The present invention relates to novel intermediate or its salt and its use in the preparation of anacetrapib.

Claims:


Abstract:

Title: PROCESS FOR PREPARATION OF ANACETRAPIB AND INTERMEDIATES THEREOF

The present invention relates to novel intermediate or its salt and its use in the preparation of anacetrapib.
PROCESS FOR PREPARATION OF ANACETRAPIB AND INTERMEDIATES THEREOF

PRIORITY
This application claims the benefit to Indian Provisional Application No. 158/MUM/2013, filed on January 17, 2013 and United States Provisional Application No. 61/772,542 filed on March 05, 2013 the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION
The present invention relates to a novel process for the preparation of anacetrapib or salt thereof. More particularly the present invention relates to novel intermediate or its salt and its use in the preparation of anacetrapib.

BACKGROUND OF THE INVENTION
Anacetrapib is chemically known as 5(R)-[3,5-Bis(trifluoromethyl)phenyl]-3-[4'-fluoro-5'-isopropyl-2-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-4(S)-methyloxazolidin-2-one, and has the following structural Formula I:

\[
\text{Formula I}
\]

Anacetrapib is a cholesterylester transfer protein (CETP) inhibitor being developed to treat arteriosclerosis and hyperlipidemia.


We have now developed a novel process for the preparation of anacetrapib which is simple, reproducible and well suited on commercial scale. The instant application presents compounds, which are useful intermediates in this novel process.

**SUMMARY OF THE INVENTION**

The present invention provides a process for the preparation of anacetrapib, a compound of formula I,

![Formula I](image)

comprising: cyclizing a compound of formula II.

![Formula II](image)

The present invention provides a compound of formula III or salt thereof.

![Formula III](image)
The present invention provides use of the compounds of formula II and formula III or salt thereof in the preparation of anacetrapib.

**DETAILED DESCRIPTION OF INVENTION**

As mentioned above, the present invention is directed to a novel process for the preparation of anacetrapib.

In one embodiment, the present invention relates to process for the preparation of anacetrapib, a compound of formula I.

**Formula I**

comprising: cyclizing a compound of formula II.

**Formula II**

Suitable cyclizing agent is selected from the group consisting of 1-hydroxybenzotriazole (HOBT), 1. 8-diazabicyclo[5.4.0]undec-7-ene (DBU), carbonyldiimidazole (GDI), diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), propylphosphonic anhydride (T3P), 4,5-dicyanoimidazole, dicyclopentyl carbodiimide and the like or mixtures thereof. Preferably carbonyldiimidazole (CDI).
The cyclization of compound of formula II may be carried out in the presence of a solvent. A suitable solvent may be selected from ether such as diethyl ether, diisopropyl ether, methyl tert-butyl ether, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, anisole and the like; polar solvent such as dimethylformamide, dimethylsulfoxide, dimethyl acetamide and the like; ester such as ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate and the like; hydrocarbon and their halogenated derivatives such as toluene, benzene, xylene, pentane, hexane, heptane, cyclohexane, methylene dichloride, ethylene dichloride; alcohol such as methanol, ethanol, isopropanol, isobutanol, n-butanol, diethylene glycol, cyclohexanol, phenol, glycerol and the like; ketone such as acetone, methyl ethyl ketone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone and the like; nitrile such as acetonitrile, propionitrile and the like, water or mixtures thereof.

Suitable temperature that may be used may be less than about 130 °C, preferably less than about 100 °C, more preferably less than about 80 °C.

The cyclization of compound of formula II may be carried out in the presence or an absence of base. A suitable base may be selected from organic or inorganic base. The inorganic base may be selected from the group consisting of hydroxides such as sodium hydroxide, potassium hydroxide, calcium hydroxide; alkoxides such as sodium methoxide, potassium methoxide, sodium tert-butoxide, potassium tert-butoxide; carbonates such as sodium carbonate, potassium carbonate; bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like. The organic base may be selected from triethyl amine, trimethyl amine, diisopropyl ethylamine, dimethyl amino pyridine, picoline, dimethyl amino pyridine and pyridine and the like aqueous mixtures thereof.

Optionally the compound of formula I, may be further purified by column chromatography, recrystallization, slurrying in a suitable solvent, acid-base treatment, treating with adsorbent materials such as, but not limited to silica gel, aluminium oxide, synthetic resin and the like; any other suitable techniques.

The compound thus obtained may be recovered as solid using conventional methods including decantation, centrifugation, filtration, or others techniques known in the art.
In one embodiment, the compound of formula I, may be in the form of an amorphous compound, a solvate, a crystalline compound, or a mixture thereof.

In one embodiment, the present invention provides anacetrapib obtained by the process herein described is amorphous compound.

In one embodiment, the present invention provides anacetrapib solvate.

Suitable solvate of anacetrapib include, but not limited to alcohol such as methanol, ethanol, isopropanol, butanol, diethylene glycol and the like; hydrocarbon such as methylene chloride, ethylene dichloride and the like; ether such as diethyl ether, diisopropyl ether, methyl ter-butyl ether, tetrahydrofuran and the like.

