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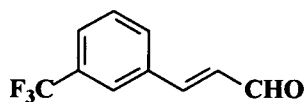
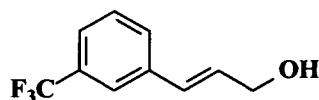
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(54) **Title:** AN IMPROVED PROCESS FOR THE PREPARATION OF INTERMEDIATE COMPOUNDS USEFUL FOR THE PREPARATION OF CINACALCET

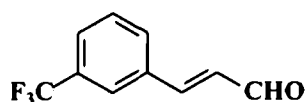
**Formula IIIa****Formula IVb**

(57) **Abstract:** The present invention provides an improved process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa), (formula IIIa) and 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb), (formula IVb). The compounds of Formula IIIa and IVb are key precursors in the preparation of Calcimimetic agent, Cinacalcet hydrochloride of Formula I.

AN IMPROVED PROCESS FOR THE PREPARATION OF INTERMEDIATE COMPOUNDS USEFUL FOR THE PREPARATION OF CINACALCET

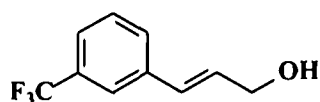
5 FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal of Formula (IIIa).



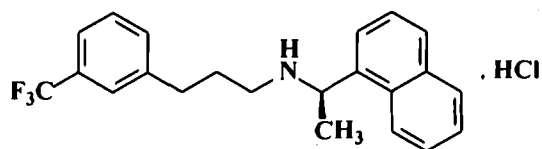
Formula IIIa

10 The present invention also relates to an improved process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb).



Formula IVb

The compounds of Formulae IIIa and IVb are key precursors in the preparation of Calcimimetic agent, Cinacalcet hydrochloride of Formula I.



Formula I

15 BACKGROUND OF THE INVENTION

N-[(1R)-1-(1-Naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propan-1-amine hydrochloride is generically known as Cinacalcet.

20 Cinacalcet is a second generation calcimimetic agent, which decreases the secretion of parathyroid hormone (PTH) by activating calcium receptors. The secretion of PTH is normally regulated by the calcium-sensing receptor. Calcimimetic agents

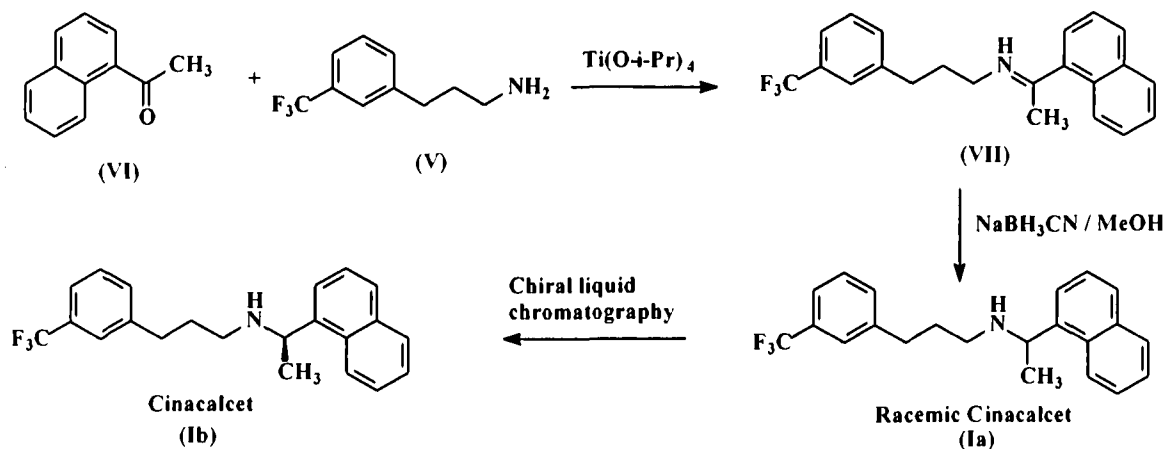
increase the sensitivity of this receptor to calcium, which inhibits the release of parathyroid hormone, and lowers parathyroid hormone levels within a few hours. Calcimimetics are used to treat hyperparathyroidism, a condition characterized by the over-secretion of PTH that results when calcium receptors on parathyroid glands fail to respond properly to calcium in the bloodstream. Elevated levels of PTH are an indicator of secondary hyperparathyroidism associated with altered metabolism of calcium and phosphorus, bone pain, fractures, and an increased risk for cardiovascular death.

Cinacalcet is marketed under the name Sensipar[®] in the US and, in Europe, it is marketed under the name Mimpara[®] and Parareg[®]. It has been approved for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis and for the treatment of hypercalcemia in patients with parathyroid carcinoma.

NPS Pharmaceuticals disclosed generically Cinacalcet and its pharmaceutically acceptable salts as calcium receptor-active molecules in US 6,011,068, US 6,313,146 and disclosed specifically in US 6,211,244. However, there is no explicit example for the preparation of Cinacalcet.

According to the generic process disclosed in US '244 Cinacalcet may be prepared by reacting 3-[3-(trifluoromethyl)phenyl]propylamine (V) with 1-acetylnaphthalene (VI) in the presence of titanium (IV) isopropoxide, to produce an imine (VII), which is further reacted with ethanolic or methanolic sodium cyanoborohydride to produce racemic Cinacalcet (Ia), and resolution of the racemic Cinacalcet by chiral liquid chromatography to produce Cinacalcet (Ib).

The process is as shown in Scheme -I below:



