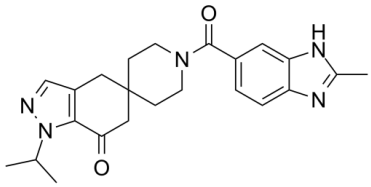
Data Sheet

Product Name:	PF-05175157
Cat. No.:	CS-7859
CAS No.:	1301214-47-0
Molecular Formula:	C23H27N5O2
Molecular Weight:	405.49
Target:	Acetyl-CoA Carboxylase
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : 30 mg/mL (73.98 mM; Need ultrasonic and warming)



BIOLOGICAL ACTIVITY:

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. IC50 & 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]. **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].

PROTOCOL (Extracted from published papers and Only for reference)

Cell Assay: PF-05175157 (Compound 9) is initially dissolved in DMSO and subsequently diluted 1:100 in MCM. An aliquot of this solution is added to the fresh MCM in each well, further diluting the PF-05175157 by 1:10. This dilution progression ensures that all wells have a final DMSO concentration of 0.1%[1].[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]. **Animal Administration:** Immediately prior to initiation of the study, the dosing solutions are prepared in dosing vehicle (0.5% methyl cellulose: 0.1% polysorbate 80), giving a final dosing volume of 5 mL/kg[1].[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].

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.

CAIndexNames:

Spiro[5H-indazole-5,4'-piperidin]-7(6H)-one, 1,4-dihydro-1'-[(2-methyl-1H-benzimidazol-6-yl)carbonyl]-1-(1-methylethyl)-

SMILES:

O=C1CC2(CCN(C(C3=CC=C4C(NC(C)=N4)=C3)=O)CC2)CC5=C1N(C(C)C)N=C5

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA