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(54) **Title:** PROCESS FOR PREPARATION OF BEMPEDOIC ACID AND ITS INTERMEDIATES

(57) **Abstract:** The present application relates to a process for preparation of Bempedoic acid of formula (I) or its pharmaceutically acceptable salts thereof. The present application also relates to a novel intermediates of formula (II) and formula (IIA) and its application in the preparation of Bempedoic aid. The present application further relates to the crystalline form of compound of formula (IIA).

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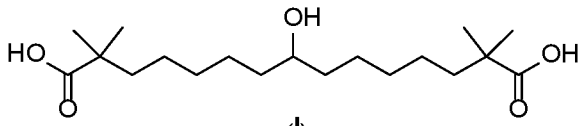
PROCESS FOR PREPARATION OF BEMPEDOIC ACID AND ITS INTERMEDIATES

FIELD OF INVENTION

The present application relates to a process for preparation of Bempedoic acid of formula (**I**) or its pharmaceutically acceptable salts thereof. The present application also relates to a novel intermediate (**II**) of Bempedoic acid, process for preparation thereof and use thereof in the preparation of Bempedoic aid.

BACKGROUND ART

Bempedoic acid (**I**) is an ATP Citrate Lyase inhibitor that, reduces cholesterol biosynthesis and lowers LDL-C by up-regulating the LDL receptor. The drug compound having the adopted name "Bempedoic Acid" has chemical name 8-Hydroxy-2,2,14,14-tetramethylpentadecanedioic acid having the following structure:

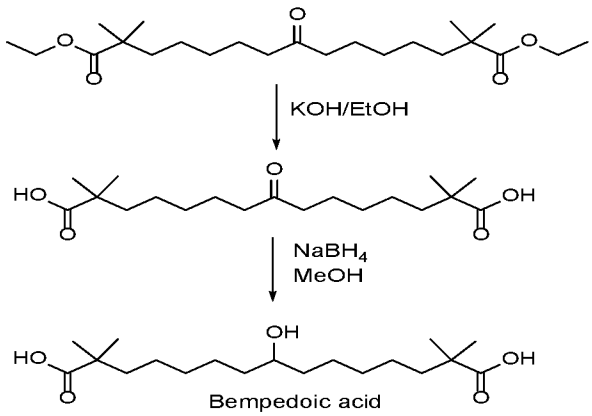


(I)

Both Bempedoic acid and a combination of Bempedoic acid/ Ezetimibe have been approved for the treatment of patients with elevated low-density lipoprotein cholesterol (LDL-C).

US7335799 discloses Bempedoic acid, its process of preparation or its pharmaceutically acceptable salt, hydrate, or solvate and pharmaceutical composition.

The following scheme-1 describe the process of Bempedoic in example 6.19 and 6.20 as given in US7335799.



Scheme-1

The process described above (Scheme-1) involves the use of excess amount (more than 4.2 mmol) of sodium borohydride ($NaBH_4$) to complete the reaction. In addition to this resulted Bempedoic acid is obtained in low yield (60%), as viscous oil, with low HPLC purity 83.8%. The low purity and viscous oily nature of Bempedoic acid is not suitable as active ingredient for use in pharmaceutical product.

Further, EP3666750A1, WO2020141419A2 and WO2020194152A1 disclose a process for preparation of Bempedoic acid by flipping the reduction and hydrolysis steps disclosed in US7335799 to provide solid Bempedoic acid with better purity. However, all those processes have limited use.

Still there is a need to provide a cost effective and commercially viable process for the preparation of highly pure Bempedoic acid which is suitable for use in pharmaceutical composition.

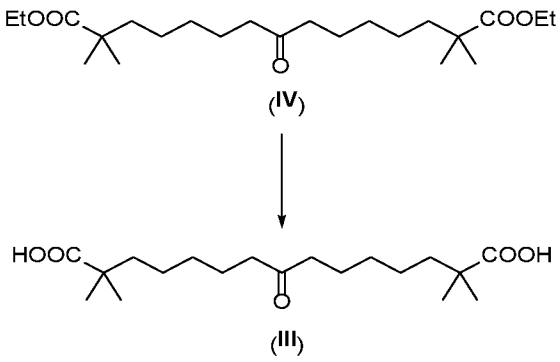
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is an illustration of a PXRD pattern of a crystalline form of formula (**IIA**), obtained by the Example-13.