Scheme-I

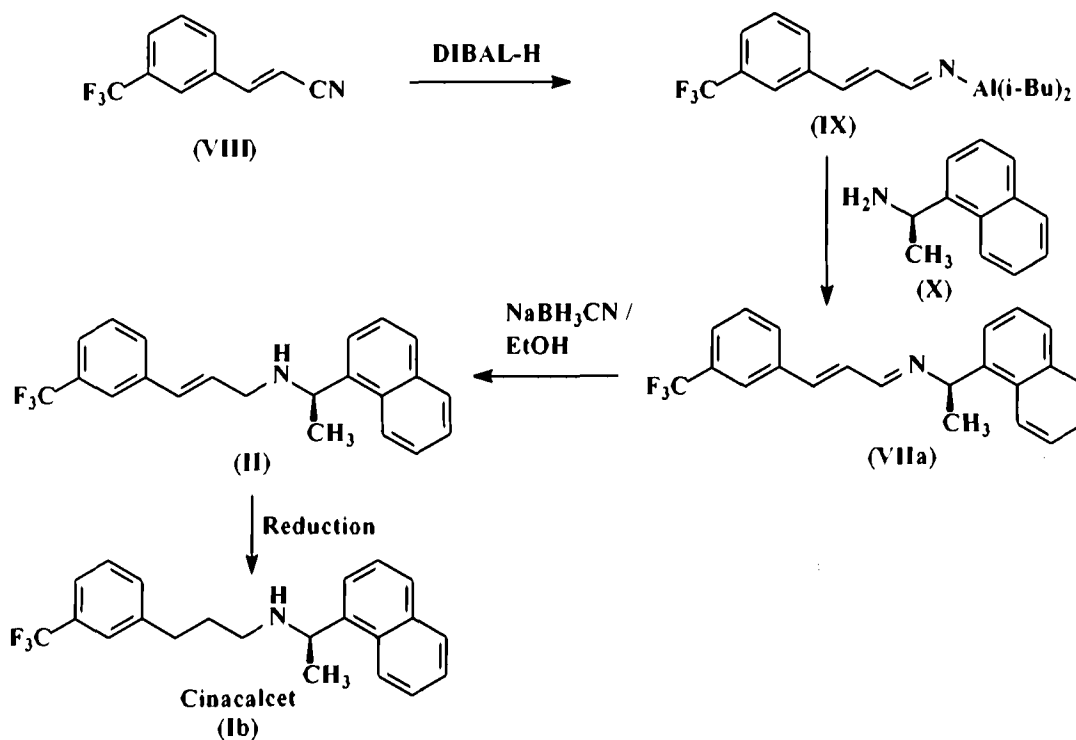
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US '244 also generically discloses a variant process for the preparation of Cinacalcet by reacting 3-trifluoromethylcinnamionitrile (VIII) with diisobutylaluminum hydride to produce intermediate aluminum-imine complex (IX), which is further reacted with (R)-1-(1-naphthyl)ethylamine (X) to produce an imine (VIIa), followed by reduction using ethanolic sodium cyanoborohydride to produce 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) and reducing unsaturated Cinacalcet to produce Cinacalcet (Ib).

10

The process is as shown in Scheme -II below:

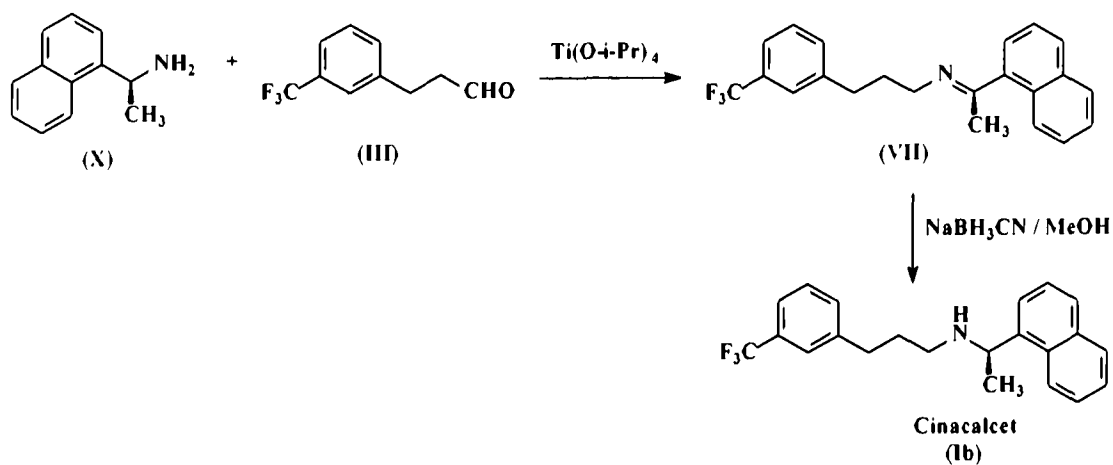
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Scheme-II

Similarly, using the process disclosed in US '244, as well as *Drugs of the Future* 2002, 27(9), 831-836, Cinacalcet may be prepared by reacting (R)-1-(1-naphthyl)ethylamine (X) with 3-[3-(trifluoromethyl)phenyl]propionaldehyde (III) in the presence of titanium (IV) isopropoxide to produce intermediate compound imine (VII), which is further reduced using ethanolic sodium cyanoborohydride.

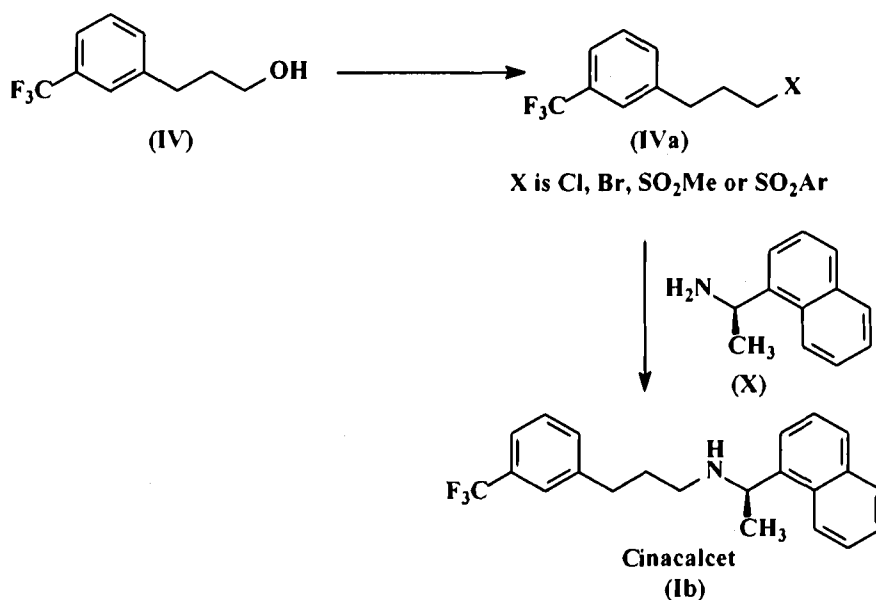
10 The process is as shown in Scheme -III below:



Scheme-III

US 7,250,533 discloses a process for the preparation of Cinacalcet, wherein 3-[3-(trifluoromethyl)phenyl]propanol (IV) is converted to a compound with a good leaving group (IVa), which is further condensed with (R)-1-(1-naphthyl)ethylamine (X) to produce Cinacalcet (Ib). The reagents described in the patent, which have good leaving groups are thionyl halide, aliphatic sulfonyl halide and aromatic sulfonyl halide.

