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产品名称: 3-(3,4-二氟苯甲酰基)-1,2,3,6-四氢-1,1-二甲基氮杂卓[4,5-B]吡啶-5-甲酸 1-甲基乙基酯
产品别名: Turofexorate isopropyl

生物活性:				
Description	Turofexorate isopropyl (WAY-362450) is a potent, selective, and orally bioavailable FXR agonist with EC50 of 4 nM.			
IC ₅₀ & Target	EC50: 4 nM (FXR)[1]			
In Vitro	Turofexorate isopropyl (WAY-362450) is a potent, selective, and orally bioavailable FXR agonist (EC50=4 nM). Turofexorate isopropyl (WAY-362450) is highly selective, as no significant cross-reactivity with these receptors (LXRα, LXRβ, PPARα, PPARγ, PPARδ, RXRα, RARγ, VDR, SXR, ERα, ERβ, GR, AR, MR, and PR) is observed at concentrations up to 10 μM. WAY-362450 displays potent agonist activity in the FXR reporter gene assays and on FXR target genes in cell-based assays. In promoter assays, utilizing reporter constructs under control of the human bile salt excretory pump (BSEP), human small heterodimer partner (SHP), and mouse intestinal bile acid binding protein (IBABP) genes are up-regulated by Turofexorate isopropyl (WAY-362450) with EC50 of 17, 230, and 33 nM, respectively. In addition, WAY-362450 significantly induces mRNAs encoding for BSEP, SHP, and IBABP in human cell cultures at 1 μM (13-, 2-, and 20-fold, respectively)[1]. Turofexorate isopropyl (WAY-362450) potently induces luciferase reporter expression with an EC50 of 16 nM. Turofexorate isopropyl (WAY-362450) is a potent stimulator of endogenous FXR gene activation in mouse AML12 cells and in primary human hepatocytes[2].			
In Vivo	Turofexorate isopropyl (WAY-362450) also shows potent effects on cholesterol and triglyceride lowering in LDLR ^{-/-} mice and antiatherogenic activity with respect to reduction of aortic arch lesions. Oral administration of Turofexorate isopropyl (WAY-362450) to LDLR ^{-/-} mice results in lowering of cholesterol and triglycerides. Chronic administration in an atherosclerosis model results in significant reduction in aortic arch lesions. Turofexorate isopropyl (WAY-362450) is dosed in rat at 3 mg/kg (po and iv) and shows good oral bioavailability (38%). There is a protracted half-life of 25 h, modest volume of distribution, and low clearance (3.3 L/kg, ~10% of hepatic blood flow). Additional pharmacokinetic studies in mice and higher species have been completed, and the data will be reported elsewhere ^[1] . In rats, Turofexorate isopropyl (WAY-362450) results in an elevation in HDLc levels, whereas in hamsters it causes a reduction similar to that observed in mice ^[2] . Treatment of wild-type mice with 30 mg/kg Turofexorate isopropyl (WAY-362450) results in induction of SHP expression in wild-type mice but not in FXR ^{-/-} mice. Consistent with the known effects of SHP induction on bile acid synthetic gene expression, Turofexorate isopropyl (WAY-362450) strongly represses expression of the CYP8B1 bile acid synthetic gene in wild-type mice but had no effect on CYP8B1 gene expression in FXR ^{-/-} mice ^[3] .			
Solvent&Solubility	<i>In Vitro:</i> DMSO : 15 mg/mL (34.21 mM; Need ultrasonic and warming)			
	Preparing Stock Solutions	Solvent Mass Concentration	1 mg	5 mg
		1 mM	2.2807 mL	11.4033 mL
		5 mM	0.4561 mL	2.2807 mL
		10 mM	0.2281 mL	1.1403 mL



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	*请根据产品在不同溶剂中的溶解度选择合适的溶剂配制储备液; 一旦配成溶液, 请分装保存, 避免反复冻融造成的产品失效。 储备液的保存方式和期限 -80°C, 6 months; -20°C, 1 month。 -80°C 储存时, 请在 6 个月内使用, -20°C 储存时, 请在 1 个月内使用。
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.
实验参考:	
Cell Assay	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 µM) 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].
Animal Administration	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



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	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.

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