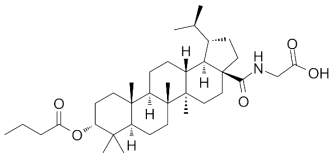
FXR antagonist 1

Cat. No.:	HY-151481
CAS No.:	2295804-68-9
Molecular Formula:	$C_{36}H_{59}NO_5$
Molecular Weight:	585.86
Target:	FXR
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (170.69 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.7069 mL	8.5345 mL	17.0689 mL
	5 mM	0.3414 mL	1.7069 mL	3.4138 mL
	10 mM	0.1707 mL	0.8534 mL	1.7069 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: 2.5 mg/mL (4.27 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: 2.5 mg/mL (4.27 mM); Clear solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

FXR antagonist 1 (compound F6) is an orally active and selective intestinal FXR antagonist (IC_{50}=2.1 μM). FXR antagonist 1 selectively inhibits intestinal FXR signalling through antagonism of intestinal FXR and feedback activation of hepatic FXR to improve hepatic steatosis, inflammation and fibrosis in NASH (nonalcoholic steatohepatitis) models. FXR antagonist 1 can be used in NASH studies[1].

IC_{50} & Target

FXR
2.1 μM (IC_{50})

In Vitro

FXR antagonist 1 (0-100 μM; 24 h) shows FXR antagonistic activities in HEK293T cells[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Viability Assay[1]

Cell Line:	HEK293T cells (co-transfected with pCMV-Script-hFXR and pGL4.11-hSHP-Luciferase)
Concentration:	0-100 μM
Incubation Time:	24 h
Result:	Exhibited FXR antagonistic activities with an IC_{50} value of 2.1 μM.

In Vivo

FXR antagonist 1 (10 mg/kg; p.o.; single daily for 12 weeks) reduces adiposity and improves glucose sensitivity and ameliorates the progress of NASH in GAN-diet-induced NASH mice[1].
FXR antagonist 1 (10 mg/kg; p.o.; single daily for 12 weeks) inhibits intestinal FXR Signaling but indirectly activates hepatic FXR signaling in GAN-diet-induced mice[1].
FXR antagonist 1 (3, 10, 30 mg/kg; p.o.; single daily for 4 weeks) dose-dependently alleviates NASH pathologies in HFMCD-diet-induced mice[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Adult male C57BL/6 mice (GAN (Gubra-amylin NASH)-diet induced NASH model)[1].
Dosage:	10 mg/kg
Administration:	Oral administration; single daily for 12 weeks.
Result:	Reversed metabolic dysfunction in GAN-induced NASH mice. Reduced GAN-diet-induced hepatic steatosis, injury, inflammation, and fibrosis. Inhibited the hepatic mRNA expression involved in lipid metabolism, inflammatory signaling, and fibrogenesis in GAN-diet-induced mice. Significantly antagonized intestinal FXR signaling and bile acid reabsorption.

Animal Model:	Adult male C57BL/6 mice (HFMCD-diet induced NASH model)[1].
Dosage:	3, 10, 30 mg/kg
Administration:	Oral administration; single daily for 4 weeks.
Result:	Significantly decreased serum ALT and AST levels at 30 mg/kg, and markedly lowered the hepatic TG concentration in both 10 and 30 mg/kg. Lowered hepatic hydroxyproline level.

REFERENCES

[1]. Zhang C, et al. Discovery of Betulinic Acid Derivatives as Potent Intestinal Farnesoid X Receptor Antagonists to Ameliorate Nonalcoholic Steatohepatitis. J Med Chem. 2022 Sep 15.

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