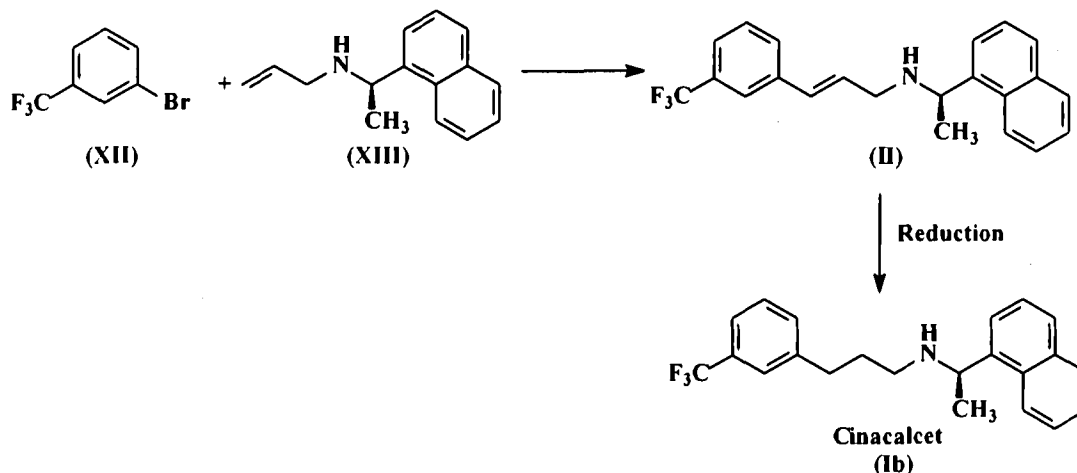
The process is as shown in Scheme -IV below:



Scheme-IV

US 7,393,967 discloses a process for the preparation of Cinacalcet, which comprises, condensing 3-bromotrifluorotoluene (XII) with allyl amine (XIII) to produce 3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II), which is further reduced in presence of Pd/C to produce Cinacalcet (Ib).

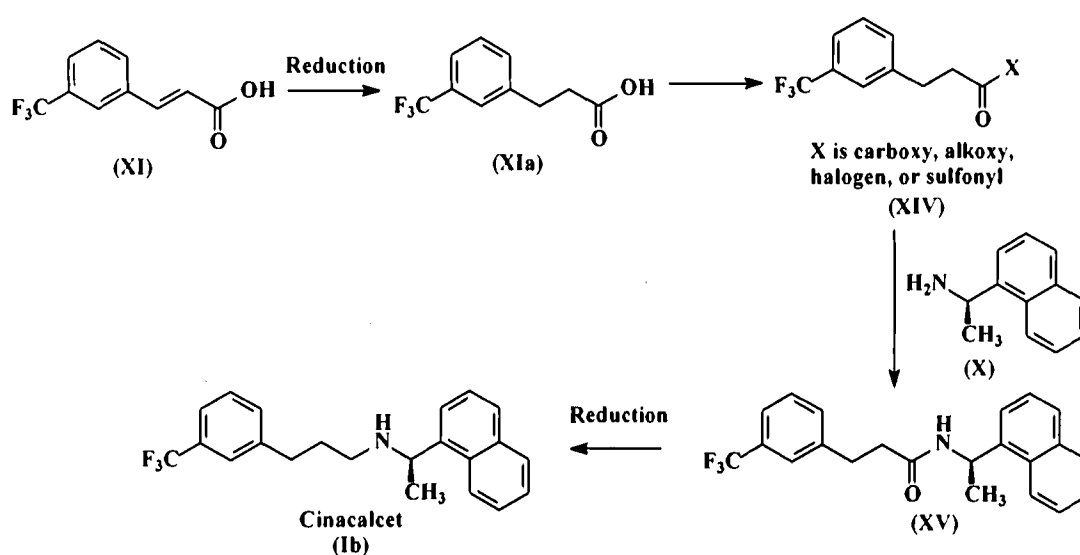
The process is as shown in Scheme -V below:



Scheme-V

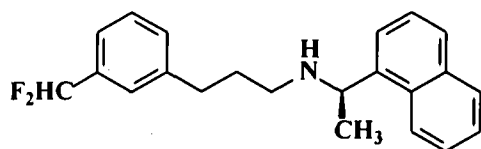
- 5 US 2007/0259964 A1 discloses a process for the preparation of Cinacalcet (Ib), wherein 3-(trifluoromethyl)cinnamic acid (XI) is reduced to obtain 3-[3-(trifluoromethyl)phenyl]propanoic acid (XIa) followed by converting to corresponding reactive derivative (XIV), which is further condensed with (R)-1-(1-naphthyl)ethylamine (X) in the presence of a base to produce N-[(1S)-1-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]propanamide (XV) and followed by reduction to produce Cinacalcet (Ib).
- 10

The process is as shown in Scheme -VI below:



Scheme-VI

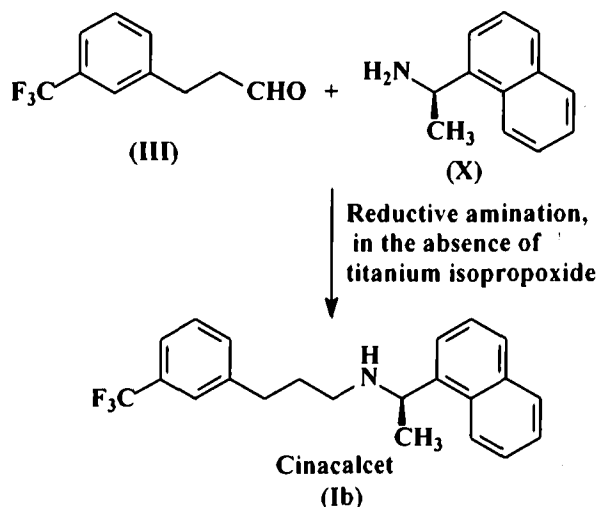
The major disadvantage with the above process is the formation of (~ 2%) desfluoro Cinacalcet (Ic), due to the use of strong reducing agent such as BH_3 . The separation of undesired desfluoro Cinacalcet (Ic) from Cinacalcet (Ib) is difficult and require repeated crystallization, resulting in a significant loss of yield.

