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(54) Title: IMPROVED PROCESS FOR THE PREPARATION OF FINERENONE

(57) Abstract: The present invention provides an improved process for the preparation of Finerenone with high yield. It also relates to industrially viable process for the preparation of Finerenone (I).

IMPROVED PROCESS FOR THE PREPARATION OF FINERENONE

FIELD OF THE INVENTION

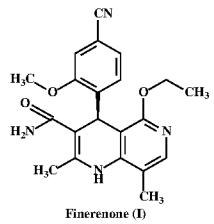
The present invention relates to an improved process for the preparation of Finerenone with high yield. It also relates to an industrially viable process for the preparation of Finerenone (I).

BACKGROUND OF THE INVENTION

Finerenone, sold under the brand name Kerendia, which is a nonsteroidal anti-mineralocorticoid that is under study for the treatment of chronic heart failure. Kerendia is indicated to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, nonfatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D).

Common side effects include hyperkalemia (high levels of potassium), hypotension (low blood pressure), and hyponatremia (low levels of sodium).

Finerenone having a chemical name; 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide is represented with structure as follows:

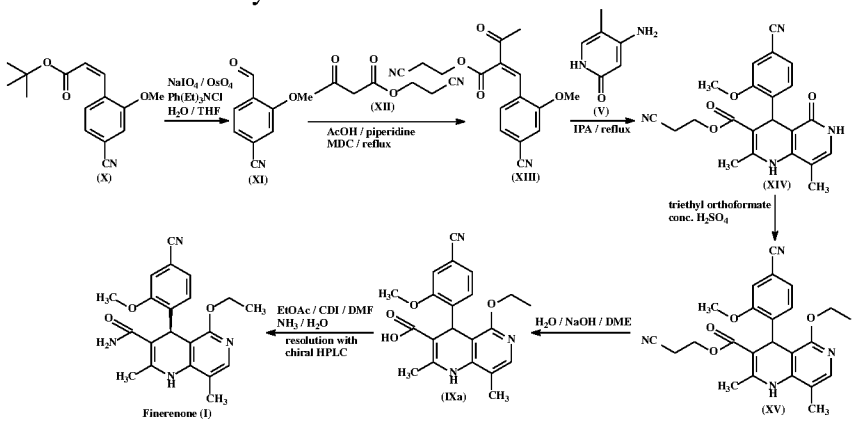


Finerenone (I)

Finerenone was first described in example 4 and 5 of US 8436180, where the process involves conversion of the compound of formula (X) to the compound of formula (XI) in the presence of $NaIO_4$ / OsO_4 / $Ph(Et)_3NCl$ / H_2O. The compound of formula (XI) is then reacted with the compound of formula (XII) in the presence of AcOH / piperidine and MDC to yield the compound of formula (XIII). The compound of formula (XIII) is subsequently reacted with the compound of formula (V) in the presence of IPA to obtain the compound of formula (XIV). The

compound of formula (XIV) is further reacted with triethyl orthoformate in presence of conc. H_2SO_4 to yield the compound of formula (XV). The compound of formula (XV) undergoes hydrolysis in presence of H_2O / NaOH to yield the compound of formula (IXa). The compound of formula (IXa) transformed into racemic Finerenone (Ia) in the presence of EtOAc / CDI / DMF / NH_3 and H_2O Finally, resolution with chiral HPLC to yield Finerenone (I).

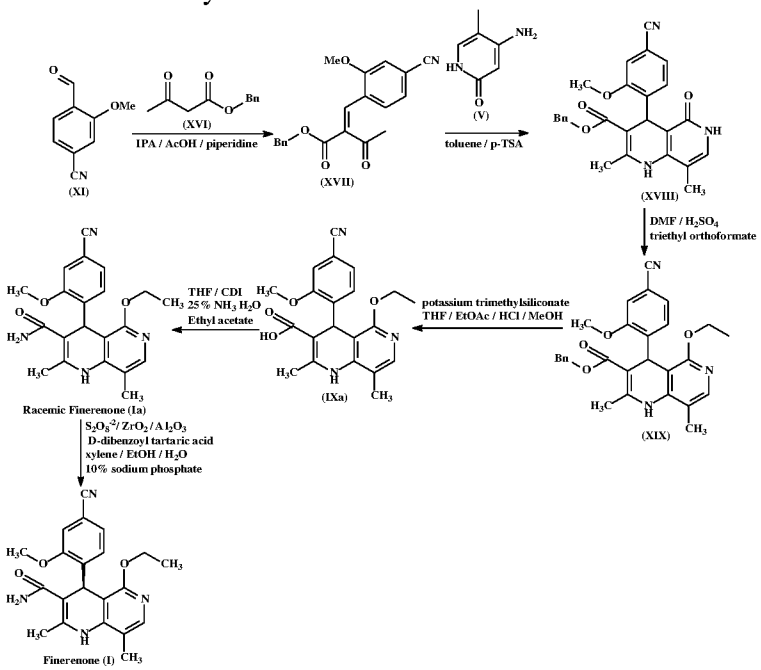
The process is schematically shown as below:



Scheme 1

CN 114605410 A of Zhejiang Chemtrue discloses a process for the preparation of Finerenone (I), by reacting the compound of formula (XI) with the compound of formula (XVI) in presence of IPA, AcOH and piperidine to yield the compound of formula (XVII). The compound of formula (XVII) is reacted with the compound of formula (V) in presence of toluene and p-TSA to yield the compound of formula (XVIII). The compound of formula (XVIII) is reacted with triethyl orthoformate in presence of DMF, H_2SO_4 to yield the compound of formula (XIX). The compound of formula (XIX) undergoes hydrolysis in presence of potassium trimethylsiliconate THF / EtOAc / HCl and MeOH to yield the compound of formula (IXa). The compound of formula (IXa) reacted with CDI and followed by hydrolysed in presence of 25% $NH_3.H_2O$ to yield the racemic Finerenone (Ia). The compound of racemic Finerenone (Ia) undergoes resolution with D-dibenzoyl tartaric acid in presence of $S_2O_8^{-2}$/ ZrO_2 / Al_2O_3 / xylene / EtOH / H_2O and 10% sodium phosphate to yield Finerenone (I).

