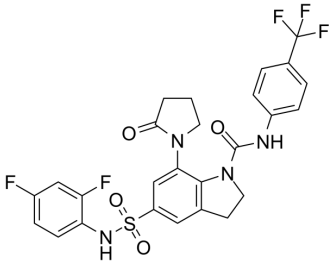
MGAT2-IN-2

Cat. No.:	HY-U00430
CAS No.:	1710630-11-7
Molecular Formula:	$C_{26}H_{21}F_5N_4O_4S$
Molecular Weight:	580.53
Target:	Acyltransferase
Pathway:	Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	MGAT2-IN-2 is a potent and selective acyl CoA:monoacylglycerol acyltransferase 2 (MGAT2) inhibitor with an IC_{50} of 3.4 nM.
IC_{50} & Target	MGAT2 3.4 nM (IC_{50})
In Vitro	MGAT2-IN-2 (Compound 24d) exhibits potent MGAT2 inhibitory activity with an IC_{50} 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]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	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 (AUC_{0-8h}=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 ($p<0.025$) at doses of 10 and 30 mg/kg. A similar effect of reducing the rate of fat entrance into the circulation is observed in MGAT2 gene knockout mice[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1]	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.

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

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.

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