In one embodiment, the present invention provides pure amorphous anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 90% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 80% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 70% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 60% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 50% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 40% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 30% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 20% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 10% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 5% crystalline anacetrapib.
crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 3% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 2% crystalline anacetrapib.

In one embodiment, the present invention provides amorphous anacetrapib, having less than 1% crystalline anacetrapib.

In one embodiment, the present invention provides pure crystalline anacetrapib.

In one embodiment, the present invention provides a process for the preparation of a compound of formula II.

\[
\text{Formula II}
\]

comprising: a) reacting a compound of formula IV,

\[
\text{Formula IV}
\]

with a compound of formula XIII,

\[
\text{Formula XIII}
\]
to form a compound of formula III; and

b) reacting the compound of formula III,

with a reducing agent to form a compound of formula II.

Suitable solvent used in step a) is selected from alcohol such as methanol, ethanol, isopropanol, isobutanol, n-butanol, diethylene glycol, cyclohexanol, phenol, glycerol and the like, water or mixtures thereof. Preferably, isopropanol.

Suitable temperature that may be used in step a) may be less than about 100 °C, preferably less than about 70 °C, more preferably less than about 55 °C or any other suitable temperature thereof.
Suitable reducing agent used in step b) may be selected from the group consisting of alkali metal hydride, alkaline earth metal hydride, alkali metal borohydride, alkaline earth metal borohydride or hydrogen in presence or absence of hydrogenation catalyst.

The hydrides and borohydride may be selected from alkali metal hydride, alkaline earth metal hydride, alkali metal borohydride, alkaline earth metal borohydride such as sodium borohydride (NaBH₄), sodium triacetoxy borohydride, sodium cyanoborohydride, lithium aluminium hydride (LAH), diisobutylaluminium hydride (DIBAL-H), sodium bis (2- methoxyethoxy) aluminium hydride, tributyltin hydride and the like. Preferably, sodium borohydride (NaBH₄).

Suitable solvent used in step b) is selected from the group consisting of alcohol such as methanol, ethanol, isopropanol, isobutanol, n-butanol, diethylene glycol, cyclohexanol, phenol, glycerol and the like; ester such as ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate and the like; hydrocarbon and their halogenated derivatives such as pentane, hexane, heptane, cyclohexane, toluene, benzene, xylene, methylene dichloride, ethylene dichloride and the like; water or mixtures thereof.

Suitable temperature that may be used in step b) may be less than about 100 °C, preferably less than about 80 °C, more preferably less than about 50 °C or any other suitable temperature thereof.

The above reaction may be carried out in a presence or an absence of base. The base is as described supra.

Optionally the compound of formula II or compound of formula III, may be purified by recrystallization, column chromatography, slurrying in a suitable solvent, acid-base treatment, treating with adsorbent materials such as, but not limited to silica gel, aluminium oxide, synthetic resin and the like; any other suitable techniques.

The compound thus obtained may be recovered as solid using conventional methods including decantation, centrifugation, filtration, or others techniques known in the art.

In one embodiment, the compound of formula II, may be used as its acid addition salt. Suitable acid addition salts include, but not limited to, salts with inorganic acids such as hydrochloric
acid, hydrobromic acid, hydro iodic acid, sulphuric acid, nitric acid; organic acids such as formic acid, acetic acid, propanoic acid, tartaric acid, oxalic acid, maleic acid, mandelic acid, malonic acid, methane sulphonic acid, p-toluene sulphonic acid or trifluoroacetic acid or any other suitable acid.

In one embodiment, the present invention provides a process for the preparation of acid addition salt of compound of formula II, comprising reacting compound of formula II with acid addition salt.

In one embodiment, the compound of formula II, may be purified by crystallizing it in hydrocarbon solvent such as pentane, hexane, heptane, cyclohexane, toluene, benzene, xylene, methylene dichloride, ethylene dichloride and the like. Preferably, heptane.

In one embodiment, the present invention provides compound of formula II, obtained by the processes herein described, having purity more than about 98% as determined by High Performance Liquid Chromatography (HPLC).

In one embodiment, the compound of formula II or the compound of formula III, may be in the form of an amorphous compound, a solvate, a crystalline compound, or a mixture thereof.

In one embodiment, the process as immediately described above the compound of formula III is isolated.

In one embodiment, the process as immediately described above the compound of formula III is used in-situ and is directly converted to compound of formula II, without isolating a compound of formula III.

In one embodiment, the present invention provides a process for the preparation of a compound of formula III, comprising: reacting a compound of formula IV, with a compound of formula XIII.

In one embodiment, the present invention provides a process for the preparation of a compound of formula XIII,
comprising: hydrogenolysing a compound of formula XII,

The hydrogenolysis may be carried out by hydrogen in presence of hydrogenation catalyst, or hydrolysis using acid or base; or with any suitable techniques known in the art.

