACS Chem Neurosci. 2017 Jan 18;8(1):100-114.

Background

PDK1 inhibitor is an potent and selective inhibitor of PDK1 with potential as anticancer agent. GSK 2334470, a inhibitor of PDK1, has IC₅₀ value of 0.00251 μ M and CHEMBL1172241 with IC₅₀ value of 0.085 μ M. [1]

PDPK1 stands for 3-phosphoinositide-dependent protein kinase 1, which is crucial for the activation of AKT/PKB and many other AGC kinases including PKC, S6K, SGK. [2]An important role for PDPK1 is in the signalling pathways activated by several growth factors and hormones including insulin signaling. PDPK1 functions downstream of PI3K through PDPK1's interaction with membrane phospholipids.[3]PI3K indirectly regulates PDPK1 by phosphorylating phosphatidylinositols which in turn generates phosphatidylinositol (3,4)-bisphosphate and phosphatidylinositol (3,4,5)-trisphosphate. [4]However, PDPK1 is believed to be constitutively active and does not always require

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA

Product Data Sheet

phosphatidylinositols for its activities. Phosphatidylinositols are only required for the activation at the membrane of some substrates including AKT. PDK1 however does not require membrane lipid binding for the efficient phosphorylation of most of its substrates in the cytosol. PDK1 is implicated in the development and progression of melanomas.[5] Many cancer-driving mutations induce activation of PDK1 targets including Akt, S6K (p70 ribosomal S6 kinase) and SGK (serum- and glucocorticoid-induced protein kinase).

GSK2334470 is more effective at inhibiting PDK1 substrates that are activated in the cytosol rather than at the plasma membrane. Consistent with this, GSK2334470 inhibited Akt activation in knock-in embryonic stem cells expressing a mutant of PDK1 that is unable to interact with phosphoinositides more potently than in wild-type cells by Immunoblotting.[6] GSK2334470 also suppressed T-loop phosphorylation and activation of RSK2 (p90 ribosomal S6 kinase 2), another PDK1 target activated by the ERK (extracellular-signal-regulated kinase) pathway.[7] GSK2334470 will be useful in probing biological processes controlled by PDK1. Therefore, GSK2334470 is much more specific than other reported PDK1 inhibitors.

Reference:

1. Murphy ST. et al. *Discovery of novel, potent, and selective inhibitors of 3-phosphoinositide-dependent kinase (PDK1)*. *J Med Chem*. 2011, 54(24):8490-500.
2. Mora A, Komander D, van Aalten DM, Alessi DR. "PDK1, the master regulator of AGC kinase signal transduction". *Semin. Cell Dev. Biol.* 2004, 15 (2): 161-70.
3. Vanhaesebroeck B, Alessi DR. "The PI3K-PDK1 connection: more than just a road to PKB". *Biochem. J.* 2000, 346 (3): 561-76.
4. Frödin M, Antal TL. Et al. "A phosphoserine/threonine-binding pocket in AGC kinases and PDK1 mediates activation by hydrophobic motif phosphorylation". *EMBO J.* 2002, 21 (20): 5396-407.
5. Scortegagna, M. et al. "Genetic inactivation or pharmacological inhibition of Pdk1 delays development and inhibits metastasis of BrafV600E::Pten^{-/-} melanoma". *Oncogene*. 2013.
6. Ayaz NAJAFOV. *Characterization of GSK2334470, a novel and highly specific inhibitor of PDK1*. *Biochem. J.* (2011) 433, 357-369.
7. Tamguney, T. et al. *Analysis of 3-phosphoinositide-dependent kinase-1 signaling and function in ES cells*. *Cell*, 2008, 314, 2299–2312.

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

Tel: (909) 407-4943 Fax: (626) 353-8530 E-mail: tech@glpbio.com

Address: 10292 Central Ave. #205, Montclair, CA, USA