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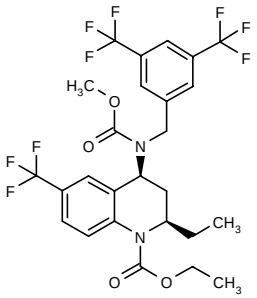
Torcetrapib

Prop INN; USAN

Atherosclerosis Therapy
Cholesteryl Ester Transfer Protein (CETP) Inhibitor

CP-529414

(2*R*,4*S*)-4-[*N*-[3,5-Bis(trifluoromethyl)benzyl]-*N*-(methoxycarbonyl)amino]-2-ethyl-6-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline-1-carboxylic acid ethyl ester



$C_{26}H_{25}F_9N_2O_4$
Mol wt: 600.4755
CAS: 262352-17-0
EN: 301547

Abstract

Atherosclerosis results from a deposition of fatty substances and cholesterol in the inner wall of arteries, and may lead to obstruction of the vessels, with resulting myocardial or cerebral infarction or peripheral vascular disease. The primary risk factor for atherosclerosis is an abnormally high level of cholesterol in the blood. High-density lipoprotein cholesterol (HDL-C), however, transports cholesterol away from the tissues and is considered to exert a protective effect. Cholesterol ester transfer protein (CETP) promotes the transfer of cholesteryl esters from HDL-C to proatherogenic apolipoproteins, and its inhibition has beneficial effects on the levels of HDL-C. The CETP inhibitor torcetrapib is in development for the treatment of atherosclerosis and lipoprotein disorders. In a rabbit model of atherosclerosis, torcetrapib inhibited CETP activity by 70-80% and elevated levels of HDL-C, which was associated with a reduction in atherosclerotic lesions. A multiple-dose study in healthy subjects showed significant, dose-dependent increases in HDL-C, up to 91% relative to placebo, after 14 days of treatment with torcetrapib. Clinical studies of torcetrapib in subjects with low levels of HDL-C treated with or without atorvastatin have also shown significant increases in HDL-C. The drug is currently in phase III clinical development as a combination with atorvastatin.

Synthesis

Torcetrapib can be obtained by several related ways:

1) Condensation of 4-trifluoromethylaniline (I) with propionaldehyde (II) using $TiCl_4$ as the dehydrating reagent and triethylamine in CH_2Cl_2 produces imine (III), which by subsequent Diels-Alder cycloaddition with benzyl *N*-vinylcarbamate (IV) by means of $BF_3.Et_2O$ in CH_2Cl_2 leads to tetrahydroquinoline (V). Acylation of compound (V) with ethyl chloroformate (VI) in the presence of pyridine in refluxing CH_2Cl_2 furnishes the bis-carbamate (VII), which is selectively deprotected at the benzyl carbamate group by transfer hydrogenolysis with cyclohexene and Pd/C in ethanol to yield *cis*-4-amino-2-ethyl-6-(trifluoromethyl)tetrahydroquinoline-1-carboxylic acid ethyl ester (VIII). Reductocondensation of compound (VIII) with 3,5-bis(trifluoromethyl)benzaldehyde (IX) and $NaBH(OAc)_3$ in dichloroethane provides the benzyl amine derivative (X), which is finally acylated with methyl chloroformate (XI) and pyridine in CH_2Cl_2, and the racemic mixture obtained is separated using chiral HPLC (1). Scheme 1.