The hydrogenation catalyst may be selected from the group consisting of Raney nickel, palladium hydroxide, palladium carbon, platinum on carbon, platinum dioxide, palladium on calcium carbonate, or palladium on alumina.

Optionally, catalytic hydrogenation may be carried out in the presence of one or more suitable reagents. Suitable reagents that may be used include, but are not limited to acids, bases, resins and any mixtures thereof, either alone or as their solutions in water, organic solvent or their mixtures.

Suitable solvent for hydrogenolysis is selected from the group consisting of alcohol such as methanol, ethanol, isopropanol, isobutanol, n-butanol, diethylene glycol, cyclohexanol, phenol, glycerol and the like; ester such as ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl
propanoate, methyl butanoate, ethyl butanoate and the like; hydrocarbon such as pentane, hexane, heptane, cyclohexane, toluene, benzene, xylene, methylene dichloride, ethylene dichloride and the like; water or mixtures thereof.

Suitable temperature for hydrogenolysis may be less than about 100 °C, preferably less than about 80 °C, more preferably less than about 50 °C or any other suitable temperature thereof.

In one embodiment, a compound of formula XIII may be purified by crystallizing it in hydrocarbon solvent.

In one embodiment, the present invention provides a compound of formula XIII, obtained by the processes herein described, having purity more than about 97% as determined by High Performance Liquid Chromatography (HPLC).

In one embodiment, the present invention provides a compound of formula XIII, obtained by the processes herein described, having chiral purity more than about 99.9% as determined by chiral HPLC.

In one embodiment, the present invention provides a compound of formula XII, can be prepared by processes described in the art.

In one embodiment, the present invention provides a process for the preparation of compound of formula IV,

![Formula IV](image)

comprising: reacting a compound of formula V, with an oxidizing agent.
Suitable oxidizing agent may be selected from Dess-Martin Periodinane (DMP), palladium complex and the like. Preferably, Dess-Martin Periodinane (DMP).

Suitable solvent for oxidation may be selected from hydrocarbon and their halogenated derivatives such as pentane, hexane, heptane, cyclohexane, toluene, benzene, xylene, methylene chloride, ethylene dichloride and the like, water or mixtures thereof. Preferably, methylene chloride.

In one embodiment, the present invention provides a process for the preparation of compound of formula V, comprising: reacting a compound of formula VI,

with a compound of formula VII, in presence of catalyst.

Suitable catalyst include bis(triphenylphosphine) palladium(II)chloride and the like,

Suitable solvent is selected from the group consisting of alcohol, ester, hydrocarbon, water or mixtures thereof.

The above reaction may be carried out in a presence of base, as described supra.

In one embodiment, the present invention provides a compound of formula II or a salt thereof.
In one embodiment, the present invention provides a compound of formula II that exhibits a $^1$H NMR spectrum: $\delta$ 7.74-7.69 (d, 4H), 7.61-7.58 (d, 1H), 7.33-7.30 (d, 1H), 7.00-6.97 (d, 1H), 6.71-6.67 (d, 1H), 4.74 (d, 1H), 3.81 (s, 3H), 3.71 (d, 1H), 3.21 (m, 1H), 2.78 (m, 1H), 1.25-1.19 (m, 6H), 0.61-0.59 (d, 3H)

$^1$H NMR spectrum was recorded in CDCl$_3$ using Varian 300 MHz spectrometer.

In one embodiment, the present invention provides a compound of formula III or a salt thereof.

In one embodiment, the present invention provides a compound of formula III that exhibits a $^1$H NMR spectrum: $\delta$ 8.34 (s, 1H), 8.07 (s, 1H), 7.85-7.70 (m, 3H), 7.40 (s, 1H), 7.01 (s, 1H), 6.67 (s, 1H), 4.93 (s, 3H), 3.68 (s, 3H), 3.53 (m, 1H), 3.17 (m, 2H), 1.24 (d, 6H), 1.00 (d, 3H)

$^1$H NMR spectrum was recorded in CDCl$_3$ using Varian 300 MHz spectrometer.

In one embodiment, the present invention provides a compound of formula IIia or its isomer or salt thereof.
wherein \( R \) is selected from the group consisting of Ci-C\(_6\)alkyl, alkylaryl and arylalkyl.

In one embodiment, the present invention provides a compound of formula XIII or a salt thereof.

wherein \( R \) is selected from the group consisting of alkylaryl, aryl, alkyl, substituted aryl, p-toluene sulfonyl, methane sulphonyl, trifluoromethane sulphonyl, benzene sulphonyl and the like and \( R \) is alkyl.
The term "alkylaryl" as used herein, refers to an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of alkylaryl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, and 2-naphth-2-ylethyl.

The term "aryl" as used herein, refers to aromatic ring systems, which may include fused rings. Representative examples of aryl include, but are not limited to, phenyl, and naphthyl, anthracenyl.

The term "alkyl" as used herein includes a straight or branched chain hydrocarbon containing from 1 to 6 carbon atoms. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, tert- butyl, n-pentyl, isopentyl, neopentyl, n-hexyl.