SUMMARY OF THE INVENTION

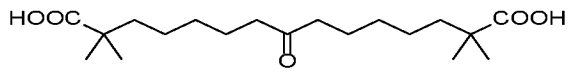
One aspect of the present application provides a process for preparation of compound of formula (**II**) comprising;

a) reacting compound of formula (**IV**) with suitable hydrolyzing agent to form compound of formula (**III**)

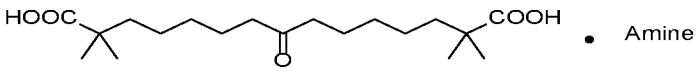


(**IV**) (**III**) ;

b) converting the compound of Formula (**III**) to compound of formula (**II**)



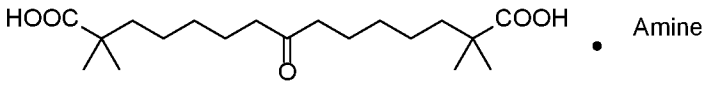
(III)



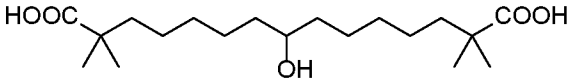
(II)

Another aspect of the present application provides a process for preparation of Bempedoic acid of formula (**I**) comprising

a) converting compound of formula (**II**) to Bempedoic acid of formula (**I**)



(II)

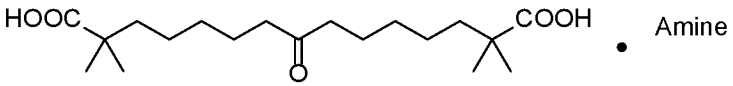


Bempedoic acid (I)

;

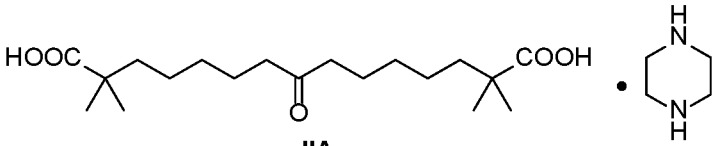
b) optionally purifying Bempedoic acid of formula (I).

Still another aspect of the present application relates to the compound of formula (**II**).



(II)

Still another aspect of the present application relates to the compound of formula (**IIA**).



(IIA)

Yet another aspect of the present application relates to a crystalline form of compound of formula (**IIA**) characterized by its powder X-ray diffraction (PXRD) pattern having peaks at about 10.5, 15.2, 15.7 and 16.3 ± 0.2 degrees 2θ.

Still another aspect of the present application relates a crystalline form of Formula (**IIA**) characterized by its powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated in the pattern of Figure 1.

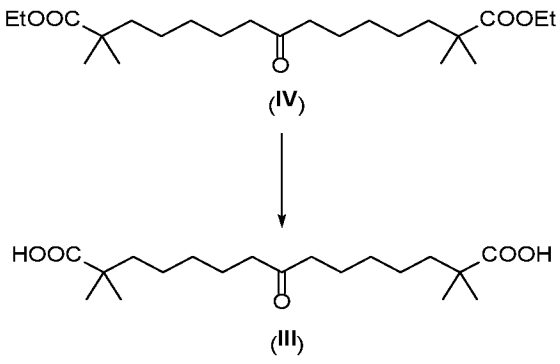
Another aspect of the present application relates to the use of compounds of formula (**II**) in the preparation of Bempedoic acid.

Another aspect of the present application relates to the use of compounds of formula (**IIA**) in the preparation of Bempedoic acid.