2) Condensation of 4-trifluoromethylaniline (I) with propionaldehyde (II) and benzotriazole (XII) in toluene gives the secondary amine (XIII), which is cyclized with benzyl *N*-vinylcarbamate (IV) in the presence of *p*-toluenesulfonic acid in hot toluene to yield the tetrahydroquinoline (V). This is converted to the bis-carbamate (VII) by treatment with ethyl chloroformate (VI). Catalytic hydrogenolysis of the benzyl carbamate group of (VII) with ammonium formate and Pd/C in MeOH gives the racemic amine (VIII), which is resolved by formation of the diastereoisomeric salts with (–)-dibenzoyl tartrate to furnish the (2*R*,4*S*)-quinoline derivative (XIV). Reductocondensation of chiral amine (XIV) with 3,5-bis(trifluoromethyl)benzaldehyde (IX) by means of $NaBH(OAc)_3$ in dichloroethane provides the chiral benzylamine (XV). Finally, this compund is acylated with methyl chloroformate (XI) and Na_2CO_3 in THF (2, 3). Scheme 2.

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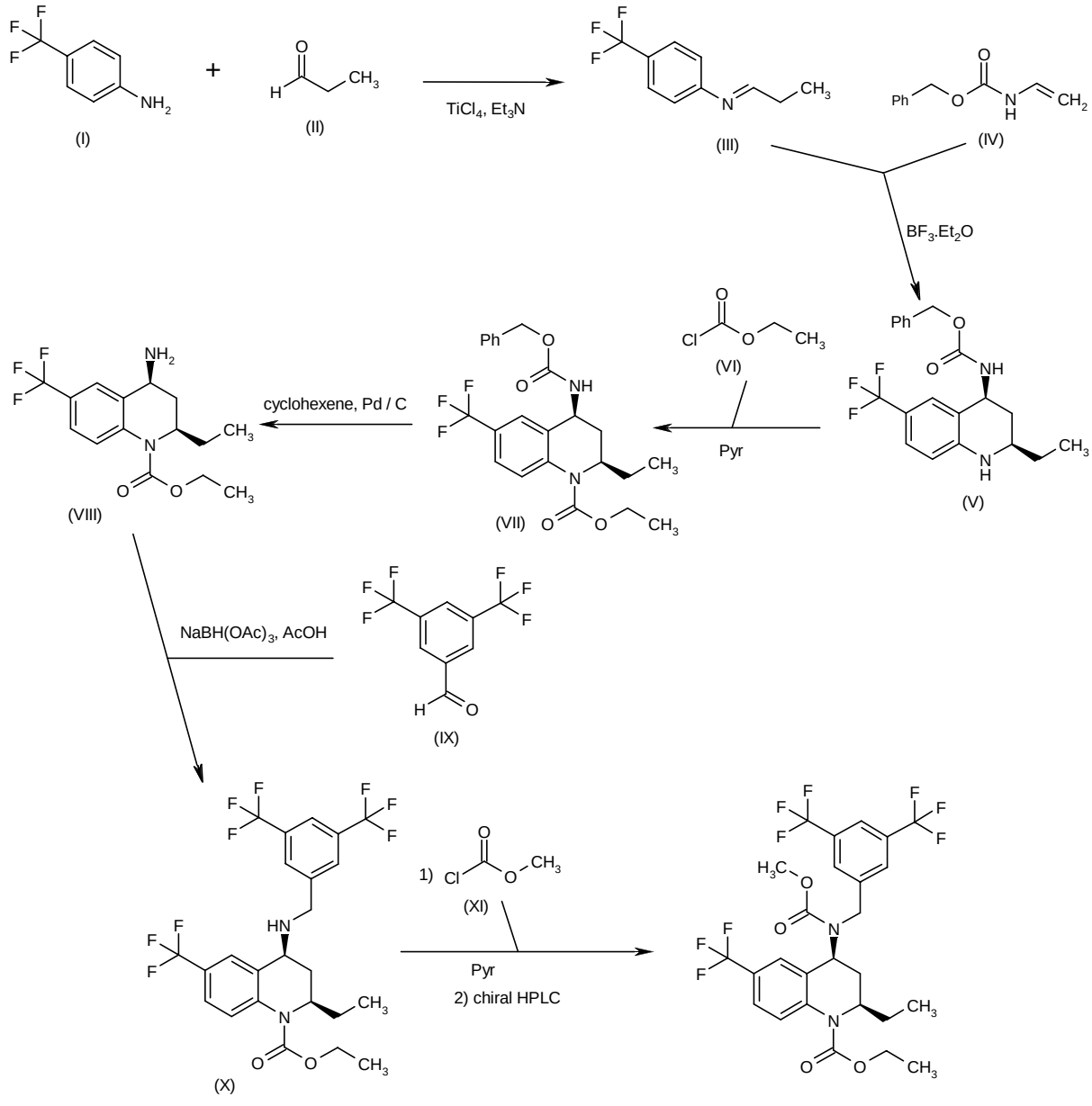
Scheme 1: Synthesis of Torcetrapib

