Product Data Sheet

Product Name: GDC-0084
Cat. No.: GC10228

Chemical Properties

Cas. No.	1382979-44-3		
Chemical Name	5-(6,6-dimethyl-4-morpholino-8,9-dihydro-6H-[1,4]oxazino[4,3-e]purin-2-yl)pyrimidin-2-amine		
SMILES	NC1=NC=C(C2=NC(N3CCOCC3)=C4N=C5C(C)(C)OCCN5C4=N2)C=N1		
Formula	$C_{18}H_{22}N_8O_2$	M.Wt	382.42
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ for several months.		
Shipping Condition	Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.		
Structure	GDC-0084		

Protocol

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Kinase experiment:

Enzymatic activity of PI3Kα is measured using a fluorescence polarization assay that monitors formation of the product 3,4,5-inositoltriphosphate molecule (PIP3) as it competes with fluorescently labeled PIP3 for binding to the GRP-1 pleckstrin homology domain protein. An increase in phosphatidyl inositide-3-phosphate product results in a decrease in fluorescence polarization signal as the labeled fluorophore is displaced from the GRP-1 protein binding site. PI3Kα is expressed and purified as heterodimeric recombinant protein. PI3Kα is assayed under initial rate conditions in the presence of 10 mM Tris (pH 7.5), 25 uM ATP, 9.75 uM PIP2, 5% glycerol, 4 mM MgCl2, 50 mM NaCl, 0.05% (v/v) Chaps, 1 mM dithiothreitol, 2% (v/v) DMSO at a 60 ng/mL concentration of PI3Kα. After assay for 30 min at 25°C, reactions are terminated with a final concentration of 9 mM EDTA, 4.5 nM TAMRA-PIP3, and 4.2 ug/mL GRP-1 detector protein before reading fluorescence polarization on an Envision plate reader. IC50s are calculated from the fit of the dose-response curves to a 4-parameter equation. Apparent Kis, where measured, are determined at a fixed concentration of ATP near the measured Km for ATP for PI3Kα, and are calculated by fitting of the dose-response curves to an equation for tightbinding competitive inhibition[1].

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Animal experiment: Mice[1] PTEN-null U-87 MG/M human glioblastoma cancer cells are cultured in RPMI 1640 media plus 1% L-glutamine with 10% fetal bovine serum. Cells in log-phase growth are harvested and resuspended in HBSS:Matrigel (1:1, v:v) for injection into female NCr nude mice aged 20 weeks. Animals receive five million cells subcutaneously in the right lateral thorax in 0.1 mL. Mice bearing established tumors in the range of 200-500 mm3 are separated into groups of equally sized tumors (n=6-7/group) to receive escalating doses of GDC-0084 (Compound 16). GDC-0084 is formulated once weekly in 0.5% methylcellulose and 0.2% Tween-80 at concentrations needed for target doses in a volume of 0.2 mL. All formulations are stored in a refrigerator and brought to room temperature and mixed well by vortex before oral administration by gavage once daily for 23 days. Tumor volumes are calculated. Changes in body weights are reported as a percentage change from the starting weight.

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References:

[1]. Heffron TP, et al. Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.

Background

GDC-0084 is a potent and brain penetrant inhibitor of PI3K and mTOR with Ki values of 2 nM and 70 nM for PI3Kα and mTOR, respectively [1].

Glioblastoma (GBM) is the most common primary brain tumor in adults and aberrant PI3K signaling is associated with more than 80% of cases. The PI3K pathway represents a potential target for the treatment of this disease and the inhibitors would need to freely cross the blood-brain barrier (BBB) [1][2].

GDC-0084 is a potent and brain penetrant inhibitor of PI3K and mTOR. In vitro kinase assay, GDC-0084 exhibited Ki values of 2 nM, 46 nM, 3 nM, 10 nM and 70 nM for PI3Kα, PI3Kβ, PI3Kδ, PI3Kγ and mTOR, respectively. In five different GBM cell lines, GDC-0084 had antiproliferative activities with EC50 values ranging from 0.3 to 1.1 μM. GDC-0084 has excellent human metabolic stability in microsomal and hepatocyte incubations [1].

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In transfected cell lines over-expressing human or mouse P-gp or BCRP, GDC-0084 was a poor substrate of these efflux transporters. In mice brain, GDC-0084 significantly lowered pAkt and pS6 levels [2].

In rats after a 15 mg/kg dose of GDC-0084, the total brain-to-plasma ratio was 1.9-3.3. In subcutaneous U87 glioblastoma tumor xenograft mice model, GDC-0084 significantly inhibited tumor growth in a dose-dependent way. GDC-0084 also concentration-dependently inhibited pAKT [1].

References:

[1]. Heffron TP1, Ndubaku CO1, Salphati L1, et al. Discovery of Clinical Development Candidate GDC-0084, a Brain Penetrant Inhibitor of PI3K and mTOR. ACS Med Chem Lett. 2016 Feb 16;7(4):351-6.

[2]. Salphati L, Alicke B, Heffron TP, et al. Brain Distribution and Efficacy of the Brain Penetrant PI3K Inhibitor GDC-0084 in Orthotopic Mouse Models of Human Glioblastoma. Drug Metab Dispos. 2016 Dec;44(12):1881-1889. Epub 2016 Sep 16.

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