LY2562175

Cat. No.: HY-103704

CAS No.: 1103500-20-4

Molecular Formula: $C_{28}H_{27}Cl_2N_3O_4$

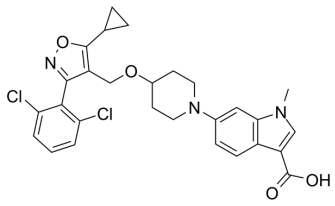
Molecular Weight: 540.44

Target: FXR; Autophagy

Pathway: Metabolic Enzyme/Protease; Autophagy

Storage:

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



SOLVENT & SOLUBILITY

In Vitro

DMSO : 62.5 mg/mL (115.65 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	1.8503 mL	9.2517 mL	18.5034 mL
	5 mM	0.3701 mL	1.8503 mL	3.7007 mL
	10 mM	0.1850 mL	0.9252 mL	1.8503 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: ≥ 2.08 mg/mL (3.85 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.08 mg/mL (3.85 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

LY2562175 is a potent and selective FXR agonist, with an EC_{50} of 193 nM[1].

IC_{50} & Target

EC50: 193 nM (FXR)

In Vitro

LY2562175 promotes transcriptional activation of human FXR in a cell-based co-transfection assay with an EC_{50} of 193 nM. LY2562175 promotes recruitment of a peptide from the nuclear receptor interaction domain of the coactivator SRC-1 with a relative EC_{50} of 121 nM and 93.5% efficacy as compare to GW4064[1].

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

In Vivo

LY2562175 causes a dose-dependent decrease in serum cholesterol and serum triglycerides. At a dose of 10 mg/kg, the

decrease in cholesterol with LY2562175 is 80% below vehicle-treated animals, and the decrease in serum triglycerides is 76% from control group. The ED_{50} for serum cholesterol is determined to be 2 and 3.4 mg/kg for serum triglycerides. Treatment of female ZDF rats with LY2562175 results in a dose dependent lowering of plasma triglycerides in the fasted and nonfasted states. When administered as a fixed dose combination with BRL49653, LY2562175 further lowers fasted and nonfasted plasma triglycerides. FPLC fractionation of the lipoproteins reveals that LY2562175 treatment results in a reduction in vLDL-C and a dramatic increase in HDL-c in this animal model[1].

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PROTOCOL

Kinase Assay [1]

LY2562175 is tested in concentration-response curves by an FXR-SRC-1 Cofactor Recruitment assay using the Alpha Screen technology according to the manufacturer instructions. Briefly, purified 6-HIS-tagged human FXR ligand-binding domain (amino acids 242-472), purified GST-tagged human SRC-1 nuclear receptor-interacting domain (amino acids 220-394), Nickel Chelate donor beads and Anti-GST antibody acceptor beads are mixed together and 12 µL per well is aliquoted into 384 well plates. Add LY2562175 in 3 µL per well for a total assay volume of 15 µL and incubate at room temperature in the dark for 4 hours. After incubation, LY2562175 that binds FXR and induces the interaction between the FXR and SRC-1 will bring the two bead types into proximity generating luminescence that is quantified using a Packard Fusion instrument. Calculate EC_{50} values for LY2562175[1].

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Animal Administration [1]

To assess the potency and efficacy of LY2562175 in vivo, studies are conducted in 8 week old, male LDLR null mice fed a “Western” diet. Animals are allowed to acclimate to the high fat/high cholesterol chow TD88137 (containing 0.15% cholesterol and 42% fat) for 2 weeks prior to the study. Animals are divided into groups of six and dosed once daily for 1 week by gavage with solutions of LY2562175 in situ sodium salt or with vehicle (5% Solutol, 5% EtOH, 1 wt %/v CMC) at a dose volume of 5 mL/kg. On the seventh day, animals are bled by cardiac puncture under anesthesia with CO_2. Serum is prepared from individual animals for determination of cholesterol and triglycerides by enzymatic analysis. Pooled samples from each treatment group are used for determination of lipoprotein subtypes. ED_{50} values (dose producing half-maximal effect) for the decrease in serum cholesterol and triglycerides are determined by nonlinear regression analysis[1].

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

REFERENCES

[1]. Genin MJ, et al. Discovery of 6-(4-{[5-Cyclopropyl-3-(2,6-dichlorophenyl)isoxazol-4-yl]methoxy}piperidin-1-yl)-1-methyl-1H-indole-3-carboxylic Acid: A Novel FXR Agonist for the Treatment of Dyslipidemia. J Med Chem. 2015 Dec 24;58(24):9768-72.

Caution: Product has not been fully validated for medical applications. For research use only.

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