The process is schematically shown as below:

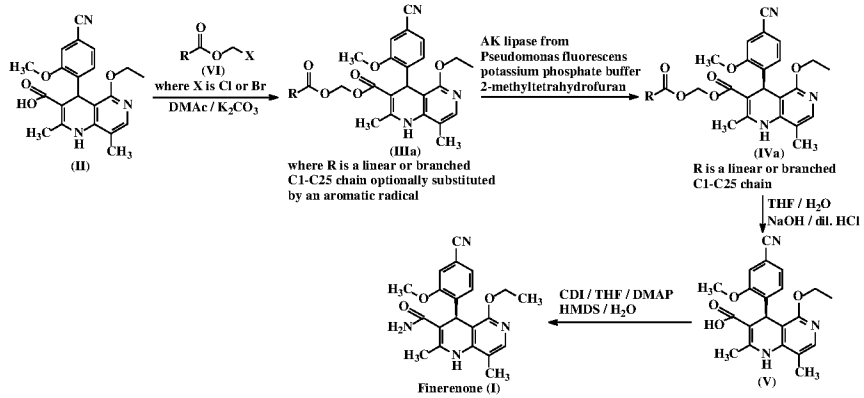


Scheme 2

The processes described in Schemes 1 and 2 all suffer from low overall yield and high production costs due to the use of chiral HPLC resolution after obtaining Finerenone racemate. This method is unsuitable for industrialized mass production.

In Bayer's 202217021498 patent, disclosed a process for the preparation of Finerenone, the process comprises the compound of formula (II) is reacted with the compound of formula (VI) in presence of DMAc / K_2CO_3 to obtain the compound of formula (IIIa). The compound of formula (IIIa) undergoes resolution with *AK lipase* from Pseudomonas fluorescens in the presence of potassium phosphate buffer 2-methyltetrahydrofuran to yield the compound of formula (IVa). The compound of formula (IVa) undergoes basic hydrolysis in the presence of NaOH / THF / H_2O and dil. HCl to yield the compound of formula (V). The compound of formula (V) is reacted with CDI in presence of THF and DMAP, followed by reaction with HMDS after hydrolysed in presence of water to afford Finerenone (I).

The process is schematically shown as below:



Scheme 3

The resolving process described in scheme 3 is an enzymatic process. Using enzymes is a very expensive process and requires a longer span of time (2-4 days) for the conversion. The crude reaction product was purified by flash chromatography, and the yield of the product is 32%.

Therefore, developing an industrially viable synthetic route is essential. Our inventors have successfully developed an improved process for the preparation of Finerenone with high yield and purity, and this process also represents a cost-effective and efficient synthesis method.

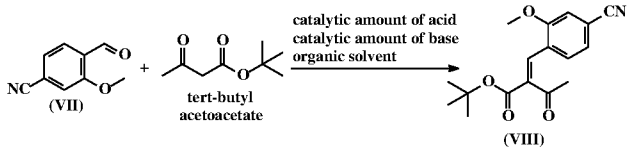
The present invention utilizes a chiral reagent for resolution, offering a cost-effective approach that significantly reduces reaction time to 4-5 hours, eliminates the need for chromatography purification, and delivers a high product yield.

SUMMARY OF THE INVENTION

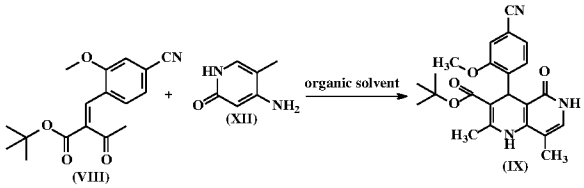
The present invention relates to an improved process for the preparation of Finerenone with high yield. It also relates to an industrially viable process for the preparation of Finerenone (I).

One aspect of the present invention provides an improved process for the preparation of Finerenone (I), comprising the steps of:

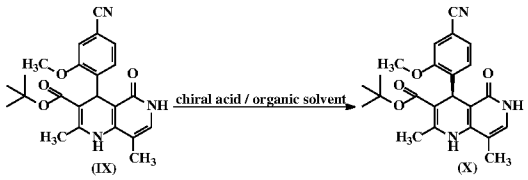
a) reacting the compound of formula (VII) with tert-butyl acetoacetate in the presence of a catalytic amount of either acid or a catalytic amount of base and an organic solvent yields the compound of formula (VIII);



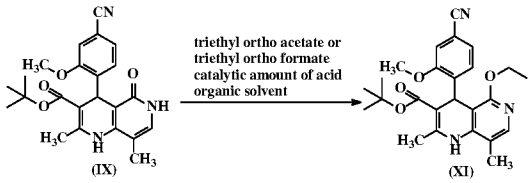
b) reacting the compound of formula (VIII) with the compound of formula (XII) in an organic solvent yields the compound of formula (IX);



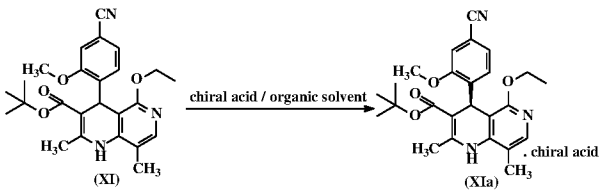
c) optionally, treating the racemic compound of formula (IX) with a chiral acid in an organic solvent yields the compound of formula (X);



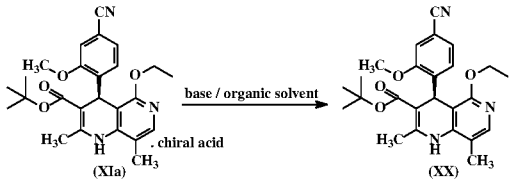
d) reacting the compound of formula (IX) with either triethyl ortho acetate or triethyl ortho formate in the presence of a catalytic amount of acid and an organic solvent yields the compound of formula (XI);



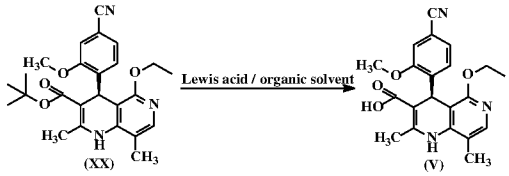
e) treating the racemic compound of formula (XI) with a chiral acid in an organic solvent yields the compound of formula (XIa);



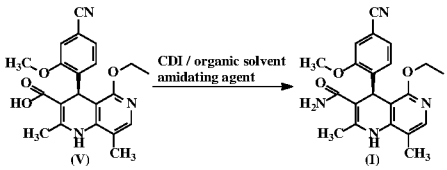
f) neutralizing the compound of formula (XIa) with a base in an organic solvent yields the compound of formula (XX);



g) hydrolyzing the compound of formula (XX) with Lewis acid in an organic solvent yields the compound of formula (V);

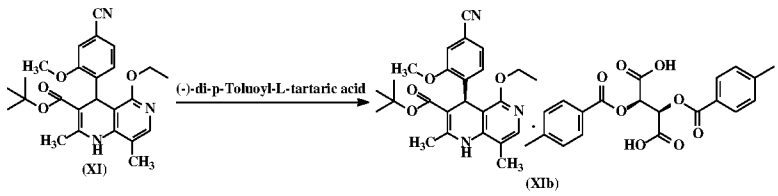


h) reacting the compound of formula (V) with CDI in an organic solvent, followed it with an amidating agent, yields Finerenone (I).