DETAILED DESCRIPTION

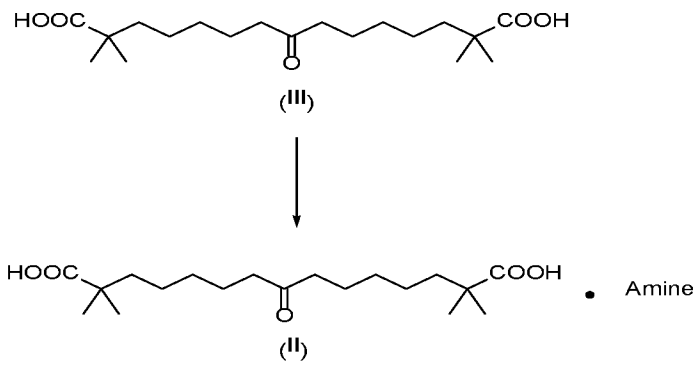
One aspect of the present application provides a process for preparation of compound of formula (**II**) comprising;

a) reacting compound of formula (**IV**) with suitable hydrolyzing agent to form compound of formula (**III**)



;

b) converting the compound of Formula (**III**) to compound of formula (**II**)



In embodiments of step a) compound of formula (**IV**) is treated with suitable hydrolyzing agent in a suitable solvent to form compound of formula (**III**).

In embodiments of step a) suitable hydrolyzing agent may include but not limited to alkali hydroxide like alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide or the like; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like. Specifically, the suitable hydrolyzing agent may be selected from alkali metal hydroxides. More specifically, the suitable hydrolyzing agent is potassium hydroxide. In another embodiment the suitable hydrolyzing agent is sodium hydroxide.

The suitable solvent of step a) may include, but are not limited to: ethers, such as diethyl ether, diisopropyl ether, tetrahydrofuran, MTBE, dioxane, and dimethoxyethane; alcohols, such as methanol, ethanol, ethylene glycol, 1-propanol, 2-propanol, 2-methoxyethanol, 1-butanol, 2-butanol, iso-butyl alcohol, t-butyl alcohol, and glycerol; halogenated hydrocarbons, such as dichloromethane, chloroform, carbon tetrachloride, and chlorobenzene; aromatic hydrocarbons, such as toluene; aliphatic hydrocarbons, such as n-hexane; nitriles, such as acetonitrile; esters, such as ethyl acetate; polar aprotic solvents such as DMF, DMSO, DMAc, water; any mixtures of two or more thereof. Specifically solvent may be a mixture of water and an alcohol solvent. More specifically solvent is a mixture of water and ethanol. In another embodiment, the solvent is a mixture of water and methanol. In embodiments of step a), the reaction may be carried out at a temperature ranging from about 0°C to about boiling temperature of the solvent. In embodiment, the reaction may be carried out from about 30°C to 80°C.

In embodiments of step a) the compound of formula (**III**) may be proceeded to the next step with or without further purification.

In embodiments of step b) compound of formula (**III**) is converted to compound of formula (**II**) by reacting compound of compound of formula (**III**) with an amine in a suitable solvent.

Suitable amines may include but not limited to trimethylamine, triethylamine, dicyclohexylamine, piperazine, cycohexylamine, ethanolamine, diethanolamine, triethanolamine, tert-butyl amine, tetra methyl guanidine, piperadine, meglumine, ethylenediamine, n-butylamine, L-proline, pyridine, dimethyl amine, picoline, quinolin and the like. Specifically, the suitable

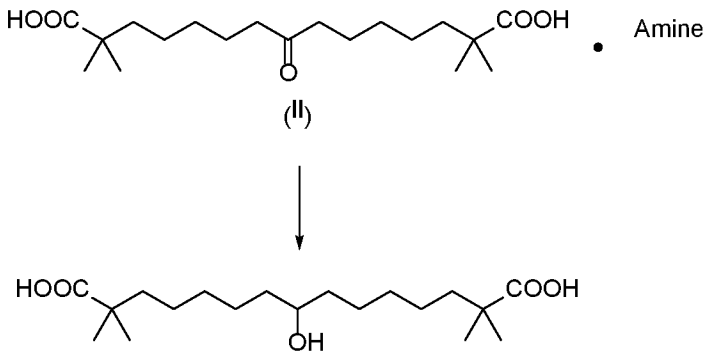
amine is selected from a group of n-butylamine, L-proline and piperazine. More specifically, the suitable amine is piperazine.