**Formula Ic**

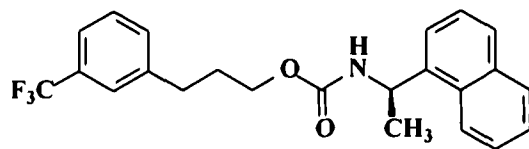
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WO 2008/068625 A2 discloses condensation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (III) with (R)-1-(1-naphthyl)ethylamine (X) in the absence of titanium isopropoxide to produce Cinacalcet (Ib).

10 **The process is as shown in Scheme -VII below:**

**Scheme-VII**

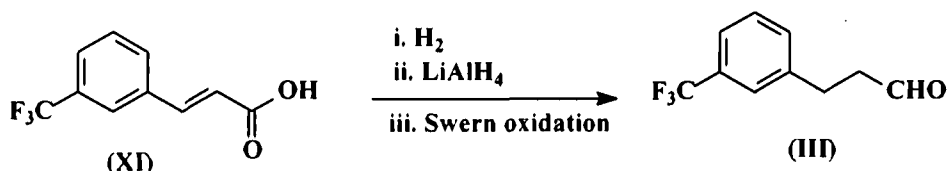
15 US 7,294,735 discloses a process for the purification Cinacalcet hydrochloride by treating Cinacalcet base having 3 to 6% of 3-(3-(trifluoromethyl)phenyl)propyl-(R)-1-(naphthalen-1-yl)ethyl carbamate (Cinacalcet carbamate) (XVI) in a solvent selected from acetone, C_{2-8} ethers and water with hydrochloric acid.



Formula XVI

Tetrahedron Letters (2004), 45, 8355, discloses a process for the preparation of precursor compound of the Cinacalcet, namely 3-[3-(trifluoromethyl)phenyl]propionaldehyde (III) by reducing 3-(trifluoromethyl)cinnamic acid (XI) to the corresponding alcohol (IV) followed by Swern oxidation.

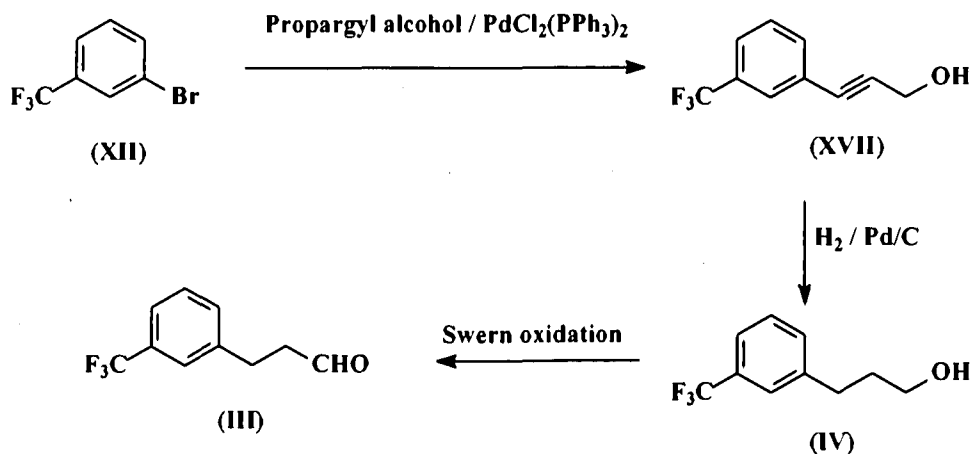
The process is as shown in Scheme -VIII below:



Scheme-VIII

EP 0 194 764 B1 discloses a process for the preparation of 3-[3-(trifluoromethyl)-phenyl]propionaldehyde (III) by reacting 3-trifluoromethylbromobenzene (XII) with propargyl alcohol in presence of bis(triphenylphosphine)palladium chloride and cuprous iodide in triethylamine, followed by catalytic hydrogenation to produce the corresponding alcohol (IV), which is further oxidised by a Swern oxidation.

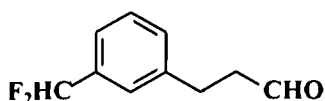
The process is as shown in Scheme -IX below:



Scheme-IX

The above processes involve the use of reagents, such as oxalyl chloride and dimethyl sulfoxide in the Swern oxidation, which are unstable and does not result in high yield, making the process difficult on industrial scale.

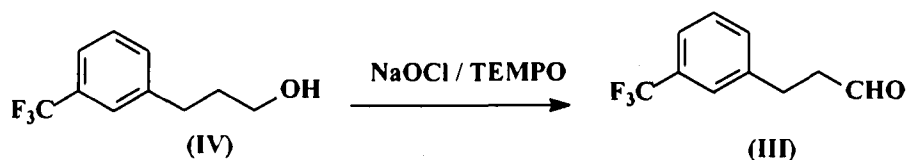
Further, the major disadvantage with the above processes is the formation of an undesired desfluoro compound (IIIb) due to the use of strong reducing agent lithium aluminum hydride (LiAlH_4). The separation of undesired desfluoro compound (IIIb) from 3-[3-(trifluoromethyl)phenyl]propionaldehyde (III), and 3-[3-(trifluoromethyl)phenyl]propanol (IV) is difficult.



Formula IIIb

WO 2008/035212 A2 discloses a process for the preparation of 3-[3-(trifluoromethyl)phenyl]propionaldehyde (III), by reacting 3-[3-(trifluoromethyl)phenyl]propanol (IV) with sodium hypochlorite / 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO).

The process is as shown in Scheme -X below:



Scheme-X

Hence, there is a need to develop a process, which provides 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa) and 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) with good yields on a commercial scale.

The present invention is specifically directed towards the process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa), which avoids very low

temperature oxidation conditions (-70 to -80°C) as well as the unpleasant odors associated with the prior-art procedures (Swern oxidation).

5 The present invention also specifically directed towards the process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) by reducing mixed anhydride of Formula (XVIII) in the absence of strong reducing agents.

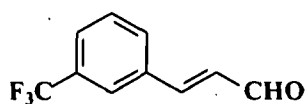
OBJECTIVE OF INVENTION

10 The main objective of the present invention is to provide a simple and cost effective process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal of Formula (IIIa) with good yields on a commercial scale.

Another objective of the present invention is to produce Cinacalcet hydrochloride
15 with good yields and quality on a commercial scale.