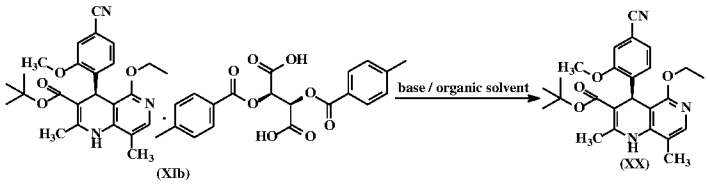


Another aspect of the present invention provides a process for the preparation of Finerenone (I), comprising the following steps:

a) treating the racemic compound of formula (XI) with (-)-di-p-Toluoyl-L-tartaric acid yields the compound of formula (XIb);

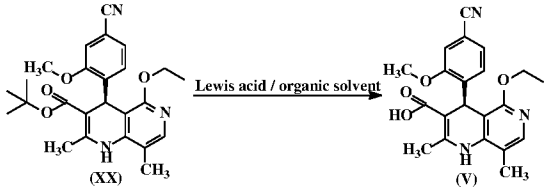


b) neutralizing the compound of formula (XIb) with a base in an organic solvent yield the compound of formula (XX);



(XIb) (XX)

c) hydrolyzing the compound of formula (XX) with Lewis acid in an organic solvent yields the compound of formula (V);

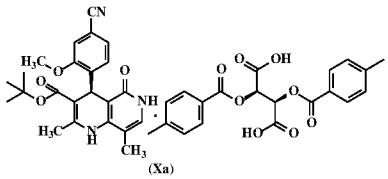


(XX) (V)

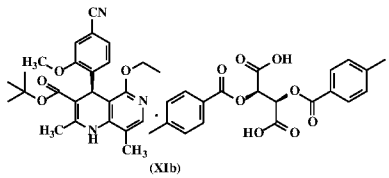
d) converting the compound (V) obtained in step (c) to Finerenone (compound I); and

e) optionally, purifying compound I.

In another aspect, the present invention provides the compounds of formulae (Xa) and (XIb).



(Xa)



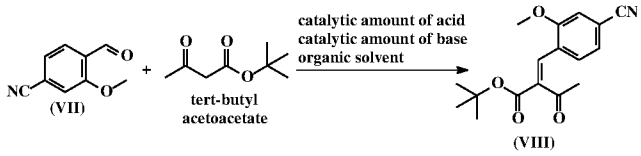
(XIb)

DETAILED DESCRIPTION OF THE INVENTION

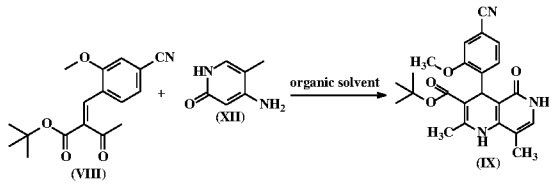
The present invention relates to an improved process for the preparation of Finerenone with high yield. It also relates to an industrially viable process for the preparation of Finerenone (I).

One embodiment of the present invention provides an improved process for the preparation of Finerenone (I), comprising the following steps:

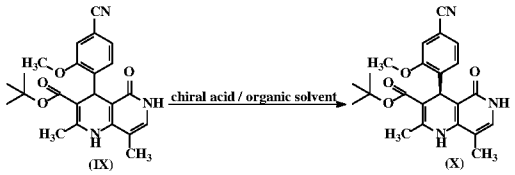
a) reacting the compound of formula (VII) with tert-butyl acetoacetate in the presence of a catalytic amount of either acid or a catalytic amount of base and an organic solvent yields the compound of formula (VIII);



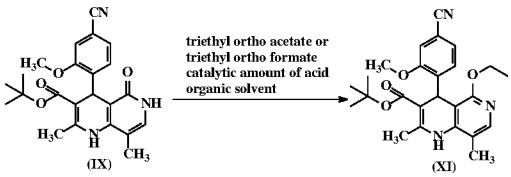
b) reacting the compound of formula (VIII) with the compound of formula (XII) in an organic solvent yields the compound of formula (IX);



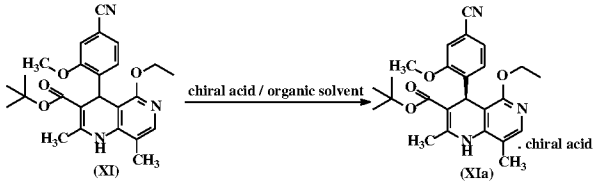
c) optionally, treating the racemic compound of formula (IX) with a chiral acid in an organic solvent yields the compound of formula (X);



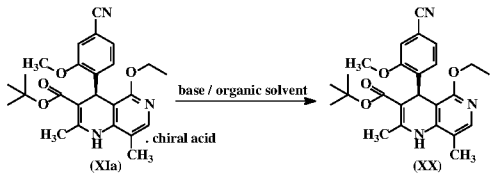
d) reacting the compound of formula (IX) with either triethyl ortho acetate or triethyl ortho formate in the presence of a catalytic amount of acid and an organic solvent yields the compound of formula (XI);



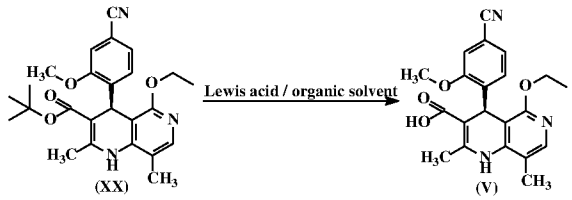
e) treating the racemic compound of formula (XI) with a chiral acid in an organic solvent yields the compound of formula (XIa);



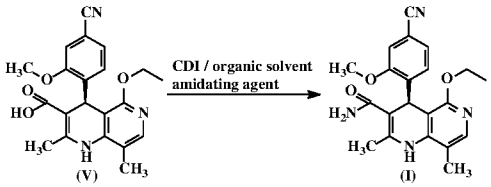
f) neutralizing the compound of formula (XIa) with a base in an organic solvent yields the compound of formula (XX);



g) hydrolyzing the compound of formula (XX) with Lewis acid in an organic solvent yields the compound of formula (V);



h) reacting the compound of formula (V) with CDI in an organic solvent, followed it with an amidating agent, yields Finerenone (I).



