Product Data Sheet

Product Name: MGAT2-IN-2
Cat. No.: GC31555

Chemical Properties

Cas. No.	1710630-11-7		
SMILES	O=C(N1CCC2=C1C(N3C(CCC3)=O)=CC(S(=O)(NC4=CC=C(F)C=C4F)=O)=C2)NC5=CC=C(C(F)(F)F)C=C5		
Formula	$C_{26}H_{21}F_5N_4O_4S$	M.Wt	580.53
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	MGAT2-IN-2		

Protocol

Kinase experiment:

The test compounds (e.g., MGAT2-IN-2) are dissolved in 5 µL of an assay buffer, which consists of 100 mM Tris-HCl (pH 7.5), 5 mM MgCl2, 200 mM sucrose, 0.01% Tween 20, 2 mM DTT, 0.01% BSA and 5% DMSO and incubated with 10 µL of 0.6 µg/mL MGAT2 enzyme for 60 min. The reaction is started with the addition of 5 µL of 13C×18 oleoyl-CoA and 2-oleoyl-glycerol at 20 µM each. After incubation at rt for 30 min, the reaction is stopped with Acetonitrile containing 0.88% formic acid and 1.3 µM 1,2-dioleoyl-glycerol as an internal standard. High-throughput online solid phase extraction is performed using a RapidFire 300. Mass spectrometric analysis is performed using an API-4000 triple quadrupole mass spectrometer in positive SRM mode[1].

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Animal experiment:

Mice[1]Male C57BL/6J mice (20-25 g) are used in the OFTT study. The animals are fed with standard chow and tap water ad libitum, maintained at 23±3 °C with a constant humidity of 40-70%, and acclimated with a cycle of 12 h of light and 12 h of darkness. Overnight fasted mice are orally treated with a single dose of 3, 10 and 30 mg/kg body weight of MGAT2-IN-2. At 6 h after the treatment of MGAT2-IN-2, mice are orally given 8 mL/kg olive oil or water.

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References:

[1]. Sato K, et al. Discovery of a Novel Series of N-Phenylindoline-5-sulfonamide Derivatives as Potent, Selective, and Orally Bioavailable Acyl CoA:Monoacylglycerol Acyltransferase-2 Inhibitors. J Med Chem. 2015 May 14;58(9):3892-909.
[2]. Sato K, et al. Optimization of a novel series of N-phenylindoline-5-sulfonamide-based acylCoA:monoacylglycerol acyltransferase-2 inhibitors: Mitigation of CYP3A4 time-dependent inhibition and phototoxic liabilities. Bioorg Med Chem. 2015 Aug 1;23(15):4544-60.

Background

MGAT2-IN-2 is a potent and selective acyl CoA:monoacylglycerol acyltransferase 2 (MGAT2) inhibitor with an IC50 of 3.4 nM.

MGAT2-IN-2 (Compound 24d) exhibits potent MGAT2 inhibitory activity with an IC50 value of 3.4 nM and a ligand lipophilicity efficiency (LLE) value of 5.4[1]. MGAT2-IN-2

(Compound 2) exhibits time-dependent inhibition (TDI) of cytochrome P450 3A4 (CYP3A4). Preincubation of MGAT2-IN-2 with microsomes leads to a significant loss of the activity of CYP3A4 relative to that under a condition without preincubation[2].

Effect of MGAT2-IN-2 on plasma TG is elevated during the oral fat tolerance test in C57BL/6J mice. MGAT2-IN-2 (3, 10 and 30 mg/kg) is orally administered 6 h prior to oil challenge. Pharmacokinetic studies reveal that MGAT2-IN-2 displays a high plasma concentration (AUC0-8h=842 ng•h/mL) and favorable oral bioavailability (F=52%), which are probably driven by the improved stability against oxidative metabolism and hydrolysis. For evaluating the in vivo efficacy, MGAT2-IN-2 is examined for its effect on hypertriglyceridemia during oral fat tolerance test (OFTT) using C57BL/6J mice. To inhibit the hydrolysis of plasma triacylglycerol (TG) by lipoprotein lipase (LPL), mice are pretreated with an LPL inhibitor, Pluronic F127, permitting measurement of the accumulation of plasma TG following olive oil administration. MGAT2-IN-2 and vehicle are administered 6 h before the oral olive oil load, and plasma chylomicron TG concentrations are monitored for 4 h. MGAT2-IN-2 effectively and dose-dependently suppresses plasma TG elevation after olive oil challenge. The TG-lowering effect of MGAT2-IN-2 is significant (p

[1]. Sato K, et al. Discovery of a Novel Series of N-Phenylindoline-5-sulfonamide Derivatives as Potent, Selective, and Orally Bioavailable Acyl CoA:Monoacylglycerol Acyltransferase-2 Inhibitors. J Med Chem. 2015 May 14;58(9):3892-909. [2]. Sato K, et al. Optimization of a novel series of N-phenylindoline-5-sulfonamide-based acylCoA:monoacylglycerol acyltransferase-2 inhibitors: Mitigation of CYP3A4 time-dependent inhibition and phototoxic liabilities. Bioorg Med Chem. 2015 Aug 1;23(15):4544-60.