SUMMARY OF THE INVENTION

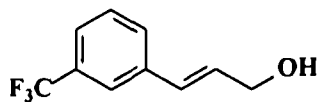
The present invention provides an improved process for the preparation of 3-[3-
20 (trifluoromethyl)phenyl]-2-propenal (IIIa),



Formula IIIa

which comprises:

oxidizing 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb)

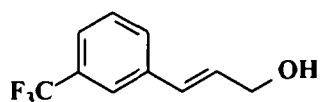


Formula IVb

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with suitable oxidizing agent, optionally in the presence of a catalyst in a solvent to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa).

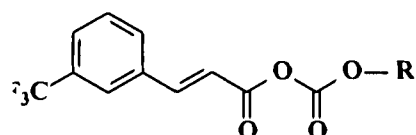
According to another embodiment, the present invention also provides a process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb),



Formula IVb

which comprises:

reducing mixed anhydride of Formula (XVIII) with a suitable reducing agent in a solvent,



Formula XVIII

wherein R represents C₁₋₃ alkyl, benzyl and substituted benzyl.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention, the present invention provides an improved process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb).

The process comprises, reacting 3-(trifluoromethyl)cinnamic acid (XI) with alkyl chloroformate in the presence of a suitable base and in a suitable solvent to produce a mixed anhydride (XVIII). The suitable base used in the reaction includes but are not limited to triethyl amine, isopropyl ethylamine, 4-(dimethylamino)pyridine, potassium carbonate. The solvent used in the reaction is ethyl acetate, tetrahydrofuran, methylene chloride, toluene and the like. The most preferred solvent is toluene. The reaction may be performed at a temperature ranging from -35°C to about 35°C based on the solvent or mixture of solvents used for the reaction. Alkyl chloroformate is added slowly in a drop-wise manner. Most preferably, this addition

is while maintaining the reaction mixture at a temperature of about -20°C to about 5°C. The reaction mixture containing mixed anhydride (XVIII) is (optionally, the salts can be removed by washing with water at low temperature) filtered to remove residual salts and reagents. The filter cake is then washed and the solvent is removed from the filtrate under reduced pressure to produce mixed anhydride (XVIII).

Reducing the mixed anhydride (XVIII) with a suitable reducing agent in a solvent to produce 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb). The suitable reducing agent is selected from sodium borohydride, lithium aluminium hydride, zinc borohydride, calcium borohydride. Most preferred reducing agent is sodium borohydride. The solvent used in the reaction includes, but not limited to water, dioxane, toluene, THF or mixtures thereof. Most preferred solvent is THF. The reaction may be performed at a temperature ranging from -10°C to about 35°C based on the solvent or mixture of solvents used for the reaction. After the completion of reaction, as ascertained by the known methods such as HPLC, acetone is added to the reaction mass and extracted with a solvent selected from toluene, ethyl acetate, dichloromethane, hexane and the solvent is removed to produce 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb).

It has been observed that Cinacalcet prepared by using 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) prepared by above reaction conditions results in desfluoro Cinacalcet impurity (Ic) to less than 0.03% by HPLC analysis.

According to another embodiment, the present invention also provides a process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa).

The process comprising, oxidizing 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) with oxidizing agent in the presence of a solvent to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa). The suitable oxidizing agent used in the reaction is selected from 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-chloranil), 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-chloranil), 1,4-benzoquinone (*p*-benzoquinone), manganese

dioxide (MnO_2), potassium permanganate (KMnO_4), potassium dichromate ($\text{K}_2\text{Cr}_2\text{O}_7$), chromium trioxide (CrO_3) and sodium hypochlorite (NaOCl).

Suitable solvent used for oxidation is inert organic solvent selected from acetonitrile, cyclic or acyclic alkanes such as hexane, heptane, methylcyclohexane, aromatic solvents such as toluene, halogenated solvents such as dichloromethane (MDC), dichloroethane, chloroform, esters such as ethyl acetate, butyl acetate, isopropyl acetate or ethers such as diethyl ether, tetrahydrofuran or tert-butyl methyl ether and/or mixtures thereof. Preferably, the solvent is MDC, toluene or acetonitrile.

Oxidation reaction is conducted at a temperature in the range of about -5°C to about 25°C and for a time in the range of about 10 min to about 2 hr. More preferably, at a temperature below 15°C , and for a time of about 20 min to about 60 min. 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa) produced in the above reaction is isolated from the reaction mass by diluting the reaction mass with a solvent selected from dichloromethane, toluene and water followed by layer separation and solvent removal.

Oxidation reaction is optionally carried out in the presence of nitroxyl compound, which is selected from 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO), when the oxidizing agent sodium hypochlorite (NaOCl) is used. It was found to be advantageous to add the oxidizing agent in portions to the reaction mixture. After addition of oxidizing agent, acid is added to maintain the pH of the reaction mixture to a pH of about 8-9.5. The acid is selected from aqueous hydrochloric acid, aqueous sulfuric acid, p-toluene sulfonic acid, trifluoroacetic acid, and acetic acid. More preferably, aqueous HCl is added.

The major advantage with the process (oxidation) of the present invention is that it avoids very low temperature oxidation conditions (-70 to -80°C) as well as the unpleasant odors associated with the prior-art procedures (Swern oxidation).

In another embodiment, the present invention also relates to the use of above compounds 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) and 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa) to produce Cinacalcet hydrochloride.

5 3-(3-(Trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine hydrochloride (unsaturated Cinacalcet hydrochloride) of Formula (IIa) can be prepared by reductive amination of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa) with (R)-1-(1-naphthyl)ethylamine (X), in the presence of a reducing agent selected from sodium borohydride, sodium triacetoxyborohydride, sodium cyanoborohydride
10 (NaBH₃CN) in a solvent selected from ethyl acetate, tetrahydrofuran, isopropyl acetate, acetonitrile to produce 3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II). The reaction may be performed at a temperature ranging from about 0°C to about 50°C based on the solvents used for the reaction. The above reaction is optionally conducted in
15 presence of an acid selected from acetic acid.

The reaction mixture containing the 3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) is cooled and optionally residual salts and reagents are filtered from the reaction mixture. The filter cake is
20 then washed and the solvent is removed from the filtrate under reduced pressure to produce crude 3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II).

3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine
25 (unsaturated Cinacalcet) (II) can also be recovered from the reaction mixture by extraction from the reaction mixture using a solvent selected from the group consisting of C₄₋₈ ethers, chlorinated solvents, C₃₋₆ esters, C₅₋₈ cyclic, aromatic and aliphatic hydrocarbons and mixtures thereof. More preferably, the solvent is ethyl acetate, dichloromethane (DCM), toluene or mixtures thereof.