According to one embodiment of the present invention, reacting the compound of formula (VII) with tert-butyl acetoacetate in the presence of catalytic amount of either acid or catalytic amount of base in an organic solvent, stirring the reaction mixture for 3-6 hours at 20-40°C, preferably 4-5 hours at 25-40°C, yields the compound of formula (VIII). Reacting the compound of formula (VIII) with the compound of formula (XII) in an organic solvent yields the compound of formula (IX). Optionally, treating the compound of formula (IX) with a chiral acid in an organic solvent yields the compound of formula (X). Further, reacting the compound of formula (IX) with either triethyl ortho acetate or triethyl ortho formate in the presence of catalytic amount of acid and an organic solvent yields the compound of formula (XI), which is treated with a chiral acid in the presence of an organic solvent at 50-60°C for 1 hour, followed by purification with alcohol solvent

yields the compound of formula (XIa). Basifying the compound of formula (XIa) with a base in an organic solvent and adjusting the pH to 6.5-7.5 using a base to yield the compound (XX), which is hydrolyzed with Lewis acid in an organic solvent yields the compound of formula (V). Reacting the compound of formula (V) with CDI (Carbonyldiimidazole) in an organic solvent, followed by reacting with an amidating, agent yields Finerenone (I).

According to an embodiment of the present invention, wherein base is selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium phosphate tribasic, triethylamine, tert-butylamine, pyridine, piperidine, or diazabicycloundecane (DBU).

According to an embodiment of the present invention, wherein lewis acid is selected from aluminium chloride, titanium chloride, Zinc bromide, aluminium bromide, boron trifluroide, boron trichloride, ferric chloride, tin(IV) chloride, calcium chloride, calcium chloride dehydrate. Magnesium and lithium salts, as well as trialkylsilyl halides, magnesium chloride, magnesium bromide, magnesium iodide, and magnesium sulphide, lithium chloride, lithium bromide, lithium iodide, and lithium sulfide. Alumium chloride is preferred.

According to an embodiment of the present invention, wherein the chiral acid is selected from tartaric acid, dibenzoyl-L-tartaric acid, mandelic acid, (+)-di-p-toluoyl-d-tartaric acid, (-)-di-p-toluoyl-d-tartaric acid, (-)-Di-p-toluoyl-L-tartaric acid, diisopropyl D-(-)-tartrate, D-(+)-malic acid, dimethyl L-(+)-tartrate and L-valine.

According to an embodiment of the present invention, the suitable solvent is selected sulfoxides such as dimethyl sulfoxide and diethyl sulfoxide; alcohols such as methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol, tert-butanol; nitriles such as acetonitrile and propionitrile; ether solvent such as tetrahydrofuran, diisopropylether, diethyl ether, 2-methyltetrahydrofuran,

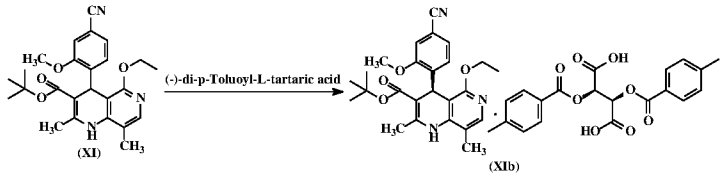
cyclopentyl methyl ether, methyl tert-butyl ether, dioxane; amides such as N,N-dimethylformamide and N,N-dimethylacetamide; and aromatic hydrocarbons such as toluene, anisole, heptane and xylene; esters such as ethylacetate, methylacetate, butyl acetate, isopropyl acetate, methoxy ethyl acetate; ketones such as acetone, methylisobutyl ketone, 2-pentanone, ethylmethylketone, diethylketone; halogenated hydrocarbons such as chloroform, dichloromethane; water; cyclohexane and N-methyl-2-pyrrolidone or mixtures thereof.

According to an embodiment of the present invention, the acid selected from, but not limited to, inorganic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, perchloric acid, carbonic acid; and organic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid, butyric acid, valeric acid, capric acid, oxalic acid, malonic acid, maleic acid, fumaric acid, lactic acid, succinic acid, citric acid, uric acid, tartaric acid, benzoic acid, 4-hydroxybenzoic acid, salicylic acid, oleic acid, octanoic acid, stearic acid, mandelic acid, adepic acid, pivalic acid, camphorsulfonic acid, substituted/unsubstituted alkyl/aryl sulfonic acids such as methanesulfonic acid, ethanesulfonic acid, propanesulfonic acid, benzenesulfonic acid, ptoluenesulfonic acid, naphthalenesulfonic acid or mixtures thereof.

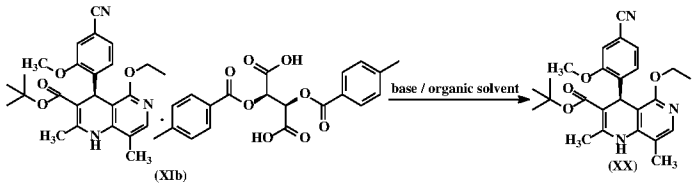
According to an embodiment of the present invention, wherein the an amidating agent is selected from, ammonia, hexamethyldisilazane, ammonium carbonate, and ammonium formate.

In another embodiment, the present invention provides a process for the preparation of Finerenone (I), comprising the following steps:

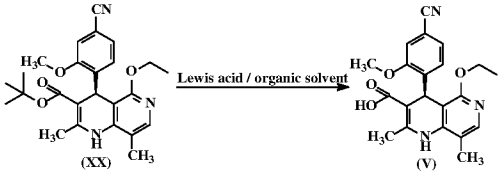
a) treating the racemic compound of formula (XI) with (-)-di-p-Toluoyl-L-tartaric acid yields the compound of formula (XIb);



b) neutralizing the compound of formula (XIb) with a base in an organic solvent yields the compound of formula (XX);



c) hydrolyzing the compound of formula (XX) with Lewis acid in an organic solvent yields the compound of formula (V);

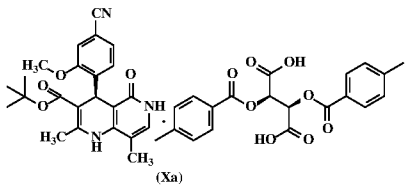


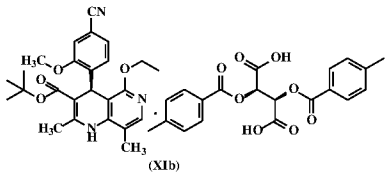
d) converting the compound (V) obtained in step (c) to Finerenone (compound I); and

e) optionally, purifying compound I.

