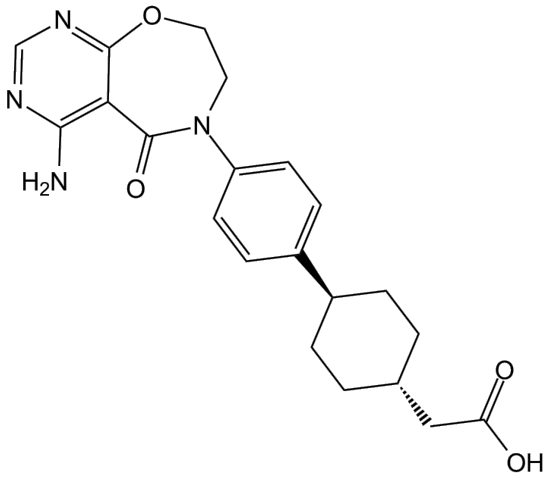
Product Data Sheet

Product Name: PF-04620110

Cat. No.: GC15274

Chemical Properties

Cas No.	1109276-89-2		
化学名	2-[4-[4-(4-amino-5-oxo-7,8-dihydropyrimido[5,4-f][1,4]oxazepin-6-yl)phenyl]cyclohexyl]acetic acid		
Canonical SMILES	C1CC(CCC1CC(=O)O)C2=CC=C(C=C2)N3CCOC4=NC=NC(=C4C3=O)N		
分子式	$C_{21}H_{24}N_4O_4$	分子量	396.44
溶解度	≥ 16.9mg/mL in DMSO	储存条件	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			

Protocol

Kinase experiment [1]:

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In Vitro Assay for DGAT-1 Enzyme Inhibition:	Human full-length diacylglycerol:acylCoA acyltransferase 1 (DGAT-1) was expressed in Sf9 insect cells which are then lysed and a crude membrane fraction (105, 000 x g pellet) was prepared. DGAT-1 activity was measured in 384-well format in a total assay volume of 25 µl that contained, Hepes buffer (50 mM, pH7.5), MgCl2 (10 mM), bovine serum albumin (0.6 mg/ml), [14C]decanoylCoA (20 µM, 58 Ci/mol) and membranes (25 µg/ml) into which 1,2 dioleoyl-sn-glycerol (75 µM) in acetone has already been incorporated. Inhibitors in DMSO were pre-incubated with membranes before initiating the DGAT-1 reaction by the addition of decanoylCoA.The reactions were allowed to proceed for 1.5 h at room temperature and then terminated by the addition of 10 µl of HCl (0.5 M). Reaction mixtures were neutralized by the addition of 15 µl of tris(hydroxy-methyl)aminomethane (1M, pH 8.0) and then mixed by trituration with 37.5 µl of Microscint-E . Plates contents were allowed to partition for 15 to 30 min before 14C was measured in a scintillation spectrometer. Percent inhibition of test compounds was computed as 100-(DPM DMSO uninhibited- DPM test compound)/(DPM DMSO uninhibited).
Cell experiment [1]:	
Cell lines	Human intestinal epithelial cells
Preparation method	Soluble in DMSO > 10 mM. General tips for obtaining a higher concentration: Please warm the tube at 37 ℃ for 10 minutes and/or shake it in the ultrasonic bath for a while. Stock solution can be stored below -20℃ for several months.
Reaction Conditions	5 hours at 37oC
Applications	PF-04620110 (IC50 39 nM) inhibits the incorporation of 3H-glycerol into TG.
Animal experiment [2]:	
Animal models	C57BL/6J and B6.129S4-Dgat1tm1Far (DGAT1 knockout mice) male mice (7–12 wk of age)
Dosage form	Oral dose of 1, 0.3, 0.1, and 0.01 mg/kg (TG/retinyl palmitate tolerance test)
Applications	Administration of a single dose of a DGAT1 inhibitor, PF-04620110, reduces postprandial plasma TG and retinyl palmitate excursions in mice.
Other notes	Please test the solubility of all compounds indoor, and the actual solubility may slightly differ with the theoretical value. This is caused by an experimental system error and it is normal.

References:
1. Dow RL, Li JC, Pence MP, Gibbs EM, LaPerle JL, Litchfield J, Piotrowski DW, Munchhof MJ, Manion TB, Zavadoski WJ, Walker GS, McPherson RK, Tapley S, Sugarman E, Guzman-Perez A, DaSilva-Jardine P. Discovery of PF-04620110, a Potent, Selective, and Orally Bioavailable Inhibitor of DGAT-1. ACS Med Chem Lett. 2011 Mar 18;2(5):407-12.
2. Maciejewski BS, LaPerle JL, Chen D, Ghosh A, Zavadoski WJ, McDonald TS, Manion TB, Mather D, Patterson TA, Hanna M, Watkins S, Gibbs EM, Calle RA, Steppan CM. Pharmacological inhibition to examine the role of DGAT1 in dietary lipid absorption in rodents and humans. Am J Physiol Gastrointest Liver Physiol. 2013 Jun 1;304(11):G958-69.

Background

PF-04620110 is a potent, selective and orally-bioavailable inhibitor of diacylglycerol acyltransferase 1 (DGAT-1), an enzyme catalyzing the final committed step in the biosynthesis of triglycerides, that inhibits DGAT-1 with values of 50% inhibition concentration IC_{50} of 19 nM and 8 nM in human and HT-29 cells respectively. PF-04620110 displays a highly selective, more than 100 fold, inhibition against DGAT-1 rather than a range of lipid processing enzymes, including human DGAT-2, human acyl-CoA:cholesterol acyltransferase 1, human acyl-CoA:wax alcohol acyltransferase 1, human acyl-CoA:wax alcohol acyltransferase 2, human acyl-CoA:monacylglycerol acyltransferase 2, human acyl-CoA:monacylglycerol acyltransferase 3 and mouse MGAT 1.

Reference

Lee KR, Choi SH, Song JS, Seo H, Chae YJ, Cho HE, Ahn JH, Ahn SH, Bae MA. Determination of PF-04620110, a novel inhibitor of diacylglycerol acyltransferase-1, in rat plasma using liquid chromatography-tandem mass spectrometry and its application in pharmacokinetic studies. Biomed Chromatogr. 2013; 27(7):846-852.

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