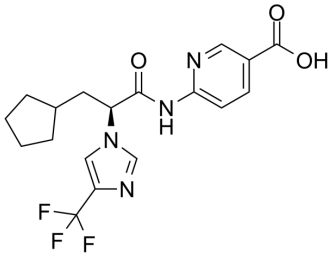
PF-04991532

Cat. No.:	HY-100181
CAS No.:	1215197-37-7
Molecular Formula:	$C_{18}H_{19}F_3N_4O_3$
Molecular Weight:	396.36
Target:	Glucokinase
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 125 mg/mL (315.37 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.5230 mL	12.6148 mL	25.2296 mL
	5 mM	0.5046 mL	2.5230 mL	5.0459 mL
	10 mM	0.2523 mL	1.2615 mL	2.5230 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

PF-04991532 is a potent, hepatoselective glucokinase activator with EC_{50}s of 80 and 100 nM in human and rat, respectively.

IC_{50} & Target

EC50: 80 nM (glucokinase in human), 100 nM (glucokinase in rat)[1]

In Vitro

PF-04991532 is a potent, hepatoselective glucokinase activator with EC_{50}s 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-[^{14}C]-deoxyglucose uptake (EC_{50} =1.261 μM) and increased glucose oxidation (EC_{50} =5.769 μM). Additionally, PF-04991532 decreases the production of glucose from 1-[^{14}C]-lactate in a dose dependent manner (EC_{50} =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].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	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-^{3}H] glucose. At the end of the in vivo studies, rats are euthanized[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

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.

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