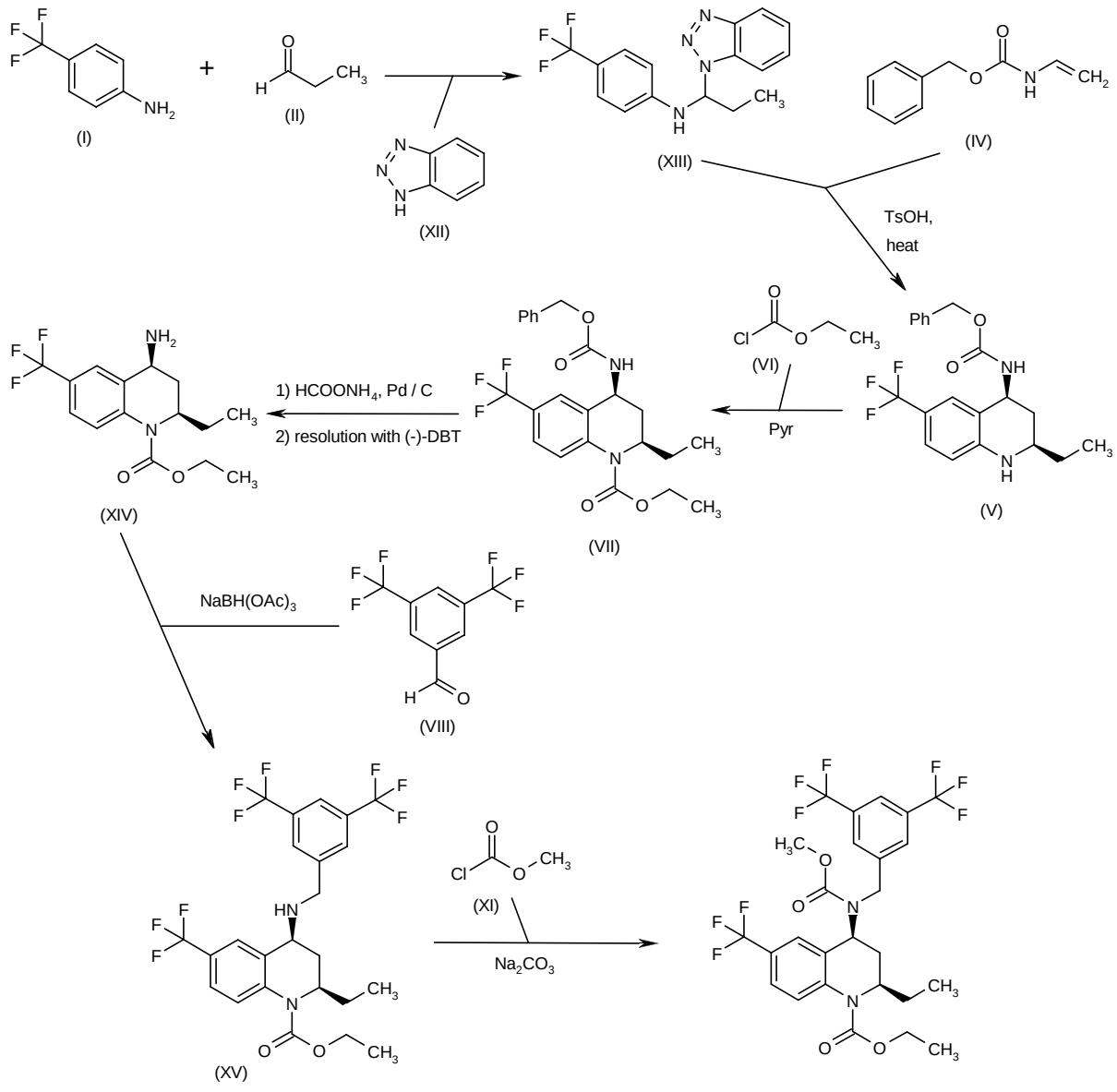


3) Condensation of 3(*R*)-aminopentanenitrile (XVI) with 1-chloro-4-(trifluoromethyl)benzene (XVII) in the presence of palladium and phosphine catalysts in toluene gives the chiral 3-anilinopentanenitrile (XVIII), which is submitted to acidic hydrolysis by means of H_2SO_4 in water to provide amide (XIX). Further acylation of amide (XIX) with methyl chloroformate (XI) and *t*-BuOLi in diisopropyl ether yields carbamate (XX), which is reduced with $NaBH_4$ in $EtOH/H_2O$, followed by intramolecular cyclization in the presence of $MgCl_2$ to afford the tetrahydroquinoline (XXI). Subsequent acylation of compound (XXI) with ethyl chloroformate (VI) and pyridine in CH_2Cl_2 affords the bis-carbamate (XXII), which is finally alkylated with 3,5-bis(trifluoromethyl)benzyl bromide (XXIII) by means of *t*-BuOK in CH_2Cl_2 (4, 5). Scheme 3.

Introduction

Atherosclerosis results from a build-up of fatty substances, cholesterol and other materials in the inner wall of medium-sized and large arteries. This deposition of

