Product Data Sheet

Product Name: PF-04991532
Cat. No.: GC31514

Chemical Properties

Cas. No.	1215197-37-7		
SMILES	O=C(C1=CC=C(NC([C@@H](N2C=C(C(F)(F)F)N=C2)CC3CCCC3)=O)N=C1)O		
Formula	$C_{18}H_{19}F_3N_4O_3$	M.Wt	396.36
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	PF-04991532		

Protocol

Cell experiment:

Primary rat hepatocytes are used to determine the expression of G6Pase. 50,000 freshly isolated rat hepatocytes are incubated in Williams E media overnight supplemented with 100 nM dexamethasone, 1×ITS, and 1×PenStrep. The following morning the media is aspirated, and changed to DMEM no glucose media supplemented with either 5 mM glucose, 25 mM glucose, 1 μM insulin, 100 nM glucagon, or 10 μM PF-04991532. Following 2 hours the media is aspirated, washed twice, and 100 μL of RLT is added to the cells. RNA is extracted with a RNeasy kit[1].

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Animal experiment:

13 week old male Goto Kakizaki rats with in-dwelling carotid artery and jugular vein catheters are used in this study. Surgeries are performed one day before shipping. Upon arrival, animals are individually housed, allowed ad libitum chow, and acclimated to their new environment for 6 to 7 days. Animals are randomly assigned either a 100 mg/kg PF-04991532 treatment or vehicle control treatment and orally gavaged at 5 mL/kg. On the day of the experiment, 0.5% Methyl cellulose vehicle is used in vehicle-treated rats. Studies are performed in unstressed, awake, chronically catheterized rats using the insulin clamp technique, in combination with [3-3H] glucose. At the end of the in vivo studies, rats are euthanized[1].

References:

[1]. Erion DM, et al. The hepatoselective glucokinase activator PF-04991532 ameliorates hyperglycemia without causing hepatic steatosis in diabetic rats. PLoS One. 2014 May 23;9(5):e97139.

Background

PF-04991532 is a potent, hepatoselective glucokinase activator with EC50s of 80 and

100 nM in human and rat, respectively.

PF-04991532 is a potent, hepatoselective glucokinase activator with EC50s of 80 nM in human and 100 nM in rat and also a Phase 2 clinical candidate. Mechanistic experiments conducted in freshly isolated primary rat hepatocytes treated for 1 hour with PF-04991532 show increased 2-[14C]-deoxyglucose uptake (EC50 =1.261 μM) and increased glucose oxidation (EC50=5.769 μM). Additionally, PF-04991532 decreases the production of glucose from 1-[14C]-lactate in a dose dependent manner (EC50 =0.626 μM). In isolated rat hepatocytes, PF-04991532 increases the expression of G6Pase compare to cells treated only with 100 nM glucagon, and the greatest increase in G6Pase mRNA expression is in the presence of 25 mM glucose, 100 nM glucagon and PF-04991532[1].

A single dose of PF-04991532 increases the glucose infusion rate in order to maintain hyperglycemia. Despite the elevations in plasma triglycerides, surprisingly, hepatic triglycerides in rats dosed with 19 days of PF-04991532 are identical to vehicle treated GK rats. In an additional cohort treated for 28 days, identical hepatic lipid concentrations are observed between vehicle and rats dosed with PF-04991532 (Vehicle: 9.89±0.31; PF-04991532 100 mg/kg: 9.91±0.31). In rats treated with PF-04991532, there is increased expression of lipogenic gene expression such as acetyl-CoA carboxylase (ACC), ATP citrate lyase (ACLY), and fatty acid synthase (FAS)[1].

[1]. Erion DM, et al. The hepatoselective glucokinase activator PF-04991532 ameliorates hyperglycemia without causing hepatic steatosis in diabetic rats. PLoS One. 2014 May 23;9(5):e97139.