According to an embodiment of the present invention, the racemic compound of formula (XI) is treated with (-)-di-p-Toluoyl-L-tartaric acid in an organic solvent at 50-60°C. The mixture was stirred and purified with alcohol solvent yields the compound of formula (XIa). The pH of the compound of formula (XIa) is adjusted to 6.5-7.5, resulting in the compound (XX). Hydrolyzing the compound of formula (XX) with Lewis acid in an organic solvent yields the compound of formula (V); This compound is further converted into Finerenone (I).

In yet another embodiment, the present invention provides the compound of formulae (Xa) and (XIb).

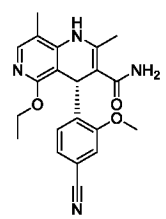




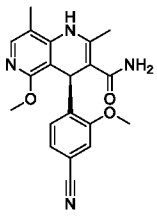
(XIb)

In an embodiment, Finerenone (compound I) obtained through the process of the present invention has a chiral purity of greater than 99%

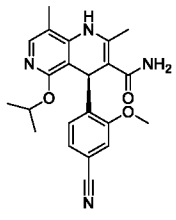
In an embodiment, Finerenone (compound I) obtained by the process of the present invention has a purity of ≥99.0%. The level of the following impurities represented by the structural formulae is less than 0.15% w/w relative to the amount of Finerenone (I).



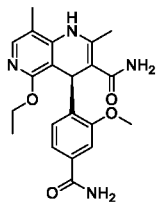
Fiberenone enantiomer impurity



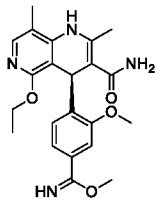
Methyl finerenone impurity



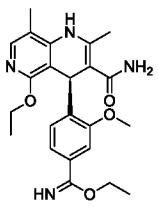
isopropyl finerenone impurity



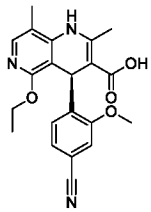
Diamide impurity



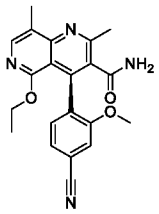
Methyl imidate impurity



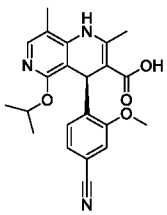
Ethyl imidate impurity



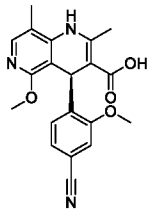
Acid impurityor N-1



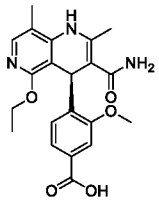
Double bond impurity



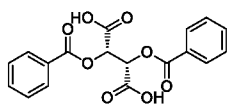
Acid isopropyl impurity



Acid methyl impurity



Hydrolized impurity



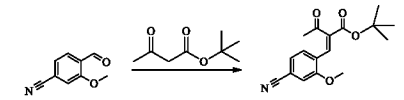
di benzoyl d-tartaric acid impurity

The level of impurities in Finerenone (compound I) is determined by high-performance liquid chromatography (HPLC).

The following examples illustrate the present invention, but should not be construed as limiting the scope of the invention.

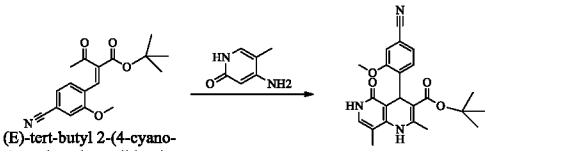
EXAMPLES

Example -1: Preparation of (E)-tert-butyl 2-(4-cyano-2-methoxybenzylidene)-3-oxobutanoate



4-Formyl-3-methoxy benzonitrile (100 grams) ¸tert-butyl acetoacetate (130 grams), acetic acid (93.72), piperidine (5.30 grams) and isopropyl alcohol (500 mL) were charged to a flask. The reaction mixture was stirred at 25-30°C for 4-5 hours. After completion of the reaction, the mixture was filtered, and the solid was washed with isopropyl alcohol. The wet material was dried at 50-55°C to yield (E)-tert-butyl 2-(4-cyano-2-methoxybenzylidene)-3-oxobutanoate (Yield: 175 grams (93%); purity = 98.5%). The Z-isomer content was around 0.5%.

Example-2: Preparation of Tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-di methyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate



A flask was charged with (E)-tert-Butyl 2-(4-cyano-2-methoxybenzylidene)-3-oxobutanoate (100 grams), 4-amino-5-methyl-pyridin-2(1H)-one (43 grams), and DMSO (400 ml). The reaction mixture was then heated to 110-120°C for 8-10 hours. Upon completion of the reaction, the mixture was cooled to 25-30°C. Water was added, and the resulting mixture was stirred for 2-3 hours at 25-30°C. The solid product was filtered, washed with ethyl acetate and dried under vacuum at 55-60°C, yielding of tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

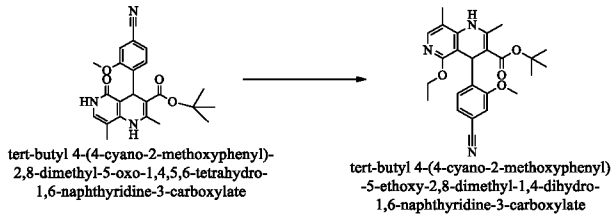
(Yield: 110 grams (81%); purity = 97%).

Example -2a: Purification of Tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-di methyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate

A flask was charged with Tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate (100 grams) and ethyl acetate (800 mL). The reaction mixture was heated to 55-60°C for 1-2 hours. After cooling to 25-30°C, the mixture was stirred for an additional 2-3 hours at the same temperature. The resulting solid was filtered, washed with ethyl acetate and then dried under vacuum at 55-60°C, yielding pure tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate.

(Yield: 95 grams (95%); purity = 98%).

Example-3: Preparation of 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-di methyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate



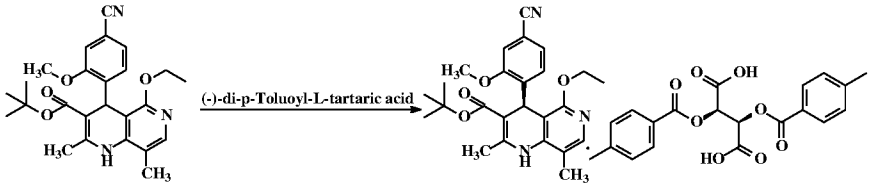
tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate

tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate

A flask was charged with Tert-butyl 4-(4-cyano-2-methoxyphenyl)-2,8-dimethyl-5-oxo-1,4,5,6-tetrahydro-1,6-naphthyridine-3-carboxylate (100 grams) and N-Methyl-2-pyrrolidone (NMP) (300 mL). To this mixture, triethyl orthoacetate (120 grams) was added, followed by the addition of sulfuric acid (4.0 grams). The reaction mixture was then heated to 100-110°C for 2-3 hours. Upon completion of the reaction, the mixture was cooled to 50-55°C, and water (600 mL) was introduced. The resulting mixture was stirred for an additional 2-3 hours at 25-30°C. The solid product was filtered, washed with water and then dried under vacuum at 55-60°C, yielding tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate.

