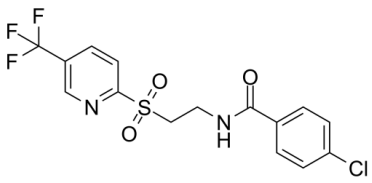
Data Sheet

Product Name:	GSK3787
Cat. No.:	CS-1262
CAS No.:	188591-46-0
Molecular Formula:	C15H12ClF3N2O3S
Molecular Weight:	392.78
Target:	PPAR
Pathway:	Cell Cycle/DNA Damage
Solubility:	DMSO : ≥ 50 mg/mL (127.30 mM); H2O : < 0.1 mg/mL (insoluble)



BIOLOGICAL ACTIVITY:

GSK3787 is a selective and irreversible peroxisome proliferator-activated receptor δ (**PPARδ**) antagonist with **pIC_{50}** of 6.6. IC50 & Target: pIC50: 6.6 (PPARδ)[1] **In Vitro:** GSK3787 is identified as a potent and selective hPPARδ ligand (pIC_{50}=6.6) with no measurable affinity for hPPARα or hPPARγ (pIC_{50} < 5) in our standard in vitro ligand displacement assay. GSK3787 is inactive against hPPARα and hPPARγ in similar functional antagonist assays. GSK3787 fails to activate the receptor in a standard hPPARδ-GAL4 chimera cell-based reporter assay. GSK3787 is a selective PPARδ antagonist with equipotent species activity against the human and mouse receptor[1]. **In Vivo:** GSK3787 has pharmacokinetic properties suitable for use as an in vivo PPARδ antagonist tool compound in mice. GSK3787 is administered intravenously (0.5 mg/kg) and orally (10 mg/kg) to male C57BL/6 mice. Mean clearance (CL) and volume of distribution at steady state (V_{ss}) following iv administration are 39±11 (mL/min)/kg and 1.7±0.4 L/kg, respectively. Following oral administration, good exposure (C_{max}=881±166 ng/mL, AUC_{inf}=3343±332 h•ng/mL), half-life (2.7±1.1 h), and bioavailability (F=77±17%) are observed [1]. Oral administration of GSK3787 (10 mg/kg) leads to a serum C_{max} of 2.2±0.4 μM in C57BL/6 male mice. Oral administration of GW0742 causes an increase in expression of Angptl4 and Adrp mRNA (known PPARβ/δ target genes) in wild-type mouse colon epithelium, and this effect is not found in Pparβ/δ-null mouse colon epithelium. Coadministration of GSK3787 with GW0742 effectively prevents the ligand-induced expression of both Angptl4 and Adrp mRNA in wild-type mouse colon epithelium, and this effect is not found in Pparβ/δ-null mouse colon epithelium. Oral administration of GSK3787 causes a modest increase in promoter occupancy of PPARβ/δ in the PPRE region of both the Angptl4 and Adrp genes, but coadministration of GSK3787 with GW0742 results in markedly less accumulation of PPARβ/δ in the PPRE region of both the Angptl4 and Adrp genes in wild-type mouse colon epithelium[2].

PROTOCOL (Extracted from published papers and Only for reference)

Animal Administration: GSK3787 is prepared in vehicle (corn oil)[2].[2]Mice[2]

For RNA and DNA analysis, **male wild-type and Pparβ/δ-null mice** are administered vehicle (corn oil), GW0742 (10 mg/kg), **GSK3787 (10 mg/kg)**, or GW0742 and GSK3787 by oral gavage 3 h before euthanasia. After euthanasia, colons are carefully dissected. To isolate colon epithelium, colons are flushed with phosphate-buffered saline, and epithelial cells are scraped from mucosa using a razor blade. The isolated tissues are used for RNA isolation. For glucose-tolerance tests, male wild-type and Pparβ/δ-null mice are administered vehicle (corn oil), GW0742 (10 mg/kg), GSK3787 (10 mg/kg), or Rosiglitazone (20 mg/kg) by oral gavage once a day for 2 weeks.

References:

[1]. Shearer BG, et al. Identification and characterization of 4-chloro-N-(2-<[5-trifluoromethyl)-2-pyridyl]sulfonyl>ethyl)benzamide (GSK3787), a selective and irreversible peroxisome proliferator-activated receptor delta (PPARdelta) antagonist. J Med Chem. 2010 Feb 25;53(4):1857-61.

[2]. Palkar PS, et al. Cellular and pharmacological selectivity of the peroxisome proliferator-activated receptor-beta/delta antagonist GSK3787. Mol Pharmacol. 2010 Sep;78(3):419-30.

CAIndexNames:

Benzamide, 4-chloro-N-[2-[[5-(trifluoromethyl)-2-pyridinyl]sulfonyl]ethyl]-

SMILES:

O=C(NCCS(=O)(C1=NC=C(C(F)(F)F)C=C1)=O)C2=CC=C(Cl)C=C2

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