The term "substituted aryl" as used refers to substituent on the aryl is present at one or more positions on the aryl ring, selected from the group consisting of halogen such as chloro, bromo, iodo, nitro, amino and the like.

In one embodiment, the present invention provides a compound of formula XIV or a salt thereof.

![Formula XIV]

In one embodiment, the present invention provides a compound of formula XVa or its isomer or salt thereof.
wherein R and R\textsubscript{i} is same as defined in formula XIVa.

In one embodiment, the present invention provides a compound of formula XV or a salt thereof.

Formula XV

In one embodiment, the present invention provides use of any of the compounds of formula III, formula IV, formula V, formula XI, formula XII, formula XIII, formula XIV/XIVa and formula XV/XVa or salt thereof in the preparation of anacetrapib.

In one embodiment, any of the compounds of formula II, formula III, formula IV, formula XIII, formula XIV and formula XV optionally, may be recrystallized or purified by solvent(s) selected from alcohols, esters, ethers, ketones, nitriles, hydrocarbons, polar solvents, water or mixtures thereof.

In one embodiment, the present invention provides a process for the preparation of a compound of formula I, as shown in Scheme 1:
In one embodiment, the present invention provides a process for purifying anacetrapib, a compound of formula I, comprising:

a) providing a solution of anacetrapib in a solvent or a mixture of solvents or their aqueous mixtures; b) crystallizing or precipitating the solid from the solution; and c) recovering the pure anacetrapib.

The solvent or mixture of solvents is selected from a C2-C5 nitrile, a C2-C6 ester, C3-C5 ketone, C1-C5 alcohol, cyclic ether, hydrocarbon solvents and their halogenated derivatives. The C2-C5 nitrile include acetonitrile, propionitrile and the like; C2-C6 ester include ethyl acetate, isopropyl acetate, isobutyl acetate, t-butyl acetate and the like; C3-C5 ketone include acetone, methyl ethyl ketone, ethyl methyl ketone and the like; C1-C5 alcohol include methanol, ethanol, isopropanol, isobutanol, 2-butanol; cyclic ether include tetrahydrofuran (THF), dioxane and the like;
hydrocarbon solvents and halogenated derivatives thereof may include pentane, n-hexane, heptane, cyclohexane, petroleum ether, m-, o-, or p-xylene, dichloromethane (MDC), chloroform, carbon tetrachloride, 1, 2-dichloroethane; polar solvent such as dimethylformamide, dimethylsulfoxide, dimethyl acetamide, water or mixtures thereof.

In one embodiment, the present invention provides a process for the purification of anacetrapib, a compound of formula I, comprising:

a) providing a solution of anacetrapib in a solvent or a mixture of solvents or their aqueous mixtures;
b) cooling the solution obtained in step a) at about 25°C to about -30°C to form a reaction mass;
c) optionally seeding the reaction mass with anacetrapib to precipitate the solid anacetrapib; and
d) isolating the pure anacetrapib.

The solvent used in step a) is selected from the group consisting of hydrocarbon and halogenated derivatives thereof may include pentane, n-hexane, heptane, cyclohexane, petroleum ether, m-, o-, or p-xylene, dichloromethane (MDC), chloroform, carbon tetrachloride, 1, 2-dichloroethane and ether include tetrahydrofuran (THF), dioxane and the like, or mixtures thereof.

In one embodiment, the present invention provides a process for the purification of anacetrapib, a compound of formula I, comprising:

a) dissolving anacetrapib in an organic solvent to form a solution; b) adding an anti-solvent to the solution obtained in step a) to precipitate the solid anacetrapib; and c) isolating the pure anacetrapib.

Temperature range for step a) and step b) from about -10°C to about 0°C

The organic solvent used in step a) is selected from the group consisting of alcohol, ketone, nitrile, ether, ester or mixtures thereof as discussed supra.

The anti- solvent used in step b) is selected from the group consisting of water, hydrocarbon or mixtures thereof.
In one embodiment, the present invention provides anacetrapib obtained by the processes herein described, having purity more than about 99.6% as determined by High Performance Liquid Chromatography (HPLC).

In one embodiment, the present invention provides anacetrapib obtained by the processes herein described, having chiral purity more than about 99.9% as determined by chiral HPLC.

In one embodiment, the present invention provides anacetrapib, where is one or more of compounds of formula II, III, IV, V, XI, XII, XIII, XIV and XV are present less than 0.15% w/w relative to the amount of anacetrapib as determined by HPLC.

In one embodiment, the present invention provides anacetrapib, obtained by the processes herein described, having individual impurities lower than about 1.0%, preferably lower than about 0.5%, more preferably lower than about 0.15%, most preferably below detection limit by a method known in the art.

In one embodiment, the present invention provides anacetrapib, having compound of formula II (genotoxic impurity) below 10 parts per million (ppm), preferably below 5 ppm.

