Torcetrapib (CP-529414) Datasheet

Technical Data

<table>
<thead>
<tr>
<th>Molecular Weight (MW)</th>
<th>600.47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula</td>
<td>C26H12F3N2O4</td>
</tr>
<tr>
<td>CAS No.</td>
<td>262352-17-0</td>
</tr>
<tr>
<td>Synonyms</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Solubility (25°C)

- DMOS 120 mg/mL
- Water <1 mg/mL
- Ethanol 90 mg/mL

Storage

- 2 years -20°C Powder
- 2 weeks 4°C in DMOS
- 6 months -80°C in DMOS

Biological Activity

**Description**
Torcetrapib (CP-529414) inhibits CETP with IC50 of 13 nM.

**Targets**
CETP

**IC50**
37 nM[^1]

**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 aldosterone 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%, 26%, 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 increases HDL cholesterol levels by 50% and 60% at dose of 60 mg daily and 120 mg daily, respectively, in both healthy and moderately hyperlipidemic subjects. Torcetrapib 60 mg daily increases HDL-mediated net cholesterol efflux from foam cells primarily by increasing HDL concentrations, whereas 120 mg daily torcetrapib increases cholesterol efflux both by increasing HDL concentration and by causing increased efflux at matched HDL concentrations.[^4] 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 cholesterol 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.[^5]

Clinical Trials
Torcetrapib is in phase 3 clinical study in patients with Hyperlipidemia.

Features
Torcetrapib is a CETP inhibitor, and CETP normally transfers cholesterol from HDL cholesterol to very low density lipoprotein.

Protocol (Only for Reference)

**Animal Study[^5]**

**Animal Models**
Male New Zealand White rabbits feed with an atherogenic diet

**Formulation**
Dietary feeding

**Doses**
90 mg/kg/day

**Administration**
Dietary feeding

References


**Biological Activity**

**Description**
Torcetrapib (CP-529414) inhibits CETP with IC50 of 13 nM.

**Targets**
CETP
CETP (human plasma)

**IC50**
13 nM[^1]

-50 nM[^2]

Torcetrapib is a CETP inhibitor, and CETP normally transfers cholesterol from HDL cholesterol to very low density lipoprotein.
Torcetrapib (CP-529414) Datasheet | Buy Torcetrapib (CP-529414) from supplier Selleckchem.com

In vitro

- Torcetrapib evokes an acute increase in blood pressure and an acute increase in plasma adrenal steroids. The acute pressor response to Torcetrapib is not mediated by adrenal steroids but is dependent on intact adrenal glands. Administration of Torcetrapib (20 mg/kg) by i.v. infusion for 30 minutes evokes a significant increase in plasma adrenal from baseline values to those measured 20 minutes post initiation of Torcetrapib infusion and remained elevated for 30 minutes after completion of the infusion. Compared to vehicle, high-fat-fed mice treated with Torcetrapib (30 mg/kg/day, 3 weeks) shows increased HDL-c levels and HDL-c/TC ratio by 41% and 37% (both p < 0.05). Torcetrapib increases in vitro macrophage cholesterol efflux by 22% and in vivo RCT through a 118% increase in (3) H-bile acids fecal excretion after (3) H-cholesterol labeled macrophage injection (p = 0.01 for both). Fecal total bile acids mass is also increased by 158% (p < 0.001).

- Clinical Trials
- Features

Torcetrapib, which is created by Pfizer, halted in 2006 when phase III studies showed excessive all-cause mortality in the treatment group receiving a combination of atorvastatin (Lipitor) and Torcetrapib.

Protocol (Only for Reference)

Kinase Assay:

- The reaction mixture typically included 1 × CETP buffer, 2.7 ng/μL donor particles (expressed as protein), 30.2 ng/μL acceptor lipoproteins, and 34 nM recombinant CETP (rCETP) in a final volume of 150 μL. Torcetrapib are supplied as dimethyl sulfoxide (DMSO) solutions at a final concentration of not more than 2% in DMSO. Due to the highly hydrophobic nature of many reported and likely prospective CETP inhibitors, human serum is also included in the assay cocktail at a final concentration of 2% to act as a solubilant. The endogenous CETP present in this added serum is insufficient to produce a noticeable additional signal to that supplied by the rCETP under the conditions of assay. An assay cocktail containing rCETP, human serum, and 1 × CETP buffer is prepared, and 100 μL is added to the wells of a Dynex Microfluor 2 U-bottom black 96-well plate. When desired, a test inhibitor is introduced to this mix in DMSO and allowed to incubate at 25 μL for 1 hour. A second assay cocktail containing donor particles, acceptor lipoproteins, and 1 × CETP buffer is prepared, and 50 μL is added to the wells of the wells lacking rCETP protein are used as a blanking standard. In practice, these wells show no background rate. Over the course of the assay, the kinetic progress curve appears as a continuously breaking line. Initial rates expressed in relative fluorescence units per second for the approximately linear portion of the curve, often 0–500 to 1000 seconds, are derived and compared with those of DMSO controls so as to calculate percent inhibitions according to the following formula: (1 – [(sample – sample blank)/(DMSO control – DMSO control blank)]) * 100.

- For determination of plasma CETP activity, transfer of 3H-CO from HDL to the non-HDL plasma fraction and from 14C-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% (w/v) 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 and, in this case, by the method of 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. Therefore, CETP activity for clinical plasma samples is determined by the apparent percent inhibition relative to the unsupplemented control for each assay, the average of the 2 values is used, and is consistent with the actual percent inhibition value determined relative to the substrate-matched controls. Therefore, CETP activity for clinical plasma samples is determined by the
Torcetrapib (CP-529414) Datasheet | Buy Torcetrapib (CP-529414) from supplier Selleckchem.com

dual-label assay, performed in triplicate at zero time and after 3 hours of incubation. Analysis of the dose response is performed using the WinNonLin nonlinear estimation program (Pharsight, v3.2).

## Animal Study

**Animal Models**
- Sprague–Dawley rats (300–400 g body weight) with surgically implanted femoral artery and vein catheters.

**Formulation**
- Torcetrapib is dissolved in acetonitrile.

**Doses**
- 20mg/kg

**Administration**
- Torcetrapib is administered via i.v. infusion for 30 minutes.

## References


---

PLEASE KEEP THE PRODUCT UNDER -20°C FOR LONG-TERM STORAGE.

NOT FOR HUMAN, VETERINARY DIAGNOSTIC OR THERAPEUTIC USE

- Specific storage and handling information for each product is indicated on the product datasheet. Most Selleck products are stable under the recommended conditions. Products are sometimes shipped at a temperature that differs from the recommended storage temperature. Many products are stable in the short-term at temperatures that differ from that required for long-term storage. We ensure that the product is shipped under conditions that will maintain the quality, but save your shipping charges by using the most economical storage conditions for an overnight shipment. Upon receipt of the product, follow the storage recommendations on the product datasheet.