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3-(3-(Trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) produced by the above methods is treated with

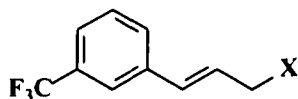
hydrochloric acid in a solvent selected from acetonitrile, THF, ethers, ethyl acetate, methyl isobutyl ketone (MIBK), ketone, toluene to produce hydrochloride salt of 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet hydrochloride) (IIa), which is isolated by evaporating the solvent or precipitation of compound from the reaction mixture, by cooling the reaction mixture, followed by addition of an organic solvent.

Alternatively, 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine hydrochloride (unsaturated Cinacalcet hydrochloride) of Formula (IIa) can also be prepared by converting 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) into a good leaving group by reacting with a reagent containing the leaving group, which is selected from thionyl halide, aliphatic sulfonyl halide and aromatic sulfonyl halide. More preferably, the thionyl halide is either thionyl bromide or thionyl chloride, while the preferred aliphatic sulfonyl halide is methanesulfonyl chloride and the preferred aromatic sulfonyl halide is benzenesulfonyl chloride, 4-nitrobenzenesulfonyl chloride or p-toluenesulfonyl chloride.

The suitable inert organic solvents for the above reaction include but are not limited to halogenated solvents, such as dichloromethane, ethylene dichloride, and chloroform; ether, toluene and the like. The reaction may be performed at a temperature ranging from 0°C to about 35°C based on the solvent or mixture of solvents used for the reaction. The reagent containing the leaving group is added to the solution of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) in organic solvent. More preferably, the reagent is added slowly in a drop-wise manner. Most preferably, this addition is while maintaining the reaction mixture at a temperature of about 0°C to about 10°C.

The reaction is carried out in presence or absence of a base. When the leaving group is sulfonyl chloride, the reaction is carried out in presence of a base. Preferably, the organic base is an amine, more preferably, triethylamine, diisopropylethylamine, and pyridine. The sufficient period of time necessary for obtaining compound (IVc) will depend on the parameters of the reaction. Preferably, maintaining the reaction

mixture for about 4 to about 24 hours. More preferably, the reaction mixture is maintained for about 8 hour to about 15 hours.



Formula IVc

- 5 wherein X represents a leaving group selected from Cl, Br, C_{1-3} alkyl sulfonate or C_{6-10} aryl sulfonate.

The compound (IVc) obtained by the above process can be isolated by precipitation of compound from the reaction mixture or by removing the solvent from the reaction
10 mixture.

The compound (IVc) is condensed with (R)-1-(1-naphthyl)ethylamine (X) in the presence of suitable base in a solvent to produce 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II). The
15 suitable base used in the reaction is selected from an inorganic base such as alkali carbonate, more preferably, K_2CO_3 , Na_2CO_3 , CS_2CO_3 , NaHCO_3 or KHCO_3 . The most preferred base is K_2CO_3 . The solvent is an organic solvent selected from acetonitrile, toluene, methyl isobutyl ketone (MIBK), and acetone, more preferably acetonitrile. The reaction may be performed at a temperature ranging from about
20 25°C to about reflux temperature of the solvent or mixture of solvents used for the reaction. The reaction time is about 5 to about 24 hours, more preferably about 10 to about 20 hours. After completion of the reaction, filtering off the salts obtained in the reaction and evaporating to obtain a residue. The residue containing 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine
25 (unsaturated Cinacalcet) (II) in a solvent selected from toluene, methyl isobutyl ketone (MIBK) is washed with acidic solution, followed by washing with sodium chloride solution and isolating 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) by removing the solvent.

30 Alternatively, 3-(3-(trifluoromethyl)phenyl-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) can also be recovered from the reaction

mixture by extraction from the reaction mixture using a solvent selected from the group consisting of C₄₋₈ ethers, chlorinated solvents, C₃₋₆ esters, C₅₋₈ cyclic, aromatic and aliphatic hydrocarbons and mixtures thereof. More preferably, the solvent is ethyl acetate, dichloromethane (DCM), toluene or mixtures thereof.

- 5 3-(3-(Trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet) (II) produced by any of the above methods is treated with hydrochloric acid in a solvent selected from acetonitrile, THF, ethers, ethylacetate, methyl isobutyl ketone (MIBK), ketone, toluene to produce hydrochloride salt of 3-
- 10 (3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine (unsaturated Cinacalcet hydrochloride) (IIa), which is isolated by evaporating the solvent or precipitation of compound from the reaction mixture, by cooling the reaction mixture, followed by addition of an organic solvent.
- 15 The process further comprises, reducing 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine hydrochloride (unsaturated Cinacalcet hydrochloride) (IIa), preferably, by catalytic hydrogenation (i.e., with hydrogen in the presence of catalyst) to produce Cinacalcet hydrochloride (I). The hydrochloride salt of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-
- 20 amine (unsaturated Cinacalcet hydrochloride) (IIa) may be dissolved in a lower alcohol selected from C₁-C₄ aliphatic, straight chain or branched alcohol, and exposed to H₂ pressure in the presence of a catalyst such as Pd/C or PtO₂ or Raney nickel. Preferably, hydrogen is present at a pressure of about 1 atmosphere to about 1000 psi and at a temperature about 0°C to 35°C. Typically, the hydrogenation is
- 25 carried out over a period of about 1 to about 6 hours to produce Cinacalcet hydrochloride. The reaction mixture containing Cinacalcet hydrochloride is cooled and filtered. The filtered cake is then washed and the solvent is removed from the filtrate under reduced pressure to produce Cinacalcet hydrochloride, which is isolated by the addition of organic solvent selected from acetonitrile, ether, heptane,
- 30 methyl isobutyl ketone (MIBK).

The present invention also relates to use of Cinacalcet hydrochloride produced by above processes in the preparation of pharmaceutical compositions.

The following examples are provided to illustrate the invention and are merely for illustrative purpose only and should not be construed to limit the scope of the invention.