The suitable solvent of step b) may include but not limited to alcoholic solvent such as, methanol, isopropanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like; aliphatic hydrocarbon solvent such as hexane, heptane and the like; aromatic hydrocarbon solvent such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane and the like. Specifically, the solvent may be an ether solvent. More specifically, the ether solvent is tetrahydrofuran. In another embodiment the ether solvent is 1,4-dioxane. In embodiments of step b), the reaction may be carried out at a temperature ranging from about 0°C to about boiling temperature of the solvent. In embodiment, the reaction may be carried out from about 15°C to 35°C.

In one embodiment of the present application, step a) and step b) may be carried out in one pot.

Another aspect the present application provides a process for preparation of Bempedoic acid of formula (**I**) comprising

a) converting compound of formula (**II**) to Bempedoic acid of formula (**I**)



Bempedoic acid (I)

;

b) optionally purifying Bempedoic acid of formula (**I**).

In embodiments of step a), the compound of formula (**I**) is prepared by reacting compound of formula (**II**) with a suitable reducing agent in a suitable solvent.

In embodiments of step a) the suitable reducing agent may include but not limited to Lithium Borohydride, Sodium Borohydride ($NaBH_4$), Lithium Aluminum hydride ($LiAlH_4$), Sodium triacetoxyborohydride, sodium Cyanoborohydride, or the like. In a specific embodiment of step a) the suitable reducing agent is sodium borohydride.

The suitable solvent of step a) may include but not limited to alcoholic solvent such as, methanol, isopropanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like; aliphatic hydrocarbon solvent such as hexane, heptane and the like; aromatic hydrocarbon solvent such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane and the like. nitrile solvent such as acetonitrile and the like; polar aprotic solvents such as DMF, DMSO, DMAc, water; any mixtures of two or more thereof. Specifically, the solvent may be an alcohol solvent. More specifically, the alcohol solvent is methanol.

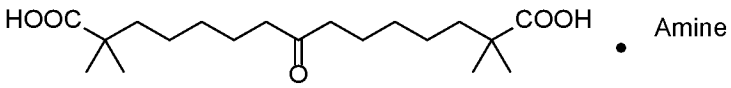
In embodiments of step a) the conversion of compound of formula (**II**) to Bempedoic acid of formula (**I**) may also involve the use of a suitable inorganic base. Suitable inorganic base may include but not limited to alkali hydroxide like alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide or the like; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like. In a preferred embodiments of step c) the base may be alkali metal hydroxides. More preferably, the base is sodium hydroxide. In embodiments of step c), the reaction may be carried out at a temperature ranging from about 0°C to about boiling temperature of the solvent. In embodiment, the reaction may be carried out from about 15°C to 35°C.

In embodiments of step b) Bempedoic acid of formula (**I**), may optionally be purified by using a suitable solvent. The suitable solvent may include but not limited to alcoholic solvent such as, methanol, isopropanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like; ester solvent such as ethyl acetate, propyl acetate and the like; aliphatic hydrocarbon solvent such as hexane, heptane, pentane, cyclohexane and the like; aromatic hydrocarbon solvent such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloromethane and the like. nitrile solvent such as acetonitrile and the like; polar aprotic solvents such as DMF, DMSO, DMAc, water; any mixtures of two or more thereof. Specifically, the solvent may be an ester solvent. More specifically, the ester solvent is ethyl acetate. In embodiments of step d), the reaction may be carried out at a temperature ranging from about 0°C to about boiling temperature of the solvent.

Yet another aspect of the present application relates to the purification of bempedoic acid using a suitable solvent. The suitable solvent may include but not limited to alcoholic solvent such as, methanol, isopropanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like; ester solvent such as ethyl acetate, propyl acetate and the like; aliphatic hydrocarbon solvent such as hexane, heptane, heptane, cyclohexane and the like; aromatic hydrocarbon solvent such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloromethane and the like. nitrile solvent such as acetonitrile and the like; polar aprotic solvents such as DMF, DMSO, DMAc, water; any mixtures of two or more thereof.

In another embodiment, the compound of formula (**IV**) is prepared by any method known in the art. In one specific embodiment compound of formula (**IV**) is prepared by a method disclosed in US7335799B2.