(Yield: 95 grams (89%); purity = 98%).

Example -4: Preparation of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate



Tert-Butyl 4-(4-cyano-2-methoxyphenyl) -5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate

(S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate

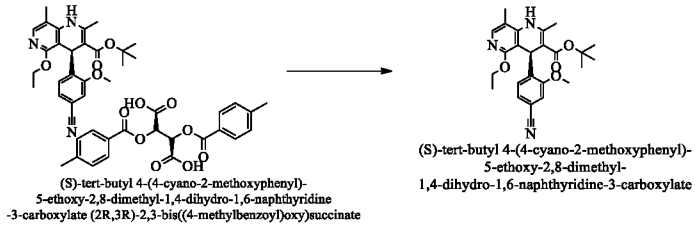
In a reaction flask, Tert-Butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (100 g) was combined with ethanol (1500 mL). The mixture was then heated to 50-60°C, and (-)-Di-p-toluoyl-L-tartaric acid (90 g) was added. Stirring continued for 1 hour at 50-60°C. Afterward, the reaction mixture was cooled to 25-30°C, filtered, washed with ethanol (100 mL) and then dried under vacuum at 55-60°C, resulting in the production of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate.

(Yield: 85 grams (45%); purity = 99%, chiral purity = 99%)."

Example-4a: Purification of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate

In a reaction flask, (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (100 grams) was combined with ethanol (1000 mL). The reaction mixture was then heated to 70-80°C and stirred for 1 hour. Following this, the reaction mixture was cooled to 25-30°C, filtered, and rinsed with ethanol. The resulting wet material was dried under vacuum at 55-60°C, yielding 95 grams of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (yield: 95%; purity of 99% and a chiral purity of 99.8%).

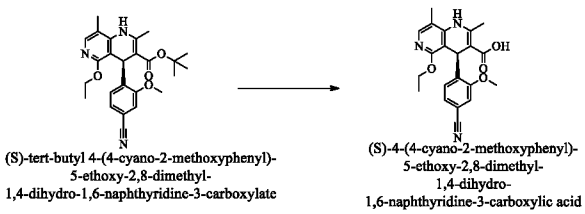
Example-5: Preparation of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate



In a reaction flask, (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate (2R,3R)-2,3-bis((4-methylbenzoyl)oxy)succinate (100 grams) was added into a mixture of dichloromethane (DCM, 500 mL) and demineralized water (DM water, 300 mL). The pH of the reaction mixture was adjusted to 6.5-7.5 using an aqueous sodium carbonate solution and stirred for 10-15 minutes at 25-30°C. The organic layer was separated and washed with purified water. Subsequently, the solvent was completely evaporated, and n-heptane (300 mL) was added. After stirring for 2 hours, the mixture was filtered and washed with n-heptane (100 mL), resulting in the production of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate.

(Yield: 50 grams (95%); purity = 99%).

Example-6: Preparation of (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid.

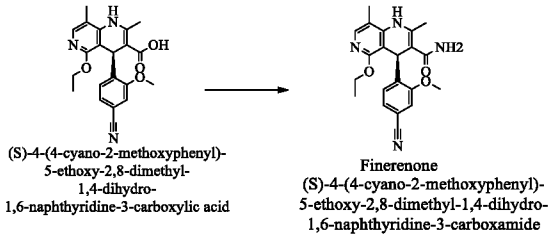


In a reaction flask, Aluminum chloride ($AlCl_3$) and methylene dichloride (MDC) were charged and stirred for 10-15 minutes. Subsequently, Anisole was slowly added to the reaction mixture over 30 minutes, and the mixture was maintained at 25-35°C for another 30 minutes. Following this, 100 grams of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate dissolved in MDC were introduced into the reaction mixture, and the

mixture was maintained for 1-2 hours. Once the reaction concluded, the compound was filtered and washed with MDC. The resulting wet solid was quenched in an ammonium chloride solution, and the compound was extracted with ethyl acetate. Subsequently, the solvent was distilled, and the compound was isolated in acetonitrile to yield (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid.

The yield was 85 grams (97%), with a purity of 98.5%.

Example -7: Preparation of (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide (Finerenone).



(S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid

Finerenone
(S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide

In a reaction flask, (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (100 g) and CDI were added into acetonitrile. The mixture was maintained at 25-30°C for 2 hours. Following the completion of the reaction, the temperature of the reaction mixture was raised to 60-65°C. HMDS was slowly added, and the mixture was maintained at 60-65°C for 3-4 hours. After the reaction concluded, the mixture was cooled to 0-5°C. Purified water was added, and the temperature of the reaction mixture was gradually increased to 65-70°C, maintaining this temperature for 1-2 hours. Following the completion of the maintenance period, the compound was extracted with ethyl acetate. The organic layer was separated, distilled, and isolated in ethyl acetate to yield (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide. The obtained yield was 85 grams (85%), with a purity of 99.5%.

Example-8: purification of (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide (Finerenone).

In a reaction flask, Finerenone and ethanol were added and maintained at 30±5°C. Add activated carbon. As the reaction mass temperature reaches 75-80°C, add activated carbon again. Stir the mixture for 10-15 minutes. Next, pass it through a high-flow bed and wash it with ethanol. Distil the reaction mass until only 5 volumes remain at 45-50°C. Further, cool it to 25-35°C and stir for 1-2 hours. Gradually decrease the temperature to 0-5°C and continue stirring for another 1-2 hours. Filter the solid, wash it with ethanol, and dry it for 30 minutes. Finally, dry the material at 50-55°C for 8-10 hours to obtain pure Finerenone. The yield is 90-95 grams (95%) with a purity of 99.8%.

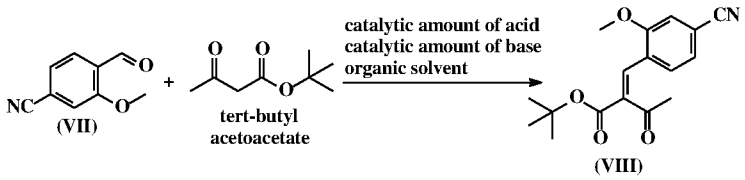
Example -9: purification of (S)-4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxamide (Finerenone).