EXAMPLES:

Example 1

Preparation of Cinacalcet HCl from 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol :

Stage-1:

Method a:

Preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb)

Ethyl chloroformate (78.05 g, 719 mmol) was slowly added to a mixture of 3-(trifluoromethyl)cinnamic acid (100 g, 463 mmol) and triethylamine (56.1 g, 555 mmol) in toluene (800 ml) at -5°C to -10°C and stirring was continued at 0°C for 3 hrs. The reaction mass was filtered to remove triethylamine HCl salts and washed with toluene (200 ml). The filtrate was concentrated to produce mixed anhydride (133 g). Aqueous sodium borohydride solution (26.38 g, 694 mmol in water 82 ml) was added slowly to a mixture of mixed anhydride in dioxane (400 ml) at $0-5^{\circ}\text{C}$ and stirred for 2 hrs. Acetone (40 ml) was added and concentrated the reaction mass. Toluene (400 ml) and water (200 ml) were added to the residue and the aqueous layer was extracted with toluene (200 ml). Combined toluene layer was washed with water and concentrated under reduced pressure to get 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (84.2 g, 90%).

Method b:

Ethyl chloroformate (19.5 g, 180 mmol) was slowly added to a mixture of 3-(trifluoro-methyl)cinnamic acid (25 g, 116 mmol) and triethylamine (14.61 g, 145 mmol) in toluene (200 ml) at -5°C to -10°C and stirring was continued at 0°C for 3 hrs. The reaction mass was filtered to remove triethylamine HCl salts and washed with toluene (50 ml). The filtrate was concentrated to get mixed anhydride (31.5 g,

95%). Aqueous sodium borohydride solution (6.6 g, 174 mmol in water 21 ml) was added slowly to a mixture of mixed anhydride in tetrahydrofuran (100 ml) at 0-5°C and stirred for 2 hrs. Acetone (10 ml) was added and concentrated the reaction mass. Toluene (100 ml) and water (50 ml) were added to the residue, and the aqueous layer was extracted with toluene (50 ml). Combined toluene layer was washed with water, concentrated under reduced pressure to produce 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (17.3 g, 74%).

Stage-2:

10 **Preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa)**

Sodium bicarbonate solution (8.3 g, 99 mmol in water 85 ml) was added to a solution of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (20 g, 99 mmol), TEMPO free radical (0.22 g) and acetonitrile (80 ml). ~13% Sodium hypochlorite solution (73.8 g) was added to the above reaction mass over a period of 20 min at 0-5°C with stirring while maintaining the pH of the reaction mass at 8.5-9.5 using dil. HCl. After 1 hr additional stirring, methylene chloride (80 ml) followed by water (70 ml) were added. The organic layer was washed with sodium sulphite solution followed by sodium chloride solution. The organic layer was concentrated to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (17.4 g, 88%).

Stage-3:

Preparation of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)prop-2-en-1-amine hydrochloride (unsaturated Cinacalcet HCl) (IIa)

3-[3-(Trifluoromethyl)phenyl]-2-propenal (10 g, 50 mmol) was added to a solution of (R)-1-(1-naphthyl)ethylamine (8.46 g, 49 mmol) in tetrahydrofuran (250 ml). The resulting clear solution was stirred for 15 min, and acetic acid (4 g) and sodium triacetoxyborohydride (prepared separately by treating 2.6 g of sodium borohydride and 12.5 g of acetic acid in 50 ml of tetrahydrofuran) were added at 10-15°C. After stirring for 2 hr at room temperature, the reaction mass was concentrated. The resulting residue was dissolved in methylene chloride (150 ml) and washed with 1N HCl solution to remove unreacted amine. Separated organic layer was washed with sodium carbonate solution. The organic layer was concentrated to produce unsaturated Cinacalcet base (16.2 g). The residue containing unsaturated Cinacalcet

base was dissolved in acetonitrile (20 ml) and acidified with HCl. The resulting mass was concentrated and product was isolated from acetonitrile to produce unsaturated Cinacalcet HCl as white solid (10.7 g, 55%). ¹H NMR (CDCl₃) (δ ppm): - 10.82 (br.s, 1H), 10.34 (br.s, 1H), 7.27-8.30 (m, 11H), 6.47 (m, 1H), 6.16 (d, 1H), 5.25 (m, 1H), 3.71 (m, 1H), 3.39 (m, 1H), 1.97 (d, 3H); MS (m/z): 356.1 [M+1].

Stage-4:

Preparation of Cinacalcet HCl

A mixture of unsaturated Cinacalcet hydrochloride (9g, 23 mmol) and 5% Pd/C (0.9g) in methanol (90 ml) was hydrogenated at 3 Kg/cm² for 2 hr. The reaction mass was filtered and concentrated under reduced pressure. Acetonitrile (36 ml) was added. The resulting precipitate was stirred at 5°C for 2 hr, filtered and dried to produce Cinacalcet hydrochloride (7.6 g, 84%).

HPLC purity: 99.7%

Desfluoro impurity: 0.02%

Example 2:

Preparation of Cinacalcet HCl from 3-[3-(trifluoromethyl)phenyl]-2-propenal :

Stage 1:

Preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa)

Method a:

3-[3-(Trifluoromethyl)phenyl]-2-propen-1-ol (25 g, 124 mmol) was added into a solution of toluene (225 ml) at 25-30°C. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (30.9 g, 136 mmol) was added to the above solution at 5-10°C. The slurry was stirred for 7 hrs at 25-30°C and filtered at the same temperature. The filtrate was washed with 5% aqueous sodium bicarbonate solution and concentrated under reduced pressure to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (22.3 g, 90%). HPLC purity: 96.21 %.

Method b:

3-[3-(Trifluoromethyl)phenyl]-2-propen-1-ol (11 g, 55 mmol) was added into toluene (110 ml) at 25°C. Activated manganese dioxide (71 g, 816 mmol) was added to the solution at 28°C. The slurry was stirred for 5 hrs and the inorganic salts were

filtered at 28°C. The filtrate was concentrated under reduced pressure to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (8.4 g, 77%).

HPLC purity: 97.62 %.

5 Stage-2:

Preparation of 3-(3-(trifluoromethyl)phenyl)-N-((R)-1-(naphthalen-1-yl)ethyl)-prop-2-en-1-amine hydrochloride (unsaturated Cinacalcet hydrochloride) (IIa)

Method a:

3-[3-(Trifluoromethyl)phenyl]-2-propenal (20 g, 100 mmol) was added to a solution
10 of (R)-1-(1-naphthyl)ethylamine (15.39 g, 90 mmol) in tetrahydrofuran (500 ml) at 25-30°C and the solution was cooled to 10-15°C. Acetic acid (7.8 g) and sodium triacetoxyborohydride (prepared separately by treating 5.17 g of sodium borohydride and 24.5 g of acetic acid in 100 ml of tetrahydrofuran) were added to the solution. The reaction mass was concentrated by removing THF after stirring for 2 hr at 5-10°
15 C. The resulting residue was dissolved in toluene (200 ml) and washed with 1N HCl solution to remove unreacted amine. The organic layer was concentrated to produce unsaturated Cinacalcet hydrochloride, which was isolated from acetonitrile and dried to produce unsaturated Cinacalcet hydrochloride (26.8 g, 68 %).

