

Product Data Sheet

Product Name: XL335
Cat. No.: GC10760

Chemical Properties

Cas. No. 629664-81-9

Chemical Name propan-2-yl 3-(3,4-difluorobenzoyl)-1,1-dimethyl-2,6-dihydroazepino[4,5-b]indole-5-carboxylate

SMILES CC(C)OC(=O)C1=CN(CC(C2=C1NC3=CC=CC=C32)(C)C)C(=O)C4=CC(=C(C=C4)F)F

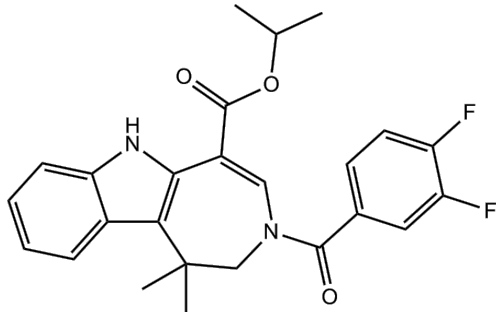
Formula C₂₅H₂₄F₂N₂O₃ M.Wt 438.48

Solubility ≥ 20.4mg/mL in DMSO Storage Store at -20°C

General tips For obtaining a higher solubility , please warm the tube at 37 °C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT , or blue ice upon request.

Structure



Protocol

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

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Cell experiment: Mouse AML12 cells are plated at 200,000 cells/well on the 24-well plate in 1 mL of growth medium [DMEM/F12 10% FBS, 1% penicillin and streptomycin, 1% insulin-transferrin-selenium-G supplement (ITS), 0.1% Dexamethasone (40 ng/mL)/well. The cells are treated with increasing concentrations of Turofexorate isopropyl (WAY-362450) (0.001, 0.01, 0.1, 1 and 10 μ M) or GW4064 for 24 h. Total RNA is prepared and analyzed by real-time RT-PCR, and short heterodimer partner (SHP) expression is normalized to GAPDH and reported as fold induction vs. vehicle-treated cells. Preplated 24-well plates of human male primary hepatocytes with matrigel overlay are obtained from Cellz Direct. Cells are maintained in serum-free Williams medium E and supplemented with penicillin/streptomycin, dexamethasone, ITS, L-glutamine, and HEPES buffer. They are treated overnight with vehicle (0.01% DMSO) or increasing concentrations of Turofexorate isopropyl (WAY-362450) or GW4064. Total RNA is purified using the Qiagen RNeasy clean kit, and gene expression is quantified by real-time RT-PCR with the Qiagen Quantitech kit using an ABI 7900. The relative amount of mRNA is normalized to 18S ribosomal RNA, and data shown represent an average of two independent experiments[2].

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Animal experiment:

Mice[3] Age- and sex-matched 8- to 12-week-old mice are fed standard chow and housed in temperature-controlled virus-free facility on a 12-h-light/dark cycle with free access to food and water. Where indicated, mice are fed either a Western diet containing 42% fat and 0.2% cholesterol by weight or this Western diet supplemented to contain 0.225 mg Turofexorate isopropyl (WAY-362450) per gram of diet. The mice consumed ~4 g diet per day, resulting in the delivery of ~30 mg of Turofexorate isopropyl (WAY-362450) per kg of body weight, assuming a 30 g body weight. Animals are maintained on these diets for 6 (apoE^{-/-}) or 12 weeks (LDLR^{-/-}). At the end of each study, animals are euthanized and blood samples collected via the orbital eye for lipid analysis. Liver and ileum tissue are removed for mRNA quantification, and aortas are removed and stored in 10% buffered formalin solution. Rats[2] Eight-week-old male Sprague Dawley rats and Syrian Golden hamsters are fed a 60% fructose/0.15% cholesterol diet. For the rat study, the rats are placed onto the diet for 2 wk and then treated by daily oral gavage with vehicle (80% polyethylene glycol/20% Tween) or varying concentrations of Turofexorate isopropyl (WAY-362450) (8/group) as indicated for 7 days (8 rats/group). The hamster study is conducted as a preventative treatment, so both the diet and drug treatments are initiated on day 1 and continued for 21 days (8 hamsters/group). On the last day after the final dose, the food is removed to allow a 3 h fast, and serum and liver are harvested for analysis as described above.

References:

- [1]. Flatt B, et al. Discovery of XL335 (WAY-362450), a highly potent, selective, and orally active agonist of the farnesoid X receptor (FXR). J Med Chem. 2009 Feb 26;52(4):904-7.
- [2]. Evans MJ, et al. A synthetic farnesoid X receptor (FXR) agonist promotes cholesterol lowering in models of dyslipidemia. Am J Physiol Gastrointest Liver Physiol. 2009 Mar;296(3):G543-52.
- [3]. Hartman HB, et al. Activation of farnesoid X receptor prevents atherosclerotic lesion formation in LDLR^{-/-} and apoE^{-/-} mice. J Lipid Res. 2009 Jun;50(6):1090-100.

Background

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XL335 is a potent, selective and orally bioavailable agonist of the farnesoid X receptor (FXR) with EC₅₀ value of 4 nM [1].

XL335 has shown to reduce IL-6-induced both mRNA and protein expression of CRP via FXR in human hepatoma Hep3B cells. XL335 remarkably reduced LPS-induced SAP and SAA3 mRNA expression in WT mice, but not in FXR/KO mice [2].

Additionally, in hepatoma cells, XL335 block the lipid accumulation induced by palmitic acid (PA). In vivo, XL335 has shown to decrease portal vein endotoxin level and reduce inflammation induced by fructose in mice. XL335 attenuated inflammation and suppressed ADRP expression in lipopolysaccharide (LPS)-induced mice [3].

References:

- [1] Flatt B1, Martin R, Wang TL, Mahaney P, Murphy B, Gu XH, Foster P, Li J, Pircher P, Petrowski M, Schulman I, Westin S, Wrobel J, Yan G, Bischoff E, Daige C, Mohan R. Discovery of XL335 (WAY-362450), a highly potent, selective, and orally active agonist of the farnesoid X receptor (FXR). J Med Chem. 2009 Feb 26;52(4):904-7. doi: 10.1021/jm8014124.
- [2] Zhang S1, Liu Q, Wang J, Harnish DC. Suppression of interleukin-6-induced C-reactive protein expression by FXR agonists. Biochem Biophys Res Commun. 2009 Feb 6;379(2):476-9.
- [3] Liu X1, Xue R2, Ji L1, Zhang X1, Wu J3, Gu J1, Zhou M4, Chen S5. Activation of farnesoid X receptor (FXR) protects against fructose-induced liver steatosis via inflammatory inhibition and ADRP reduction. Biochem Biophys Res Commun. 2014 Jul 18;450(1):117-23.

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