Fenofibrate

Cat. No.: HY-17356

CAS No.: 49562-28-9

Molecular Formula: $C_{20}H_{21}ClO_4$

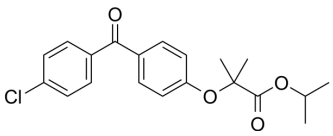
Molecular Weight: 360.83

Target: Cytochrome P450; PPAR; Autophagy

Pathway: Metabolic Enzyme/Protease; Cell Cycle/DNA Damage; Vitamin D Related/Nuclear Receptor; Autophagy

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	1 year
	-20°C	6 months



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (277.14 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.7714 mL	13.8569 mL	27.7139 mL
	5 mM	0.5543 mL	2.7714 mL	5.5428 mL
	10 mM	0.2771 mL	1.3857 mL	2.7714 mL

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

In Vivo

1. Add each solvent one by one: corn oil
   Solubility: 33.33 mg/mL (92.37 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (27.71 mM); Suspended solution; Need ultrasonic
3. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (6.93 mM); Clear solution
4. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (6.93 mM); Suspended solution; Need ultrasonic
5. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (6.93 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

Fenofibrate is a selective PPARα agonist with an EC_{50} of 30 μM. Fenofibrate also inhibits human cytochrome P450 isoforms, with IC_{50}s of 0.2, 0.7, 9.7, 4.8 and 142.1 μM for CYP2C19, CYP2B6, CYP2C9, CYP2C8, and CYP3A4, respectively.

IC_{50} & Target				
	CYP2C19 0.2 μM (IC_{50})	CYP2B6 0.7 μM (IC_{50})	CYP2C9 9.7 μM (IC_{50})	CYP2C8 4.8 μM (IC_{50})
	CYP3A4 142.1 μM (IC_{50})	PPARα 30 μM (IC_{50})		

In Vitro

Fenofibrate is a relatively potent inhibitor of CYP2B6 (IC_{50}=0.7±0.2 μM) and CYP2C19 (IC_{50}=0.2±0.1 μM). Fenofibrate is also a moderate inhibitor of CYP2C8 (IC_{50}=4.8±1.7 μM) and CYP2C9 (IC_{50}=9.7 μM)[1]. Fenofibrate binds to and inhibits cytochrome P450 epoxygenase (CYP)2C with higher affinity than to PPARα. Fenofibrate is a well-known PPARα agonist, but an in vitro assessment of 209 frequently prescribed drugs and related xenobiotics suggests that Fenofibrate is also a potent inhibitor of cytochrome P450 epoxygenase (CYP)2C. The affinity of Fenofibrate to CYP2C is >10 times higher (EC_{50}=2.39±0.4 μM) than to PPARα (EC_{50}=30 μM). Fenofibrate at a low dose inhibits CYP2C8 activity without PPARα activation[2].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

Daily intake of Fenofibrate at this low dose (10 μg/g/day) inhibits retinal and choroidal neovascularization induced by CYP2C8 overexpression by 29% (P=0.021) and 36% ($P=1.2\times10^{-9}$) respectively[2].

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PROTOCOL

Kinase Assay [1]

The half-maximal inhibitory concentrations (IC_{50}s) of Fenofibrate, statins (atorvastatin, lovastatin, pravastatin, simvastatin and simvastatin acid, the active form of simvastatin) and glipizide for recombinant human CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are determined using fluorometric CYP450 inhibition assays. Briefly, the drugs are dissolved in methanol or acetonitrile. In 96 well assay plates, the drugs are diluted to a series of concentrations in a solution containing cofactors including $NADP^+$ (final concentration 1.3 mM), $MgCl_2$ (final concentration 3.3 m M), glucose-6-phosphate (G6P, final concentration 3.3 mM) and glucose 6-phosphate dehydrogenase (final concentration 0.4 U/mL). The mixture is pre-incubated at 37°C for 10 min. The enzymes and fluorogenic substrates are diluted to desired concentrations in sodium phosphate reaction buffer (pH 7.4, final concentration 200 mM) and mixed. Reactions are initiated with addition of the enzyme and substrate mixture to the cofactor and drug mixture. The final reaction volume of all assays is 200 μL. After incubating at 37°C for a pre-specified period of time (15 to 45 min), the reactions are stopped with addition of 75 μL quenching solution (0.5 M Tris base or 2N NaOH). Fluorescence is determined using a BioTek Synergy 2 fluorescence reader. Each of the drugs is tested at eight concentrations in duplicate. To estimate IC_{50}s, percent of inhibition is calculated using net fluorescence that is corrected for the background. The values of percent of inhibition are then fitted to a three or four parameter log-logistic model[1].

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Animal Administration [2]

Mice[2]

The mouse oxygen-induced retinopathy (OIR) model is used. Briefly to induce retinal neovascularization, mouse pups and their nursing mother are exposed to 75±3% oxygen from P7 to P12. For the higher dose Fenofibrate (F6020) treatment (100 mg/kg/day). Fenofibrate is dissolved in corn oil to make 100mg/mL solution and pure corn oil is used as vehicle control. For the lower dose treatment (10 mg/kg/day), Fenofibrate is dissolved in 10% DMSO, D2650 to make a 10 mg/mL solution and 10% DMSO is used as vehicle control. After return to room air, mice are orally gavaged with Fenofibrate (100 or 10 mg/kg) or vehicle control daily from P12 to P16. At P17, eyes are enucleated immediately after euthanasia and fixed in 4% paraformaldehyde in PBS for 1 h at room temperature. Retinas are then dissected and stained overnight with Alexa Fluor 594 conjugated isolectin GS-IB4 (10 μg/mL) at room temperature. After washing with PBS, retinas are mounted onto microscope slides with photoreceptor side down and embedded in SlowFade antifade mounting medium. Retinal images are taken using a fluorescence microscope with image software. Retinal neovascularization is analyzed.

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CUSTOMER VALIDATION

- Mol Cell. 2023 Nov 20:S1097-2765(23)00914-0.
- Hepatology. 2018 Jul;68(1):289-303.
- Acta Pharmacol Sin. 2024 Mar 8.
- Acta Pharmacol Sin. 2021 Mar 26.
- Phytomedicine. 2022 May 6;102:154147.

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REFERENCES

[1]. Schelleman H, et al. Pharmacoepidemiologic and in vitro evaluation of potential drug-drug interactions of sulfonylureas with fibrates and statins. Br J Clin Pharmacol. 2014 Sep;78(3):639-48.

[2]. Gong Y, et al. Fenofibrate Inhibits Cytochrome P450 Epoxygenase 2C Activity to Suppress Pathological Ocular Angiogenesis. EBioMedicine. 2016 Sep 30. pii: S2352-3964(16)30448-0.

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