PF-05175157

Cat. No.: HY-12942

CAS No.: 1301214-47-0

Molecular Formula: $C_{23}H_{27}N_5O_2$

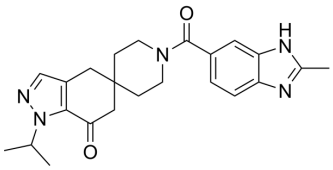
Molecular Weight: 405.49

Target: Acetyl-CoA Carboxylase

Pathway: Metabolic Enzyme/Protease

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 30 mg/mL (73.98 mM; Need ultrasonic and warming)

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.4662 mL	12.3308 mL	24.6615 mL
5 mM	0.4932 mL	2.4662 mL	4.9323 mL
10 mM	0.2466 mL	1.2331 mL	2.4662 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 1 mg/mL (2.47 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 1 mg/mL (2.47 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 1 mg/mL (2.47 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

PF-05175157 is broad spectrum acetyl-CoA carboxylase (ACC) inhibitor with IC_{50}s of 27.0, 33.0, 23.5 and 50.4 nM for ACC1 (human), ACC2 (human), ACC1 (rat), ACC2 (rat), respectively.

IC_{50} & Target

IC50: 27.0 nM (ACC1 (human)), 33.0 nM (ACC2 (human)), 23.5 nM (ACC1 (rat)), 50.4 nM (ACC2 (rat))[1]

In Vitro

PF-05175157 is broad spectrum acetyl-CoA carboxylase (ACC) inhibitor with IC_{50}s of 27.0±2.7, 33.0±4.1, 23.5±1.1 and 50.4±2.6 nM for ACC1 (human), ACC2 (human), ACC1 (rat) and ACC2 (rat), respectively. The in vitro metabolism of PF-05175157

	(Compound 9) is evaluated in microsomes from rat, dog, and human hepatocytes. PF-05175157 is not metabolized in rat, dog, or human microsomes. PF-05175157 is also stable in human hepatocyte incubations, but is minimally metabolized by recombinant human CYP3A4 and CYP3A5. PF-05175157 inhibits formation of malonyl-CoA in a concentration-dependent manner with a potency (EC_{50}=30 nM) in rat hepatocytes consistent with its potency against rat ACC1 (24 nM)[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Oral administration (3 mg/kg) to rats and dogs show bioavailability of 40% and 54%, respectively, consistent with the low microsomal clearance and good solubility at low pH. Formation of the direct product of ACC, malonyl-CoA, in the skeletal muscle and liver of lean rats is assessed 1 h following an acute oral dose of PF-05175157, showing concentration-dependent reductions in both skeletal muscle and liver malonyl-CoA. At the nadir, quadriceps and liver malonyl-CoA levels are reduced by 76% and 89%, respectively. The EC_{50}s for inhibition of quadriceps and liver malonyl-CoA are 870 and 540 nM, respectively, determined from unbind plasma concentrations of PF-05175157. Acute oral administration of PF-05175157 inhibits hepatic DNL in rats in an unbind plasma drug concentration-dependent manner. PF-05175157 inhibits up to 82% of the incorporation of [^{14}C]acetate into [^{14}C]lipids with an EC_{50} of 326 nM[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	On the day of the study, media is aspirated and cells are treated with fresh MCM media containing DMSO vehicle or varying concentrations of PF-05175157 (Compound 9). After 5 h at 37 °C, incubation media is removed and the experiment is terminated by washing the cells with ice-cold PBS[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Male SD rats are weighed and randomized by body weight into treatment groups consisting of vehicle, 0.25, 0.5, 1, 2, 4, 8, 15, 25, 50, and 100 mg/kg of PF-05175157 (Compound 9). Animals are orally dosed 2 h into the light cycle with their respective treatments and fed ad libitum. One hour postdose, the animals are sacrificed via CO_2 asphyxiation following by cervical dislocation. Blood for plasma exposure of PF-05175157 is collected via cardiac puncture, transferred to tubes with K_2EDTA, centrifuged at 4 °C, and the plasma transferred to a 96-well microtiter plate and stored at -20 °C. Liver and quadriceps are rapidly removed, freeze-clamped in a clamp, and subsequently stored at -80 °C[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Acta Pharmacol Sin. 2020 Mar;41(3):336-347.

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REFERENCES

[1]. David A, et al. Decreasing the Rate of Metabolic Ketone Reduction in the Discovery of a Clinical Acetyl-CoA Carboxylase Inhibitor for the Treatment of Diabetes. J Med Chem. 2014 Dec 26; 57(24): 10512–10526.

Caution: Product has not been fully validated for medical applications. For research use only.

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