In a reaction flask, charge Finerenone and ethanol and maintained at 30 ± 5°C. Then add activated carbon. Raise the temperature to 75-80°C and stir the mixture for 10-15 minutes. Wash the reaction mass with ethanol and subsequently maintain it at 50-55°C. Add pure seed material and maintain for 2 hours. Distil the mixture at 45-50°C, then further cool it to 25-35°C while stirring for 1-2 hours. Slowly decrease the temperature to 0-5°C and stir for another 1-2 hours. Filter the solid, wash it with ethanol, and dry it for 30 minutes. Finally, dry the material at 50-55°C for 8-10 hours to obtain pure Finerenone (Yield: 90-95 grams (95%); purity: 99.8%).

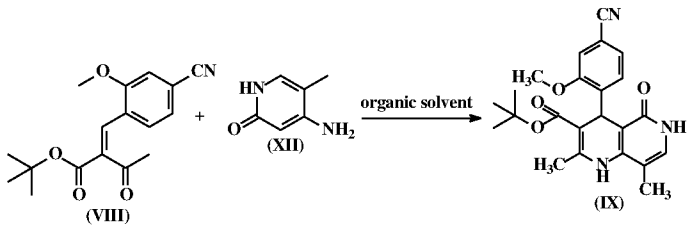
We Claim:

1. A process for preparing Finerenone (I), comprising the following steps:

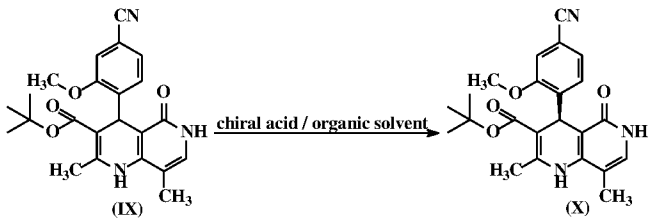
a) reacting the compound of formula (VII) with tert-butyl acetoacetate in the presence of a catalytic amount of either acid or base and an organic solvent yields the compound of formula (VIII);



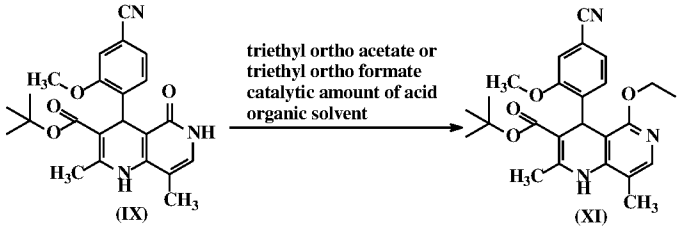
b) reacting the compound of formula (VIII) with the compound of formula (XII) in an organic solvent yields the compound of formula (IX);



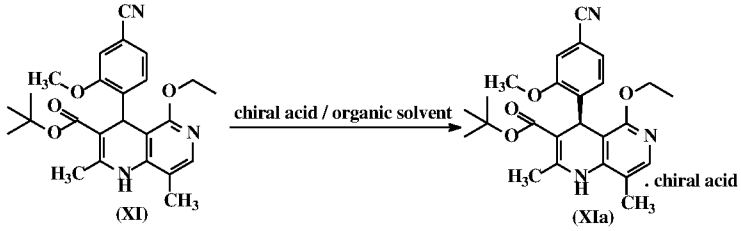
c) optionally, treating the racemic compound of formula (IX) with a chiral acid in an organic solvent yields the compound of formula (X);



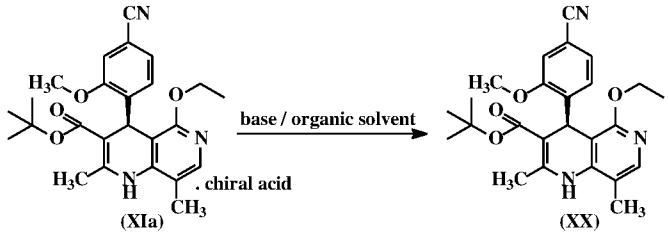
d) reacting the compound of formula (IX) with either triethyl ortho acetate or triethyl ortho formate in the presence of a catalytic amount of acid and an organic solvent yields the compound of formula (XI);



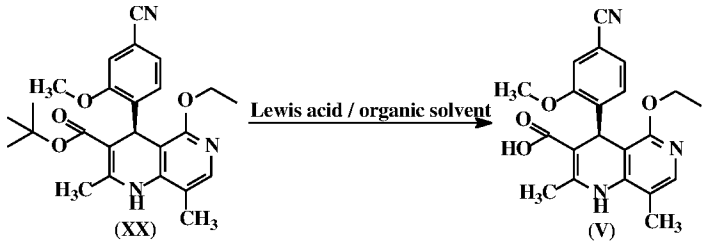
e) treating the racemic compound of formula (XI) with a chiral acid in an organic solvent yields the compound of formula (XIa);



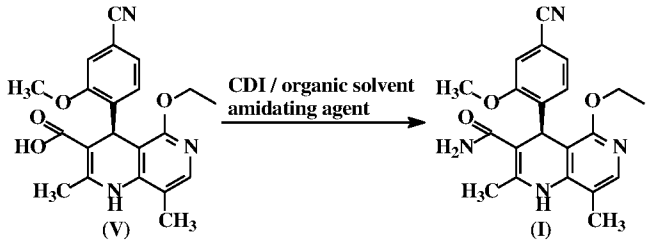
f) neutralizing the compound of formula (XIa) with a base in an organic solvent yields the compound of formula (XX);



g) hydrolyzing the compound of formula (XX) with a Lewis acid in an organic solvent yields the compound of formula (V);



h) reacting the compound of formula (V) with CDI in an organic solvent, followed it with an amidating agent, yields Finerenone (I).



2. The process as claimed in claim 1, wherein the base is selected from a group comprising sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium

phosphate tribasic, triethylamine, tert-butylamine, pyridine, piperidine, and diazabicycloundecane (DBU).

3. The process as claimed in claim 1, wherein the chiral acid is selected from a group comprising tartaric acid, dibenzoyl-L-tartaric acid, mandelic acid, (+)-di-p-toluoyl-d-tartaric acid, (-)-di-p-toluoyl-d-tartaric acid, (-)-Di-p-toluoyl-L-tartaric acid, diisopropyl D-(-)-tartrate, D-(+)-malic acid, dimethyl L-(+)-tartrate, and L-valine.