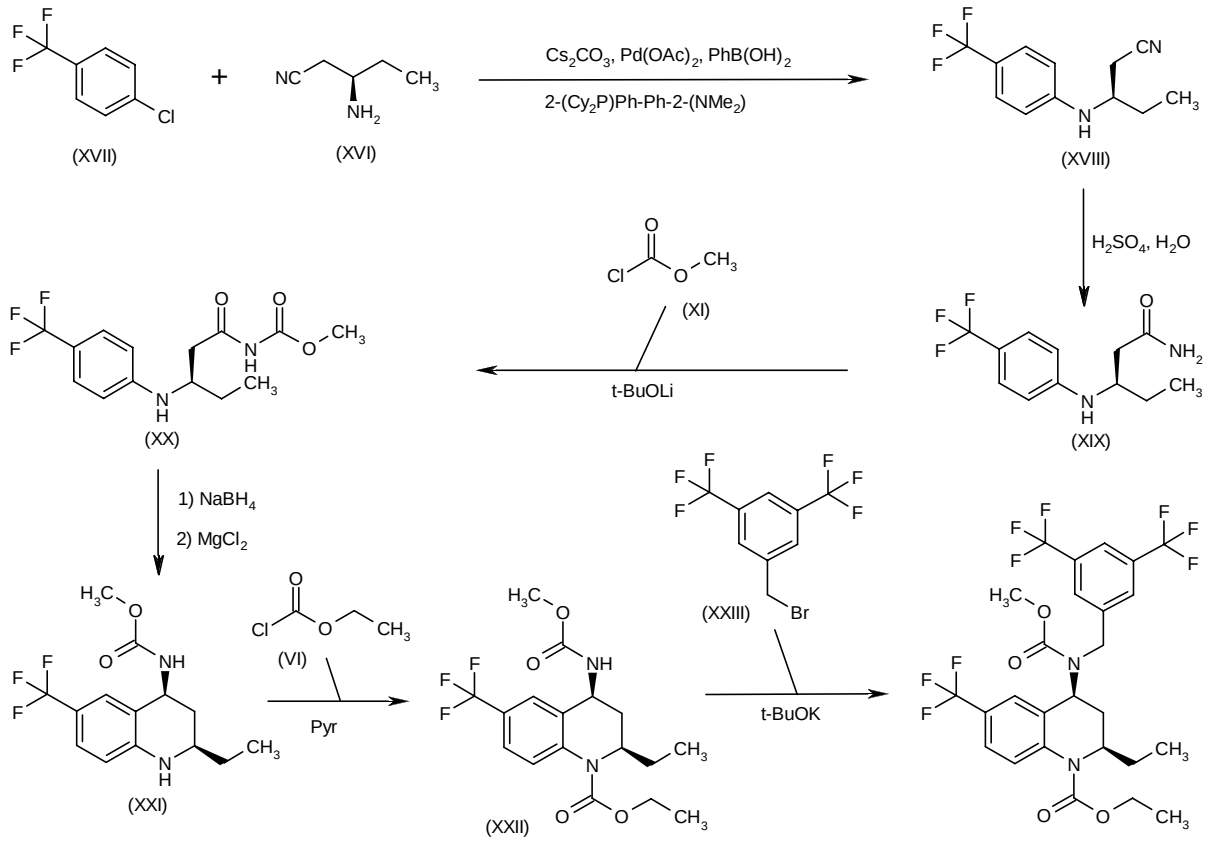
Scheme 2: Synthesis of Torcetrapib



plaque and subsequent inflammatory processes lead to further accumulation of cells in the arterial wall, which may result in eventual obstruction of the arterial vessels. Atherosclerosis leading to coronary artery disease can result in myocardial or cerebral infarction or peripheral vascular disease. The primary risk factor for atherosclerosis is an abnormally high level of cholesterol in the blood, but other established risk factors include diabetes mellitus, hypertension, obesity and smoking. Cardiovascular disease due to atherosclerosis is a major public health problem and is a leading cause of death in the U.S. and developing countries (6, 7).

In an effort to reduce morbidity and mortality from atherosclerosis, dietary recommendations exist for reducing levels of cholesterol and lipoproteins in the blood. Cholesterol is transported in the blood by three forms of lipoproteins: low-density lipoprotein (LDL), very-low-density lipoprotein (VLDL) and high-density lipoprotein (HDL). The latter transports cholesterol away from the tissues and to the liver, and is considered to exert a protective effect on the heart and circulation. Increasing the levels of HDL is thus a therapeutic goal in the treatment and prevention of atherosclerosis. Cholesterol ester transfer protein (CETP) is a glycoprotein secreted from

Scheme 3: Synthesis of Torcetrapib



the liver that promotes the transfer of cholesteryl esters from antiatherogenic HDL-C to the proatherogenic apolipoproteins VLDL and LDL. Thus, the inhibition of CETP represents a novel target for the treatment of atherosclerosis by means of its beneficial effects on levels of HDL-C (8). Torcetrapib (CP-529414) was identified from an active series of reversible CETP inhibitors and is in development for the treatment of atherosclerosis and lipoprotein disorders (9).

Pharmacological Actions

Torcetrapib was evaluated in a rabbit model of atherosclerosis. In rabbits fed an atherogenic diet for 16 weeks, concomitant torcetrapib treatment resulted in inhibition of CETP activity of 70-80% and elevated levels of HDL-C throughout the treatment period compared with controls (HDL-C = 207 mg/dl *vs.* 57 mg/dl at week 16). Assessments of preparations of unstained aortic tissue also showed that the percentage of aortic surface covered with lesions was 60% lower in torcetrapib-treated animals. The reduction in aortic atherosclerosis was significantly associated with elevated levels of HDL (10, 11).