In one embodiment, the present invention provides anacetrapib, having compound of formula VI (genotoxic impurity) below 10 parts per million (ppm), preferably below 5 ppm.

In one embodiment, the present invention provides anacetrapib, having compound of formula VII (genotoxic impurity) below 10 parts per million (ppm), preferably below 5 ppm.

In one embodiment the present invention provides anacetrapib, compound of formula I having surface area of from about 1 m$^2$/g to about 5 m$^2$/g as measured by Brunauer-Emmett-Teller (B.E.T) method.

In one embodiment the present invention provides anacetrapib, compound of formula I having a $D_{90}$ particle size of about 300 microns, $D_{50}$ particle size of about 100 microns and $D_{10}$ particle size of about 50 microns.

In one embodiment the present invention provides anacetrapib, compound of formula I having a $D_{90}$ particle size of about 200-microns, $D_{50}$particle size of about 65 microns and $D_{10}$ particle size of about 15 microns.
In one embodiment, the present invention provides pharmaceutical compositions comprising anacetrapib obtained by the processes herein described, having a D_{90} particle size of about 200 microns, D_{50} particle size of about 65 microns and D_{10} particle size of about 15 microns.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example 1: Preparation of Benzyl (lS)-l-methyl-2-morpholin-4-yl-2-oxoethylcarbamate (Formula IX)

In a clean round bottom flask, 50gm of (2S)-2-[[[(benzyloxy)carbonyl]amino propanoic acid (formula VIII), 500ml of tetrahydrofuran and 25.35 gm of morpholine were added at about 40-45°C under stirring. The mixture was stirred for about 2 hours at about the same temperature. The reaction mass was concentrated under vacuum to form an oily mass. To the obtained oily mass, 250ml of water and 250ml of ethyl acetate were added and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with 250ml of ethyl acetate. The first and second organic layers were combined and washed with dilute hydrochloric acid followed by water. Then, the resultant organic layer was concentrated under vacuum and 250ml of isopropyl ether was added. The reaction mixture was stirred for about 2 hours at about room temperature, then filtered, washed with isopropyl ether and dried to yield 50gm of titled compound as white solid.
Example 2: Preparation of Benzyl (1S)-1-methyl-2-morpholin-4-yl-2-oxoethylcarbamate (Formula IX)

In a clean round bottom flask, added 100gm of (2S)-2-[(benzyloxy)carbonyl]amino propanoic acid (formula VIII), to a solution of 84gm of 1,1'-Carbonyldiimidazole (CDI) in 700ml methylene chloride at about 0-5°C. Content was stirred for 30 min at about 0-5°C and added 46.82gm of morpholine. The mixture was stirred for about 2 hours at about 25-30°C. To the reaction mass 250ml of water was added and the organic layer was separated from the aqueous layer. The aqueous layer was extracted with 250ml methylene chloride. The first and second organic layers were combined and washed with 250ml water. Then, the resultant organic layer was concentrated under vacuum and 250ml of ethanol was added. The mixture was stirred for about 2 hours at about room temperature, then filtered, washed with isopropyl ether and dried to yield 110gm of titled compound as white solid.

Example 3: Preparation of Benzyl (1S)-2-[3,5-bis(trifluoromethyl)phenyl]-1-methyl-2-oxoethylcarbamate (Formula XI)

In a clean round bottom flask, 25gm of benzyl (1S)-1-methyl-2-morpholin-4-yl-2-oxoethylcarbamate (formula IX, obtained as in Example 1 or Example 2), 30gm of 1-bromo-3,5-bis(trifluoromethyl)benzene, 250ml of toluene and isopropyl magnesium chloride (150 ml 2.0 M solution in tetrahydrofuran) were added at about 0-5°C. The reaction mass was stirred for
about 2 hours and 125ml of water was added to the reaction mass at about 0-5°C. The organic layer was washed with brine, dried over sodium sulphate and concentrated under vacuum to yield 30gm of titled compound as yellow oily mass.

**Example 4: Preparation of Benzyl (lS)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-l-methylethylcarbamate (Formula XII)**

In a clean round bottom flask, 31gm of benzyl (lS)-2-[3,5-bis(trifluoromethyl)phenyl]-methyl-2-oxolethylcarbamate (formula XI, obtained as in Example 3), 310ml of methanol and 5.6gm of sodium borohydride were added at about room temperature. The reaction mixture was stirred for about 2 hours at about room temperature and concentrated under vacuum below 40°C to form a gummy mass. 310ml of ethyl acetate and 155ml of water were added to the gummy mass. The organic layer was separated and washed with 20% brine solution (2 x 100ml). The organic layer was concentrated under vacuum to form an oily mass (28.5gm). The product was crystallized in n-hexane and dried at about 35-40°C to yield 22.5gm of titled compound as a white solid.

