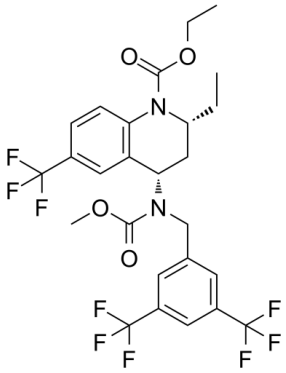
Data Sheet

Product Name:	Torcetrapib
Cat. No.:	CS-3497
CAS No.:	262352-17-0
Molecular Formula:	C26H25F9N2O4
Molecular Weight:	600.47
Target:	CETP
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 100 mg/mL (166.54 mM)



BIOLOGICAL ACTIVITY:

Torcetrapib(CP-529414) is a CETP inhibitor with IC50 of 37 nM, elevates HDL-C and reduces nonHDL-C in plasma. IC50 value: 37 nM [1] Target: CETP inhibitor in vitro: Torcetrapib dose-dependently increases aldosterone release from H295R cells after either 24 or 48 h of treatment with an EC50 of approximately 80 nM, this effect is mediated by calcium channel as calcium channel blockers completely blocks torcetrapib-induced corticoid release and calcium increase. Torcetrapib (1 μM) significantly increases the expression of steroidogenic gene, CYP11B2 and CYP11B1, in H295R cell lines [2]. in vivo: Torcetrapib (< 100 mg, daily) changes the plasma distribution of CETP, as the apparent molecular weight of the CETP has shifted to a larger form, by 2 hours after the dose in healthy young subjects. Torcetrapib treatment with 10 mg, 30 mg, 60 mg, and 120 mg daily and 120 mg twice daily results in 16%, 28%, 62%, 73%, and 91% increases in plasma HDL-C, respectively, with no significant changes in TPC in healthy young subjects. [1] Torcetrapib results in an increase of 72.1% in high-density lipoprotein cholesterol and a decrease of 24.9% in low-density lipoprotein cholesterol, in addition to an increase of 5.4 mm Hg in systolic blood pressure, a decrease in serum potassium, and increases in serum sodium, bicarbonate, and aldosterone, in patients at high cardiovascular risk after 12 months' treatment [3]. Torcetrapib (90 mg/kg/day) results in a 70% inhibition of CE transfer in rabbits fed an atherogenic diet. Torcetrapib (90 mg/kg/day) increases mean HDL-C levels by above 3-fold and apoA-I levels by 2.5-fold in plasma in rabbits fed an atherogenic diet. Torcetrapib-treated animal has a multiple-fold increase in HDL-C AUC and a corresponding reduction in aortic lesion area with 60% reduction of aortic free cholesterol (FC) and cholesteryl ester (EC) in rabbits fed an atherogenic diet. Torcetrapib-treated rabbits stimulate free cholesterol efflux to a significantly greater extent than does sera from control rabbits [4].

PROTOCOL (Extracted from published papers and Only for reference)

Enzyme assay(CETP Activity) [1]: For determination of plasma CETP activity, transfer of 3H-CO from HDL to the nonHDL plasma fraction and from 14C-CO-labeled LDL to HDL are determined simultaneously. For in vitro assay, tracer levels of 3H-HDL and 14C-LDL are added to plasma and the samples incubated for 1.5, 2.25, and 3 hours in quadruplicate; after which, the nonHDL fraction is precipitated by adding an equal volume of 20% (wt/vol) PEG8000, and radioactivity in the HDL containing supernatant is determined by scintillation counting. The fraction of CE transferred is calculated from the loss of 3H- and 14C-radioactivity from the HDL and nonHDL fractions, respectively, relative to the non-incubated zero time sample, by the method of Pattnaik based on first-order isotope kinetics. To determine if the single exponential decay function is sufficient for calculating relative inhibition, plasma and HDL free and total cholesterol are measured and CE is calculated by subtracting free from total. This allowed the actual specific activity of 3H-HDL-CE and 14C-nonHDL-CE at each time point to be determined, and it therefore eliminated error caused by dissolution of specific activity through exchange. In this case, the decay rate for label divided by the specific activity produced the transfer rate (nmol/h) that, on integration, gives the nmol of CE transferred per time period. The percent inhibition, relative to control, is calculated using data for the linear portion of the transfer curve. The near equivalence of demonstrated that for the purposes of the clinical trial, the former method would be sufficient. Animal adminstration [4]: Rabbits (n = 47) were fed an atherogenic diet (0.2% cholesterol, 10% coconut

oil, and 1.2% ethyl lactate) (Harlan-Teklad, Madison, WI) for 5 days and assigned to one of the treatment groups based on their total plasma cholesterol (TPC) responses (n = 23 or 24 per group). Control animals continued consuming the cholesterol-containing diet for an additional 16 weeks; the treated group was fed the same diet but with increasing amounts of torcetrapib [0.15, 0.3, and 0.6% (w/w), 1 week at each dose] to identify the dose necessary to achieve at least 3-fold increases of HDL. Despite the fact that the targeted level of HDL-C increase was achieved at the 0.15% dose level, the dose-escalation phase of the experiment was completed as initially planned. Because of the known variability of rabbits to an atherogenic diet, we were unsure that the starting dose of torcetrapib would maintain HDL-C levels at greater than three times control levels throughout the study. After dose escalation, rabbits were returned to the 0.15% dose level for the remaining 13 weeks of the study. This level of dietary feeding equated to ~90 mg/kg/day torcetrapib at the start of the study, gradually declining as the rabbits gained weight to 60-65 mg/kg/day by the end of the study. There was no difference in body weight or food consumption in torcetrapib-treated rabbits relative to controls.

References:

[1]. Clark RW, et al. Raising high-density lipoprotein in humans through inhibition of cholesteryl ester transfer protein: an initial multidose study of torcetrapib. Arterioscler Thromb Vasc Biol. 2004 Mar;24(3):490-7.

[2]. Hu X, et al. Torcetrapib induces aldosterone and cortisol production by an intracellular calcium-mediated mechanism independently of cholesteryl ester transfer protein inhibition. Endocrinology. 2009 May;150(5):2211-9.

[3]. Barter PJ, et al. Effects of torcetrapib in patients at high risk for coronary events. N Engl J Med. 2007 Nov 22;357(21):2109-22.

[4]. Morehouse LA, et al. Inhibition of CETP activity by torcetrapib reduces susceptibility to diet-induced atherosclerosis in New Zealand White rabbits. J Lipid Res. 2007 Jun;48(6):1263-72.

CAIndexNames:

1(2H)-Quinolinecarboxylic acid, 4-[[[3,5-bis(trifluoromethyl)phenyl]methyl](methoxycarbonyl)amino]-2-ethyl-3,4-dihydro-6-(trifluoromethyl)-, ethyl ester, (2R,4S)-

SMILES:

O=C(N1[C@H](CC)C[C@H](N(CC2=CC(C(F)(F)F)=CC(C(F)(F)F)=C2)C(OC)=O)C3=C1C=CC(C(F)(F)F)=C3)OCC

Tel: 732-484-9848 Fax: 888-484-5008 E-mail: sales@ChemScene.com

Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA