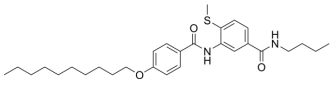
RP-64477

Cat. No.:	HY-16437
CAS No.:	135239-65-5
Molecular Formula:	$C_{29}H_{42}N_2O_3S$
Molecular Weight:	498.72
Target:	Acyltransferase
Pathway:	Metabolic Enzyme/Protease
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 8.33 mg/mL (16.70 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.0051 mL	10.0257 mL	20.0513 mL
	5 mM	0.4010 mL	2.0051 mL	4.0103 mL
	10 mM	0.2005 mL	1.0026 mL	2.0051 mL

Please refer to the solubility information to select the appropriate solvent.

BIOLOGICAL ACTIVITY

Description

RP-64477 is a potent inhibitor of the cholesterol esterifying enzyme Acyl-coenzyme A:cholesterol O-acyltransferase (ACAT).

IC_{50} & Target

ACAT[1]

In Vitro

RP-64477 is a potent inhibitor of the cholesterol esterifying enzyme Acyl-coenzyme A:cholesterol O-acyltransferase (ACAT). Inhibitory potencies of RP-64477 in vitro in tissue preparations are obtained from a range of species and in human cell cultures. For animal tissues, IC_{50} values in the range 6 to 283 nM are recorded, with no obvious species/tissue differences apparent. Potent inhibitory activity of RP-64477 is also recorded in human cell lines of hepatic (HepGZ), intestinal (CaCo-2), and monocytic (THP-1) origin with IC_{50}s of 503, 113, and 180 nM, respectively. No inhibitory activity is recorded against rat PCEH or LCAT at test concentrations up to 200 μM and 20 μM, respectively[1].

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

In Vivo

Administration of RP-64477 (0.01% and 0.03% w/w by diet) reduces significantly plasma cholesterol levels in cholesterol/cholic acid-fed rats by 29% and 61%, respectively. Food consumption is not affected by dietary incorporation of RP-64477. Animals receiving RP-64477 (10 and 30 mg/kg b.i.d.) over this period exhibit significantly lower plasma cholesterol

	levels on both days 4 and 7 when compare to values recorded from vehicle treated animals fed the cholesterol-containing diet. Compare to cholesterol-fed controls, after 7 days of dosing, plasma cholesterol levels are 35% and 53% lower in animals receiving 10 and 30 mg/kg b.i.d. doses of RP-64477, respectively[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [1]	ACAT activity is determined in CaCo-2 cells. Cells cultured in 6-well plates are preincubated for 2 hr in 2 mL of Medium 199 supplemented with 10 mM Hepes, pH 7.4, and cholesterol-rich micelles in the presence or absence of RP-64477 that has been initially prepared in neat DMSO. The final concentration of DMSO in the culture medium is 0.2% v/v. Preincubation medium is then replaced with the same medium containing 50 μM [^{14}C] oleic acid complexed with 17 μM bovine serum albumin (fatty acid-free) and cells incubated for a further 2 hr. RP-64477 or vehicle is present during both incubations[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Hypocholesterolaemic activity of RP-64477 is investigated by administering RP-64477 (0.00l% to 0.03% w/w by diet) to rats maintained for 3 days on powdered laboratory diet supplemented with cholesterol/cholic acid. Animals are then killed by asphyxiation in carbon dioxide, and terminal blood samples taken by cardiac puncture into a heparinised syringe for preparation of plasma. Plasma cholesterol concentrations are determined enzymatically using standard assay kits. Hypocholesterolaemic activity of RP-64477 in rabbits is investigated by administering RP-64477 at doses of 1, 3, 10, and 30 mg/kg b.i.d. for 7 days to animals receiving standard laboratory diet supplemented with cholesterol. Blood samples are obtained from the central ear artery on days 0 (predosing), 4, and 7 of the study[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Bello AA, et al. RP 64477: a potent inhibitor of acyl-coenzyme A:cholesterol O-acyltransferase with low systemic bioavailability. Biochem Pharmacol. 1996 Feb 23;51(4):413-21.

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