4. The process as claimed in claim 1, wherein the suitable solvent is selected from a group comprising dimethyl sulfoxide, methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, isobutanol, tert-butanol, acetonitrile, tetrahydrofuran, diisopropylether, diethyl ether, 2-methyltetrahydrofuran, methyl tert-butyl ether, dioxane, N,N-dimethylformamide, toluene, anisole, heptane, xylene, ethylacetate, isopropyl acetate, acetone, methylisobutyl ketone, chloroform, dichloromethane, water, cyclohexane and N-methyl-2-pyrrolidone, or mixtures thereof.

5. The process as claimed in claim 1, wherein the acid is selected from a group comprising hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, boric acid, perchloric acid, formic acid, acetic acid, trifluoroacetic acid, oxalic acid, malonic acid, maleic acid, fumaric acid, lactic acid, succinic acid, citric acid, tartaric acid, benzoic acid, 4-hydroxybenzoic acid, salicylic acid, mandelic acid, pivalic acid, camphorsulfonic acid, methanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid and naphthalenesulfonic acid, or mixtures thereof.

6. The process as claimed in claim 1, wherein the Lewis acid is selected from a group comprising aluminium chloride, titanium chloride, Zinc bromide, aluminium bromide, boron trifluroide, boron trichloride, ferric chloride, tin(IV) chloride, calcium chloride, calcium chloride dehydrate. Magnesium and lithium salts, as well as trialkylsilyl halides, magnesium chloride,

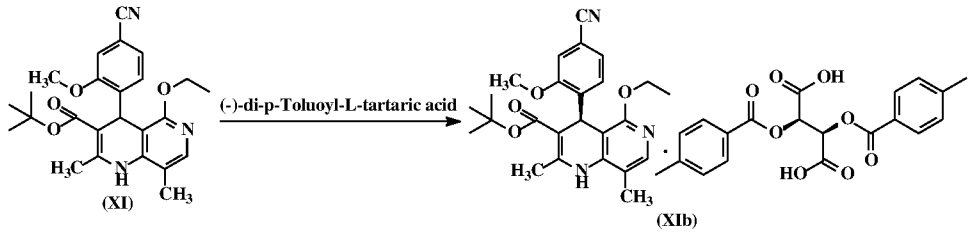
magnesium bromide, magnesium iodide, and magnesium sulphide, lithium chloride, lithium bromide, lithium iodide, and lithium sulfide.

7. The process as claimed in claim 1, wherein the amidating agent is selected from ammonia, hexamethyldisilazane, ammonium carbonate, and ammonium formate.

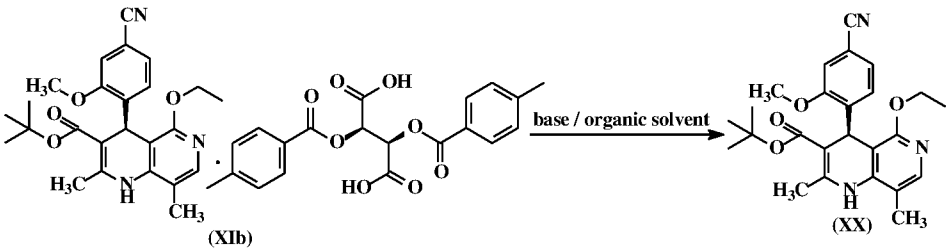
8. The process for the preparation of Finerenone as claimed in claim 1, wherein the Finerenone has a purity of ≥99%.

9. A process for preparing Finerenone (XX), comprising the following steps:

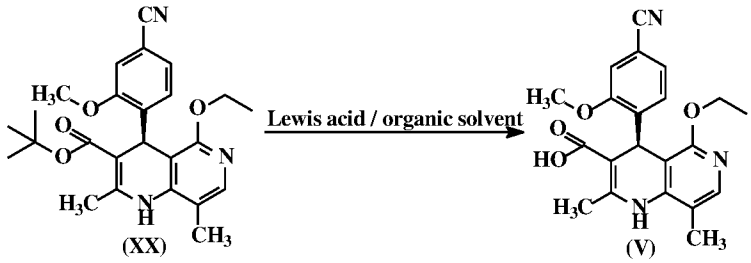
a) treating the racemic compound of formula (V) with (-)-di-p-Toluoyl-L-tartaric acid yields the compound of formula (XIb);



b) neutralizing the compound of formula (XIb) with a base in an organic solvent yields the compound of formula (XX);



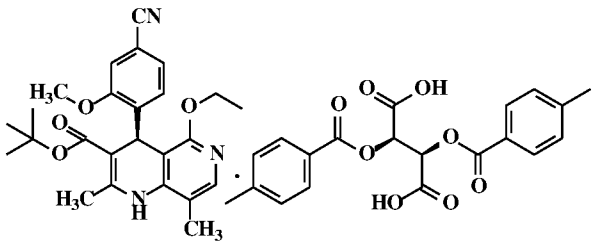
c) hydrolyzing the compound of formula (XX) with a Lewis acid in an organic solvent yields the compound of formula (V);



d) converting the compound (V) obtained in step (c) to Finerenone (compound I); and

e) optionally, purifying compound I.

10. A diastereomeric salt of (S)-tert-butyl 4-(4-cyano-2-methoxyphenyl)-5-ethoxy-2,8-dimethyl-1,4-dihydro-1,6-naphthyridine-3-carboxylate with (-) di-p-toluoyl-L-tartaric acid, represented by the compound of formula (XIb).



(XIb)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2023/062975

A. CLASSIFICATION OF SUBJECT MATTER
C07D471/04,C07D213/73,A61K31/4375,A61P9/00 Version=2024.01

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)

A61K, A61P, C07D

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

PatSeer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO2021074079A1 (BAYER AKTIENGESELLSCHAFT) 22 April 2021 (22-04-2021) whole document	1-8
Y	claims 7-13; description	9-10
A	EP3560922A1 (BAYER AG, BAYER PHARMA AG) 30 October 2019 (30-10-2019) whole document	1-8
Y	claims 10-14; description	9-10
Y	WO2021074078A1 (BAYER AKTIENGESELLSCHAFT) 22 April 2021 (22-04-2021) abstract; claims; description; examples 4a, 4c, 5a, 5b	1-10
Y	US10399977B2 (BAYER PHARMA AG) 03 September 2019 (03-09-2019) abstract; claims 13-14; schemes 1,2 in description; example 9	1-10
Y	WO2016016287A1 (BAYER PHARMA AKTIENGESELLSCHAFT) 04 February 2016 (04-02-2016) abstract; claims;	

☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed
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Date of the actual completion of the international search	Date of mailing of the international search report
28-03-2024	28-03-2024

Name and mailing address of the ISA/	Authorized officer
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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	scheme 1, description; example 9	1-10

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2023/062975

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