HPLC purity: 99.63 %.

20

Method b:

3-[3-(Trifluoromethyl)phenyl]-2-propenal (8 g, 40 mmol) was added to a solution of
(R)-1-(1-naphthyl)ethylamine (6.15 g, 36 mmol) in tetrahydrofuran (200 ml) at 25-30°C and the solution was cooled to 10-15°C. Acetic acid (3.12 g) and sodium triacetoxyborohydride (prepared separately by treating 2.06 g of sodium borohydride and 9.75 g of acetic acid in 40 ml of tetrahydrofuran) were added to the solution.
25 The reaction mass was concentrated by removing THF after stirring for 2 hr at 5-10° C. The resulting residue was dissolved in toluene (80 ml) and washed with 1N HCl solution to remove unreacted amine. The organic layer was concentrated to produce
30 unsaturated Cinacalcet hydrochloride, which was isolated from acetonitrile and dried to produce unsaturated Cinacalcet hydrochloride (10.4 g, 66 %).

HPLC purity: 99.28 %.

Stage-3:

Preparation of Cinacalcet HCl

Method a:

A mixture of unsaturated Cinacalcet hydrochloride (25g, 64 mmol) and 5% Pd/C (2.5g) in methanol (90 ml) were hydrogenated at 3 Kg/cm² for 2.5 hr at 20-25°C. The reaction mass was filtered and concentrated to remove methanol under reduced pressure. Acetonitrile (87.5 ml) was added. The resulting precipitate was stirred at 0-5°C for 3 hr, filtered and dried to produce Cinacalcet hydrochloride (22.3 g, 89%).

HPLC purity: 99.9%

Method b:

A mixture of unsaturated Cinacalcet hydrochloride (9g, 23 mmol) and 5% Pd/C (0.9g) in methanol (72 ml) was hydrogenated at 3 Kg/cm² for 3 hr at 20-25°C. The reaction mass was filtered and concentrated to remove methanol under reduced pressure. Acetonitrile (31.5 ml) was added. The resulting precipitate was stirred at 0-5°C for 3 hr, filtered and dried to produce Cinacalcet hydrochloride (7 g, 77 %).

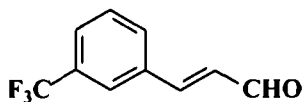
HPLC purity: 99.6%

Method c:

Titanium isopropoxide (2.13 g, 7.5 mmol) was added to the mixture of 3-[3-(Trifluoromethyl)phenyl]-2-propenal (15 g, 75 mmol) and (R)-1-(1-naphthyl)ethylamine (11.54 g, 68 mmol) at 10-15° and stirred for 6 hrs. Ethyl acetate (360 ml) was added and filtered to remove the salts. The resulting clear solution was hydrogenated at 1Kg/cm² in the presence of 5% pd on carbon (1.2 g) at 0-5°C. The reaction mass was filtered to remove the catalyst. The resulting filtrate was washed with 1N HCl solution to remove impurities. The resulting organic layer was concentrated under reduced pressure. Ethyl acetate was added to the resulting residue, filtered and dried to produce pure Cinacalcet hydrochloride. (13 g, 44%).

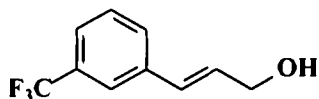
WE CLAIM

1. A process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa),

**Formula IIIa**

which comprises:

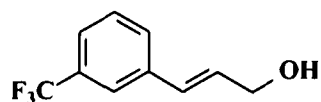
oxidizing 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb)

**Formula IVb**

- with suitable oxidizing agent, optionally in the presence of a catalyst, in a solvent to produce 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa).
2. The process according to claim 1, wherein suitable oxidizing agent used in the reaction is selected from 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), 3,4,5,6-tetrachloro-1,2-benzoquinone (*o*-chloranil), 2,3,5,6-tetrachloro-1,4-benzoquinone (*p*-chloranil), 1,4-benzoquinone (*p*-benzoquinone), manganese dioxide (MnO₂), potassium permanganate (KMnO₄), potassium dichromate (K₂Cr₂O₇), chromium trioxide (CrO₃) and sodium hypochlorite (NaOCl).
3. The process according to claim 1, wherein the catalyst is selected from a nitroxyl compound.
4. The process according to claim 3, wherein the nitroxyl compound is selected from 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO).
5. The process according to claim 1, wherein solvent is inert organic solvent, selected from acetonitrile, cyclic or acyclic alkanes such as hexane, heptane, methylcyclohexane; aromatic solvents such as toluene; halogenated solvents such as dichloromethane, dichloroethane, chloroform; esters such as ethyl

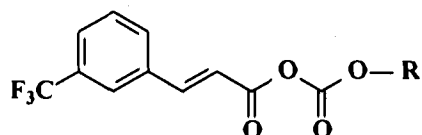
acetate, butyl acetate, isopropyl acetate or ethers such as diethyl ether, tetrahydrofuran or tert-butyl methyl ether and/or mixtures thereof.

6. The process as claimed in claim 1, wherein 3-[3-(trifluoromethyl)phenyl]-2-propenal (IIIa) is converted to Cinacalcet hydrochloride.
7. A process for the preparation of 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb),

**Formula IVb**

which comprises:

reducing mixed anhydride of Formula (XVIII) with a suitable reducing agent in a solvent,

**Formula XVIII**

wherein R represents C₁₋₃ alkyl, benzyl and substituted benzyl.

8. The process according to claim 7, wherein suitable reducing agent is selected from sodium borohydride, lithium aluminium hydride, zinc borohydride, and calcium borohydride.
9. The process according to claim 7, wherein solvent is selected from water, dioxane, toluene, THF and mixtures thereof.
10. The process as claimed in claim 7, wherein 3-[3-(trifluoromethyl)phenyl]-2-propen-1-ol (IVb) is converted to Cinacalcet hydrochloride.
11. A pharmaceutical composition of Cinacalcet hydrochloride prepared by the process according to any of the claims 6 & 10.