**Example 5: Preparation of Benzyl (IS, 2R)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-l-methylethylcarbamate (Formula XII)**

In a clean round bottom flask, to a solution of 80gm of benzyl (IS)-2-[3,5-bis(trifluoromethyl)phenyl]-methyl-2-oxolethylcarbamate (formula XI, obtained as in Example
3) in 160ml trifluoroacetic acid was added 32.48gm of dimethyl phenyl silane at about 0-5°C and stirred for about 5 hours at the same temperature. The reaction mass was quenched in a mixture of 400ml water and 1000ml ethyl acetate at about 5-10°C. The organic layer was separated and washed with 250ml water. The organic layer was concentrated under vacuum to form an oily mass. The product was crystallized in n-heptane and dried at about 35-40°C to yield 65gm of titled compound as a white solid.

Example 6: Preparation of (1R, 2S)-2-amino-l-[3,5-bis(trifluoromethyl)phenyl]propan-l-ol (Formula XIII)

In a clean round bottom flask, 20gm of benzyl (lS,2R)-2-[3,5-bis(trifluoromethyl)phenyl]-2-hydroxy-l-methylethylcarbamate (formula XII, obtained as in Example 4 or Example 5), 400ml of methanol and 2gm of 20% Pd/C were added. The reaction mixture was charged in an autoclave and stirred for about 3 hours at about room temperature under hydrogen pressure (5kg). The reaction mass was filtered through a celite bed and washed with 50ml of methanol. The filtrate was concentrated under vacuum to form an oily mass. The oily mass was dissolved in 200ml of ethyl acetate and washed with water (2 x 100ml). The organic layer was dried over sodium sulphate and concentrated under vacuum below 40°C to yield an oily mass. The product was crystallized in heptane and dried at about 35-40°C to yield 9.5gm of the titled compound as an off-white solid. HPLC purity: 97.80%; Chiral purity: 99.99%. Mass: 288.31 [M+1]

IR: 3366.92, 3289.69, 3098.46, 2910.51, 1621.77, 1599.29, 1468.15, 1379.54, 1353.27, 1328.19, 1290.19, 1162.65, 1125.38, 1059.75, 1020.93, 1006.69, 982.48, 948.64 cm⁻¹

¹H NMR (300 MHz in DMSO): δ 7.97(s, 1H), 7.96(s,lH), 7.92(s,lH), 7.63(brs, 1H), 4.53-4.47(m, 1H), 2.95-2.87(m, 1H), 1.38(brs, 2H), 0.84-0.81(d, 3H)
Example 7: Preparation of \([4'-\text{fluoro}-5'-\text{isopropyl}-2'-\text{methoxy}-4-(\text{trifluoromethyl})-\text{l,l'}-\text{biphenyl}-2-\text{yl}]\) methanol (Formula V)

\[
\begin{array}{c}
\text{Formula VI} \\
\text{Formula VII} \\
\text{Formula V}
\end{array}
\]

In a clean round bottom flask, 5gm of 2-iodo-5-(trifluoromethyl)phenyl)methanol (formula VI), 3.85gm of 4-fluoro-5-isopropyl-2-methoxyphenyl)boronic acid (formula VII), 0.58gm of bis(triphenylphosphine) palladium(II)chloride, 9.12gm of potassium carbonate, 125ml of ethanol and 30ml of water were heated to about reflux temperature and stirred for about 10 hours. The reaction mixture was filtered to remove the catalyst and the filtrate was concentrated under vacuum to form a residue. 25 ml of water and 25ml of ethyl acetate were added to residue. The organic layer was separated from the aqueous layer. The aqueous layer was extracted with 25 ml ethyl acetate. The first and second organic layers were combined and concentrated under vacuum to form an oily mass obtained. 25ml of n-hexane was added to the oily mass and stirred for about 30 minutes at about room temperature. The slurry was filtered to give a pale yellow solid and dried in an oven at about 40-45°C for about 12 hours to yield 4.2gm of the titled compound.

Example 8: Preparation of \(4'-\text{fluoro}-5'-\text{isopropyl}-2'-\text{methoxy}-4-(\text{trifluoromethyl})-\text{l,l'}-\text{biphenyl}-2-\text{carbaldehyde} \) (Formula IV)

\[
\begin{array}{c}
\text{Formula V} \\
\text{Formula IV}
\end{array}
\]

In a clean round bottom flask, 4gm of \([4'-\text{fluoro}-5'-\text{isopropyl}-2'-\text{methoxy}-4-(\text{trifluoromethyl})-\text{l,l'}-\text{biphenyl}-2-\text{yl}]\) methanol (formula V, obtained as in Example 7), 40ml of methylene chloride
and 6.44gm of Dess-Martin Periodinane (DMP) was added and stirred for about 2 hours at about room temperature. The reaction mixture was filtered and the filtrate was washed with water. The organic layer was concentrated under vacuum and degassed to yield 3.5gm of the titled compound as a pale yellow solid.