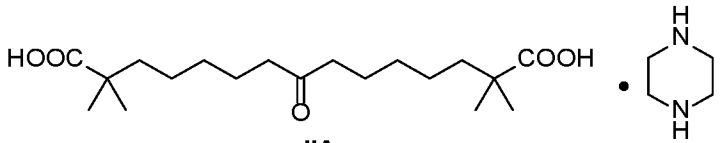
Still another aspect of the present application relates to the compound of formula (**II**).



(**II**)

Another aspect of the present application relates to the use of compounds of formula (**II**) in the preparation of Bempedoic acid.

Still another aspect of the present application relates to the compound of formula (**IIA**).



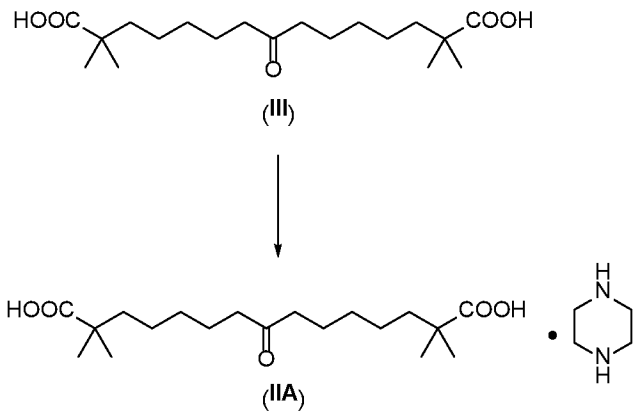
(**IIA**)

Another aspect of the present application relates to the use of compounds of formula (**IIA**) in the preparation of Bempedoic acid.

Yet another aspect of the present application relates to a crystalline form of compound of formula (**IIA**) characterized by its powder X-ray diffraction (PXRD) pattern having peaks at about 10.5, 15.2, 15.7 and 16.3 ± 0.2 degrees 2θ.

Still another aspect of the present application relates a crystalline form of Formula (**IIA**) characterized by its powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated in the pattern of Figure 1.

Another aspect of the present application relates to a process for preparation of compound of formula (**IIA**) comprising converting compound of formula (**III**) to compound of formula (**IIA**)



(III) (IIA)

The suitable solvent may include but not limited to alcoholic solvent such as, methanol, isopropanol and the like; ethers such as 1,4-dioxane, tetrahydrofuran and the like; aliphatic hydrocarbon solvent such as hexane, heptane and the like; aromatic hydrocarbon solvent such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane and the like. Specifically, the solvent may be an ether solvent. More specifically, the ether solvent is tetrahydrofuran. In another embodiment the ether solvent is 1,4-dioxane. In embodiments of step b), the reaction may be carried out at a temperature ranging from about 0°C to about boiling temperature of the solvent. In embodiment, the reaction may be carried out from about 15°C to 35°C.

The process for the preparation of Bempedoic acid, as described above, have the following advantages over the prior art process:

1. Isolation of solid Bempedoic acid in contrast to the oily syrup obtained in prior art process (US7335799);
2. Achieved high purity of Bempedoic acid (more than 99%) by crystalization.

Moreover, the intermediate compounds of formulae (**IV**) and (**III**) were known to be oily in nature and hence Bempedoic acid produced from the compound of formula (**III**) is of low quality and in low yield (US7335799). A solid intermediate would have ensured that the chemist would have a chance to purify the compound in intermediate state and hence Bempedoic acid could have been produced in high quality with higher yield. This application teaches a solid intermediate of compound of formula (**II**) or compound of formula (**IIA**) for the first time and its importance to obtain Bempedoic acid in better quality with higher yield.

All the process related impurities that are generated during the preparation of intermediates of formulae (**IV**) and (**III**) are washed away in the process for preparation of solid intermediate of compound of formula (**II**) or compound of formula (IIA); so that Bempedoic acid, obtained from compound of formula (**II**) or compound of formula (IIA) is of better quality and higher yield.

In embodiments, the present application provides a pharmaceutical composition comprising the crystalline form of Bempedoic acid as described in the present application together with at least one pharmaceutically acceptable excipient.

