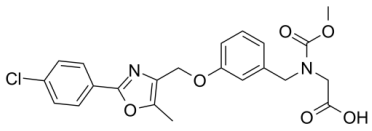
Data Sheet

Product Name:	BMS-687453
Cat. No.:	CS-5523
CAS No.:	1000998-59-3
Molecular Formula:	C22H21ClN2O6
Molecular Weight:	444.86
Target:	PPAR
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : ≥ 31 mg/mL (69.68 mM)



BIOLOGICAL ACTIVITY:

BMS-687453 is a potent and selective **PPARα** agonist, with an **EC_{50}** and **IC_{50}** of 10 nM and 260 nM for human **PPARα** and 4100 nM and >15000 nM for PPARγ in PPAR-GAL4 transactivation assays. IC50 & Target: EC50: 10 nM (GAL4-human PPARα), 4100 nM (GAL4-human PPARγ)[1]

IC50: 260 nM (Human PPARα), >15000 nM (Human PPARγ)[1]

In Vitro: BMS-687453 is a potent and selective PPARα agonist, with an EC_{50} and IC_{50} of 10 nM and 260 nM for human PPARα and □ 410-fold and more than 57-fold selectivity vs human PPARγ of 4100 nM and >15000 nM in PPAR-GAL4 transactivation assays. BMS-687453 exhibits high PPARα potency (EC_{50} = 47 nM) with □50-fold selectivity vs PPARγ (EC_{50} = 2400 nM) in HepG2 cells. However, BMS-687453 shows less potent activities in rodent PPARα functional assays, with a moderate EC_{50} of 426 nM for mouse and 488 nM for hamster but remains a full PPARα agonist in both species[1]. **In Vivo:** BMS-687453 (10, 50, 100, p.o.) dose-dependently increases serum ApoA1 protein levels and low-density lipoprotein-cholesterol (LDLc) levels in mice. BMS-687453 (1, 3, 10 mg/kg, p.o.) decreases HDLc levels in high fat-fed hamsters[1]. BMS-687453 induces PDK4 mRNA in the liver, with ED_{50} value of 0.24 mg/kg[2]. BMS-687453 (300 mg/kg, p.o.) causes skeletal myofiber degeneration and necrosis characterized by observed discoid changes, myofibril lysis, hyalinization, and cellular infiltration in male rats. BMS-687453 (300 mg/kg, p.o.) induces a mild toxicity in both fast and slow-twitch muscles in male rats[3].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase Assay: [1]A homogeneous, fluorescent polarization **PPARα** and **PPARγ** binding assay is used as the primary screen for determining the PPARα and PPARγ binding affinity of compounds. The human functional activity of PPARα and PPARγ agonists is determined by using the GAL4-LBD assays. The in vitro hamster, rat, and mouse PPARα functional activities are tested in the chimeric **GAL4/PPARα** assay format. The data are reported as an EC_{50} value calculated using XLfit 4 parameter fit and floating all parameters. Full length human PPARα and PPARγ co-transfection assays in HepG2 cells are employed for further testing the leading compounds (**BMS-687453**)[1]. **Animal Administration:** BMS-687453 is formulated in 2% Tween 80 and 0.5% CMC (carboxymethylcellulose) in 97.5% Gibco distilled water.[1]**Male 6−8 week old human apoA1 transgenic mice** are randomly assigned into different treatment groups and weighed and dosed by **oral gavage** (5 mL/kg body weight) once a day in the morning with vehicle alone or with compound (**BMS-687453**) and allowed free access to food and water. The study duration is 10 days. After dosing on day 10, mice are fasted for 4 h and sacrificed by CO_2 asphyxiation, and blood samples are collected in serum-separating tubes via cardiac puncture for lipid measurements. Livers are dissected out, weighed, and quickly frozen in liquid nitrogen for future RNA analysis. Human apoA1 concentration in serum is measured using the apolipoprotein A1 kit[1].

References:

[1]. Li J, et al. Discovery of an oxybenzylglycine based peroxisome proliferator activated receptor alpha selective agonist 2-((3-((2-(4-chlorophenyl)-5-methyloxazol-4-yl)methoxy)benzyl)(methoxycarbonyl)amino)acetic acid (BMS-687453). J Med Chem. 2010 Apr 8;53(7):2854-64.

[2]. Mukherjee R, et al. Novel peroxisome proliferator-activated receptor alpha agonists lower low-density lipoprotein and triglycerides, raise high-density lipoprotein, and synergistically increase cholesterol excretion with a liver X receptor agonist. J Pharmacol Exp Ther. 2008 Dec;327(3):716-26.

[3]. Vassallo JD, et al. Biomarkers of drug-induced skeletal muscle injury in the rat: troponin I and myoglobin. Toxicol Sci. 2009 Oct;111(2):402-12.

CAIndexNames:

Glycine, N-[[3-[[2-(4-chlorophenyl)-5-methyl-4-oxazolyl]methoxy]phenyl]methyl]-N-(methoxycarbonyl)-

SMILES:

ClC(C=C1)=CC=C1C2=NC(COC3=CC=CC(CN(C(OC)=O)CC(O)=O)=C3)=C(C)O2

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