**Example 9:** Preparation of (IR,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[(E)-({2-[4-fluoro-3-(propan-2-yl)phenyl]-5-(trifluoromethyl)phenyl}methylidene) amino]propan-1-ol (Formula III)

![Formula IV](attachment:formula IV.png) + ![Formula XIII](attachment:formula XIII.png) → ![Formula III](attachment:formula III.png)

In a clean round bottom flask, 6gm of [4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)-1,1'-biphenyl-2-carbaldehyde (formula IV, obtained as in Example 8), 5.1gm of (IR,2S)-2-amino-1-[3,5-bis(trifluoromethyl)phenyl]propan-1-ol (formula XIII, obtained as in Example 6) and 60ml of isopropyl alcohol were added and stirred for about 2 hour at about 35-40°C. The reaction mass was cooled to about room temperature and 120ml of water was added. The product was isolated by filtration, washed with water and dried at about 40-45°C to yield 9.5gm of the titled compound as an off-white solid. Mass: 610.39[M+1]

IR: 3422.54, 3179.82, 2963.79, 2927.36, 1645.74, 1618.22, 1585.70, 1491.39, 1397.52, 1371.84, 1337.88, 1309.50, 1284.33, 1162.76, 1128.54, 1113.40, 1083.13, 1030.22, 974.86 cm⁻¹.

**H NMR** (300 MHz in CDC13): δ 8.34 (s,1H), 8.07(s,1H), 7.85-7.70(m,3H), 7.40(s,1H) 7.01(s,1H), 6.67(s,1H), 4.93(s,3H), 3.68(s,3H), 3.53(m,3H), 3.17(m,2H), 1.24(d,6H), 1.00 (d, 3H)

**Example 10:** Preparation of (IR,2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[(2-[4-fluoro-3-(propan-2-yl)phenyl]-5-(trifluoromethyl)phenyl)methyl]amino]propan-1-ol (Formula II)
In a clean round bottom flask, 9gm of (IR,2S)-l-[3,5-bis(trifluoromethyl)phenyl]-2-{(E)-([2-[4-fluoro-2-methoxy-5-(propan-2-yl)phenyl]-5-(trifluoromethyl)phenyl]methylidene)amino]propan-l-ol (formula III, obtained as in Example 9), 90ml of methanol and 1.5gm of sodium borohydride were added and stirred for about 2 hours at about room temperature. The reaction mass was concentrated under vacuum and extracted with 50ml of ethyl acetate. The ethyl acetate layer was washed with water (2 x 15ml) and dried over sodium sulphate. The organic layer was concentrated under vacuum to form an oily mass. The product obtained was crystallized in heptane, filtered and dried at about 35-40°C under vacuum to yield 7gm of titled compound as a white solid. HPLC Purity: 98.88%. Mass: 612.35[M⁺-1]

IR: 3737.17, 3445.20, 2969.54, 1618.13, 1493.47, 1447.35, 1397.00, 1370.49, 1350.11, 1332.09, 1283.34, 1233.81, 1159.76, 1128.91, 1116.31, 1087.87, 1031.21, 973.85, 896.56 cm⁻¹.

H NMR (300 MHz in CDC13): δ 7.74-7.69 (d, 4H), 7.61-7.58 (d, 1H), 7.33-7.30 (d, 1H), 7.00-6.97 (d, 1H), 6.71-6.67 (d, 1H), 4.74 (d, 1H), 3.81 (s, 3H), 3.71 (d, 1H), 3.21 (m, 1H), 2.78 (m, 1H), 1.25-1.19 (m, 6H), 0.61-0.59 (d, 3H)

Example 11: Preparation of 5(R)-[3,5-Bis(trifluoromethyl)phenyl]-3-[4'-fluoro-5'-isopropyl-2'-methoxy-4-(trifluoromethyl)biphenyl-2'-yImethyl]-4(S)-methyl-oxazolidin-2-one (Anacetrapib, Formula I)
In a clean round bottom flask, 10gm of (1R, 2S)-1-[3,5-bis(trifluoromethyl)phenyl]-2-[(2-[4-fluoro-2-methoxy-5-(propan-2-yl)phenyl]-5-(trifluoromethyl)phenyl)methyl]amino]propan-1-ol (formula II, obtained as in Example 10), 50ml of tetrahydrofuran, 6.63gm of 1,1-carbonyl imidazole (CDI) and 25ml of dimethyl formamide was added at about room temperature. The reaction mixture was heated to about 70-75°C and stirred for about 2 hours. The reaction mass was concentrated under vacuum to form an oily mass. The oily mass was dissolved in ethyl acetate and washed with water. The organic layer was dried over sodium sulphate and concentrated under vacuum to form an oily mass. The oily mass was purified by column chromatography using hexane: ethyl acetate (95:5) to yield 4.5gm of titled compound as a white solid. Melting point range: 70-73°C; HPLC Purity: 99.74%; Chiral Purity: 99.9%; Surface Area in (m²/g): 1.18; Particle size: d (0.1) 12.989 µm, d (0.5) 62.241 µm, d (0.9) 200.380 µm.