Clinical Studies

The ability of torcetrapib to increase HDL-C levels was evaluated in a randomized, placebo-controlled, multiple-dose phase I study in healthy subjects aged 18-55 years. A total of 40 subjects were randomized to treatment with torcetrapib at doses of 10, 30, 60 or 120 mg once daily or 120 mg b.i.d. for 14 days. Two subjects per group received matching placebo. The extent and duration of CETP inhibition increased with increasing dose, and modeling of the plasma concentration *versus* percent inhibition data for all subjects on day 1 indicated an EC_{50} value of 43 nM, consistent with *in vitro* data for human plasma. There were significant increases in HDL-C, expressed as the mean of individual percent changes from baseline, relative to placebo at all doses after 14 days. The increases were dose-dependent, ranging from 16% in the 10 mg once daily group to 91% in the 120 mg b.i.d. group. A reciprocal decrease in LDL-C was observed (21% with 120 mg once daily and 42% with

120 mg b.i.d.). Consequently, there was a significant decrease in the LDL-C/HDL-C ratio for doses of 30 mg and greater. In the non-HDL plasma fraction, cholesteryl ester content decreased and triglycerides increased, with contrasting changes observed in the HDL fraction. Torcetrapib was well tolerated, with no serious treatment-related adverse events reported (12).

The effect of torcetrapib on plasma lippoprotein levels was evaluated in a single-blind, placebo-controlled study in 19 subjects with low levels of HDL-C. Nine subjects were treated concomitantly with atorvastatin 20 mg daily. All subjects received placebo for 4 weeks, followed by torcetrapib 120 mg once daily for 4 weeks. Six subjects (not receiving atorvastatin) were treated with torcetrapib 120 mg b.i.d. for a further 4 weeks. Torcetrapib significantly increased plasma HDL-C levels measured at the end of each treatment period. Plasma levels were increased by 61% in patients receiving 120 mg once daily concomitantly with atorvastatin, and by 46% in patients who received torcetrapib alone. In subjects treated with 120 mg b.i.d. the increase was 106%. Plasma levels of the HDL apolipoproteins A-I (apoA-I) and A-II (apoA-II) were also significantly increased by torcetrapib. There were significant increases in cholesterol levels within large HDL particles, as assessed by nuclear magnetic resonance spectroscopy, in all groups, with a maximum 446% increase following the dose of 120 mg b.i.d. Further study to define the mechanisms responsible for the increased HDL levels revealed a normalization of apoA-I levels within α_1-migrating HDL and a delay in apoA-I catabolism. Torcetrapib was well tolerated, with no clinically significant changes in routine clinical or laboratory parameters. The most frequently reported adverse event was headache (13, 14).

The efficacy and safety of torcetrapib when administered with and without atorvastatin were also assessed in two phase II studies in subjects with low HDL-C levels. The studies were multicenter, randomized, double-blind, placebo-controlled trials evaluating torcetrapib doses of 10, 30, 60 or 90 mg daily for 8 weeks. In the first study (n=162), subjects were not taking any concomitant lipid-modifying therapy. In this study, there was a significant increase in HDL-C relative to placebo at week 8 for all torcetrapib doses above 30 mg (54.5% at 90 mg/day). In the second study, subjects (n=174) received atorvastatin 20 mg daily during an 8-week run-in period and concomitantly with torcetrapib. Significant increases in HDL-C relative to placebo at week 8 were also observed, with a maximum increase of 40.2%. Significant decreases in LDL-C were also observed at the higher doses in both studies and were more homogeneous with concomitant atorvastatin treatment. Particle size for both HDL and LDL increased with torcetrapib. The drug was generally well tolerated in both studies, with no dose-related increases in adverse events (15).

A recent study investigated the inhibition of 9 genetic variants of CETP by torcetrapib and found no significant differences in inhibition. Three separate clinical populations comprising 3,560 individuals were examined, and the results were consistent with the relatively uniform level of inhibition observed in clinical trials (16).

Pfizer has decided to develop the drug in combination with atorvastatin and large phase III trials are now in progress, with results expected in 2007 (17-20).

Source

Pfizer, Inc. (US).

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