Pharmaceutically acceptable excipients that are useful in the present application include, but are not limited to, any one or more of: diluents such as starches, pregelatinized starches, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar, or the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidones, hydroxypropyl celluloses, hydroxypropyl methylcelluloses, pregelatinized starches, or the like; disintegrants such as starches, sodium starch glycolate, pregelatinized starches, crospovidones, croscarmellose sodium, colloidal silicon dioxide, or the like; lubricants such as stearic acid, magnesium stearate, zinc stearate, or the like; glidants such as colloidal silicon dioxide or the like; solubility or wetting enhancers such as anionic, cationic, and neutral surfactants; complex forming agents such as various grades of cyclodextrins and resins; and release rate controlling agents such as hydroxypropyl celluloses, hydroxymethyl celluloses, hydroxypropyl methylcelluloses, ethylcelluloses, methylcelluloses, various grades of methyl methacrylates, waxes, or the like. Other pharmaceutically acceptable excipients that are useful include, but are not limited to, film-formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants, or the like.

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Variations of the described procedures, as will be apparent to those skilled in the art, are intended to be within the scope of the present application.

EXAMPLES

Example-1: Preparation of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (III)

To a solution of diethyl 2,2,14,14-tetramethyl-8-oxopentadecanedioate (**IV**) (50 g) in ethanol (500 mL) and water (250 mL) was added potassium hydroxide (112 g) at room temperature. The reaction mixture is slowly heated to about 70-75 °C and maintained at the same temperature for overnight. After completion, the reaction mixture is slowly cooled to about 50 °C and distilled under vacuum at about 50 °C. Water (500 mL) and methyl tertiary butyl ether (250 mL) were added to the above reaction mixture and stirred for about 1 hour. Organic and aqueous layers were separated. Aqueous layer was extracted with methyl tertiary butyl ether (250 mL). pH of aqueous layer was adjusted to 1-2 using 1:1 aqueous HCl and extract with MTBE (3X250ml). The combined organic layers were mixed and distilled under vacuum at 50 °C. The crude residue was dissolved in ethyl acetate (250ml) and Charcoal (50 g) is added to the above reaction mixture at about 45-50 °C and stirred for 30 minutes at the same temperature. The reaction mixture is then filtered and washed with ethyl acetate (100 mL) and distilled under vacuum to obtain the title compound as crude residue (52 g), which is proceeded to the next step without further purification.

Example-2: Preparation of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (III)

To a solution of diethyl 2,2,14,14-tetramethyl-8-oxopentadecanedioate (**IV**) (18.7 g) in methanol (187 mL) was added potassium hydroxide (112 g) in water (94 mL) at room temperature. The reaction mixture is slowly heated to about 60 °C and maintained at the same temperature for overnight. After completion, the reaction mixture is slowly cooled to about 45 °C and distilled under vacuum at about 45 °C. Water (187 mL) and methyl tertiary butyl ether (94 mL) were added to the above reaction mixture and stirred for about 1 hour. Organic and aqueous layers were separated. Aqueous layer was mixed with methyl tertiary butyl ether (94 mL) and adjusted its pH below 1-2 using aq.HCl. Organic layer was separated and aqueous layer extract with MTBE (94 mL). The combined organic layers were washed with brine (94 mL). The combined organic layers were distilled under vacuum to obtain the title compound.

Example-3: Preparation of piperazine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (IIA)

To the crude material (26 g) as obtained from example 1 was added tetrahydrofuran (250 mL) at room temperature. A solution of piperazine (6.59 g) in tetrahydrofuran (100 mL) was slowly added to the above reaction mixture at room temperature and maintained at the same temperature for about for 3 hours to precipitate the solids. The precipitated solids were filtered, washed with tetrahydrofuran (50 mL) and dried under vacuum to obtain the title compound

Yield: 22.5 g

Purity by HPLC: 84.52%

Example-4: Preparation of piperazine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (IIA)

To the crude 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (5 g), as obtained from example 1, was added tetrahydrofuran (125 mL) at room temperature. A solution of piperazine (2.52 g) in tetrahydrofuran (75 mL) was slowly added to the above reaction mixture at room temperature. The reaction mixture is slowly heated to about 40 °C and maintained at the same temperature for about for 3 hours. The reaction mixture is then slowly cooled to 25 °C. The precipitated solids were filtered, washed with tetrahydrofuran (50 mL) and dried under vacuum to obtain the title compound

Yield: 5 g.

