

PF-06409577

Chemical Properties

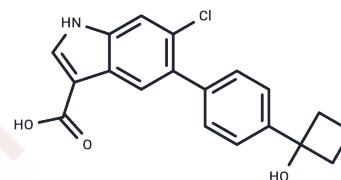
CAS No. : 1467057-23-3

Formula: C₁₉H₁₆ClNO₃

Molecular Weight: 341.79

Storage: Powder: -20°C for 3 years | In solvent: -80°C for 1 year

Actual storage temperature shall be subject to the COA.



Biological Description

Description	PF-06409577 is an effective, orally active, and specific allosteric activator of AMPK (EC ₅₀ : 7 nM, for $\alpha 1\beta 1\gamma 1$).
Targets(IC ₅₀)	AMPK
In vitro	In human and rat , PF-06409577 has similar effectiveness for $\alpha 1\beta 1\gamma 1$ isoforms. PF-06409577 exhibits minimal off-target effects on a panel of receptors, ion channels, PDEs, and kinases. PF-06409577 has no inhibition of hERG in a patch-clamp assay (100 μ M) and is not an inhibitor (IC ₅₀ >100 μ M) of the microsomal activities of major human cytochrome P450 isoforms[1].
In vivo	In rats, monkeys, and dogs, PF-06409577 has moderate plasma clearance and is well distributed with steady-state distribution volume. Following oral administration of crystalline PF-06409577 in 0.5% methylcellulose suspension, PF-06409577 is rapidly absorbed in dogs, rats, and monkeys. The corresponding oral bioavailability values in rats, monkeys, and dogs are 15%, 59%, and 100%, respectively. Dose-dependent increases in pAMPK relative to total AMPK (tAMPK) in whole kidney tissue are observed with a maximal 3.8-fold response at 300 mg/kg PF-06409577 treatment[1]. Oral administration of PF-06409577 (10, 30, and 100 mg/kg every day) resulted in dose-dependent reductions in proteinuria in the obese ZSF1 animals, with greater than 2-fold reduction in 24-hour urinary albumin loss compared with vehicle control after 60 days of treatment [2].
Kinase Assay	PF-06409577 is prepared in DMSO. PF-06409577 is incubated with fully phosphorylated AMPK in assay buffer at room temperature for 15 min followed by addition of PP2a and another incubation for 60 min at room temperature. The phosphatase treatment is quenched and the kinase assay initiated with the addition of okadaic acid (50 nM final), 50 nM Cy-5 SAMS peptide and ATP equal to K _m for each isoform. Reactions are incubated for an additional 60 min and the kinase reaction is quenched with the addition of 10 mM EDTA and 2 nM Eu-pACC antibody in detection Buffer. Kinase activity is monitored by excitation at 320 nM and measuring emission at 665 and 615 nM, respectively[2].
Animal Research	PF-06409577 is prepared in 0.5% methylcellulose[2].Daily administration of 0.5% methylcellulose (p.o.), PF-06409577 at 10, 30, or 100 mg/kg (p.o.), PF- 249 at 3, 10, or 30 mg/kg (p.o.), or ramipril in drinking water (1 mg/kg/day) is initiated and continued for 68 days. Urine is collected for 24-hours and volume recorded from all lean and obese

A DRUG SCREENING EXPERT

Animal Research	rats after 14, 28, 42, and 60 days of dosing. On Day 63 all rats are administered a final dose after 16-hour overnight fasting. One hour following the final dose, blood glucose is measured by glucometer and a 100 µL tail vein blood sample collected and processed for determination of insulin levels and total protein. Each rat is then anesthetized with isoflurane. The right kidney is collected and immediately freeze-clamped and transferred to liquid nitrogen storage; the left kidney is fixed in 10% formalin. Rats are then euthanized by exsanguination from the vena cava[2].
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Solubility Information

Solubility	Ethanol: 6.8 mg/mL (19.9 mM),Sonication is recommended. DMSO: 88.33 mg/mL (258.43 mM),Sonication is recommended. H2O: Insoluble, (< 1 mg/ml refers to the product slightly soluble or insoluble)
In vivo Formulation	10% DMSO+40% PEG300+5% Tween 80+45% Saline: 2 mg/mL (5.85 mM),Sonication is recommended. <i>Please add the solvents sequentially, clarifying the solution as much as possible before adding the next one. Dissolve by heating and/or sonication if necessary. Working solution is recommended to be prepared and used immediately. The formulation provided above is for reference purposes only. In vivo formulations may vary and should be modified based on specific experimental conditions.</i>

Preparing Stock Solutions

	1mg	5mg	10mg
1 mM	2.9258 mL	14.6289 mL	29.2577 mL
5 mM	0.5852 mL	2.9258 mL	5.8515 mL
10 mM	0.2926 mL	1.4629 mL	2.9258 mL
50 mM	0.0585 mL	0.2926 mL	0.5852 mL

Please select the appropriate solvent to prepare the stock solution, according to the solubility of the product in different solvents. Please use it as soon as possible.

Note: The dilution table applies only to solid products. For liquid products, please calculate the stock solution based on the stated concentration and/or density.

Reference

Cameron K O, Kung D W, Kalgutkar A S, et al. Discovery and preClinicalal characterization of 6-chloro-5-[4-(1-hydroxycyclobutyl) phenyl]-1 H-indole-3-carboxylic Acid (PF-06409577), a direct activator of adenosine monophosphate-activated protein kinase (AMPK), for the potential treatment of diabetic nephropathy[J]. Journal of medicinal chemistry, 2016, 59(17): 8068-8081.

Salatto C T, Miller R A, Cameron K O, et al. Selective activation of AMPK β1-containing isoforms improves kidney function in a rat model of diabetic nephropathy[J]. Journal of Pharmacology and Experimental Therapeutics, 2017, 361(2): 303-311.

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