IR: 3840.85, 3736.11, 3444.19, 2969.51, 2876.62, 1763.00, 1621.58, 1590.83, 1514.39, 1497.01, 1466.56, 1447.94, 1398.77, 1331.48, 1280.77, 1234.31, 1181.19, 1132.26, 1081.14, 1028.16, 973.06, 952.86, 902.53, 844.68 cm⁻¹.

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**Formula IX**
Example 12: Purification of 5(R)-[3,5-Bis(trifluoromethyl)phenyl]-3-[4′-fluoro-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-4(S)-methyloxazolidin-2-one (Anacetrapib, Formula I): In a clean round bottom flask, 10gm of anacetrapib was dissolved in 10ml ethanol and cooled to about -5°C to 0°C. Water was added to the reaction mixture and stirred for about one hour at about -5°C to 0°C, filtered and dried under vacuum to yield 7gm of titled compound.

Example 13: Purification of 5(R)-[3,5-Bis(trifluoromethyl)phenyl]-3-[4′-fluoro-5′-isopropyl-2′-methoxy-4-(trifluoromethyl)biphenyl-2-ylmethyl]-4(S)-methyloxazolidin-2-one (Anacetrapib, Formula I): In a clean round bottom flask, 5gm of anacetrapib was dissolved in 20ml heptane and cooled to about -20°C. 0.1 gm of seed of anacetrapib was added to the reaction mixture and stirred for about one hour at about -20°C, filtered and dried under vacuum to yield 4.3gm of titled compound.
We claim:

1) A process for the preparation of anacetrapib, a compound of Formula I,

![Formula I]

comprising: cyclizing a compound of formula II.

![Formula II]

2) The process as claimed in claim 1, wherein the cyclizing agent is selected from the group consisting of 1-hydroxybenzotriazole (HOBT), 1, 8-diazabicyclo [5.4.0] undec-7-ene (DBU), carbonyldimidazole (CDI), diisopropylcarbodiimide (DIC), dicyclohexylcarbodiimide (DCC), 4,5-dicyanoimidazole, dicyclopentyl carbodiimide and the like or mixtures thereof.

3) The process as claimed in claim 1, wherein the compound of formula II,
is prepared by a process comprising: a) reacting a compound of formula IV,

![Formula IV](image)

with a compound of formula XIII,

![Formula XIII](image)

and to form a compound of formula III; and

b) reacting the compound of formula III with a reducing agent to form a compound of formula II.

4) The process as claimed in claim 3, wherein the reducing agent is selected from the group consisting of alkali metal hydride, alkaline earth metal hydride, alkali metal borohydride and alkaline earth metal borohydride.

5) The process as claimed in claim 3, wherein the compound of formula IV, is prepared by a process comprising: reacting a compound of formula V, with an oxidizing agent.
6) The process as claimed in claim 3, wherein the compound of formula XIII, is prepared by a process comprising: hydrogenolysing a compound of formula XII,

Formula XII

7) A compound of formula III or salt thereof.

Formula III

8) Use of any of the compounds of formula II, formula III and formula XIII or salt thereof in the preparation of anacetrapib.

9) A process for the purification of anacetrapib, a compound of formula I, comprising:
   a) providing a solution of anacetrapib in a solvent or a mixture of solvents or their aqueous mixtures;
   b) cooling the solution obtained in step a) at about 25°C to about -30°C to form a reaction mass;
   c) optionally seeding the reaction mass with anacetrapib to precipitate the solid anacetrapib; and
   d) isolating the pure anacetrapib.
10) The process as claimed in claim 9, wherein the solvent in step a) is selected from the group consisting of hydrocarbon, ether or mixtures thereof.

11) A process for the purification of anacetrapib, a compound of formula I, comprising:
   a) dissolving anacetrapib in an organic solvent to form a solution;
   b) adding an anti-solvent to the solution obtained in step a) to precipitate the solid anacetrapib;
   and c) isolating the pure anacetrapib.

12) The process as claimed in claim 11, wherein the organic solvent in step a) is selected from the group consisting of alcohol, ketone, nitrile, ether, ester or mixtures thereof.

13) The process as claimed in claim 11, wherein the anti-solvent in step b) is selected from the group consisting of water, hydrocarbon or mixtures thereof.
INTERNATIONAL SEARCH REPORT

PCT/IN2014/000028

A. CLASSIFICATION OF SUBJECT MATTER
C07D 263/22(2006.01)i; C07D 263/20(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 263/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CNABS,CNTXT,VEN,EPTXT,USTXT,CATXT,CAPLUS,CNKI:anacetrapib,CDI,DCC,preparation,synthesis,purificat|

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C.  

Date of the actual completion of the international search 21 May 2014  
Date of mailing of the international search report 16 June 2014

Name and mailing address of the ISA/Authorized officer  
STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA/ISA/CN  
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HOU,Baoguang

Facsimile No. (86-10)62019451 Telephone No. (86-10)61648350

Form PCT/ISA/210 (second sheet) (July 2009)
### INTERNATIONAL SEARCH REPORT

**Information on patent family members**

**International application No.**

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