Example-5: Preparation of Bempedoic acid (I)

Piperazine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (**IIA**) (22 g) as obtained in example 3 was mixed with water (100 mL) and methyl tertiary butyl ether (100 mL), stirred for 10 minutes at room temperature. Organic and aqueous layers were separated. The pH of the aqueous layer is adjusted to 2.7 and then extracted with methyl tertiary butyl ether (100 mL). The combined organic layers were distilled under vacuum to obtain crude residue (8 g). The resulting residue is mixed with methanol (80 mL) and sodium hydroxide (2.57 g), stirred for 10 minutes at room temperature. The temperature of the reaction mixture is slowly cooled to 0-10 °C and added sodium borohydride (0.97 g) at the same temperature. The reaction mixture is stirred for about 1.5 hours at about 0-5 °C. After completion, the pH of the reaction mixture is adjusted to 2.1 with hydrochloric acid. Water (160 mL) is added to the above reaction mixture and stirred for about 1 hour. The resulting solids were filtered and washed

with n-heptane (10 mL). Further the resulting wet material is mixed with acetonitrile (80 mL) and heated to about 60-65 °C to obtain a clear solution. The resulting clear solution is cooled to 25-35 °C to precipitate the solid. The resulting solid was filtered, washed with acetonitrile (10 mL) and dried at 50 °C to obtain the title compound.

Yield: 6.1 g

Example-6: Purification of Bempedoic acid (I)

A solution of bempedoic acid (6 g) in ethyl acetate (30 mL) is heated to 60-65 °C and maintained the reaction mixture at the same temperature for about 3 hours. The reaction mixture is slowly cooled to 25-35 °C to precipitate the solid. The resulting solid was filtered, washed with ethyl acetate (6 mL) and dried at 50 °C to obtain the title compound as white solid.

Yield: 5.3 g

Purity by HPLC: 99.7%

Example-7: Preparation of Bempedoic acid (I)

Piperazine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (**IIA**) (7 g), as obtained in example 4, was treated with sodium hydroxide (1.6 g) and sodium borohydride (0.6 g) in methanol (60 mL) at about 0-5 °C. The reaction mixture is stirred for 3 hours at the same temperature. The reaction mixture is quenched with 50% aqueous hydrochloric acid (20 mL) at the same temperature. Water (35 mL) added to the above reaction mixture at about 28 °C and maintained for overnight. The resulting solid is filtered, washed with water (35 mL) and suck dried. The resulting solid is further dried in VTD at 48 °C for about 4 hours. The resulting solid was mixed with acetonitrile and heated to about 75 °C to obtain clear solution. The reaction mixture is slowly cooled to 30 °C and maintained for about 4.5 hours at the same temperature. The precipitated solid is filtered and mixed with ethyl acetate (19 mL). The reaction mixture is slowly heated to 50 °C to obtain a clear solution. The reaction mixture is slowly cooled to 30 °C to precipitate the solid. The resulting solid was filtered, washed with chilled ethyl acetate (8 mL) and dried. The resulting solid was further dried in VTD at about 50 °C for about 4 hours to obtain the title compound.

Yield: 2.6 g

Purity by HPLC: 99.79%

Example-8: Preparation of diethyl 8-cyano-8-((4-cyanophenyl)sulfonyl)-2,2,14,14-tetramethylpentadecanedioate.

A solution of toluenesulfonylmethyl isocyanide (TosMIC) (162 g) in DMSO (800 mL) was added to a solution of sodium hydride (47.1 g, 60% in oil) in DMSO (2.4 L) and toluene (800 mL) mixture at a temperature about 16 °C. Tetrabutylammonium iodide (55.7 g) was added to the above reaction mixture and stirred for about 90 minutes at the same temperature. The reaction mixture is slowly cooled to 10 °C and added a solution of ethyl 7-bromo-2,2-dimethylheptanoate (400 g) in toluene (800 mL). The temperature of the reaction mixture is slowly raised to 15 °C and stirred for 5 hours at the same temperature. To this reaction mixture was added an additional amount of toluenesulfonylmethyl isocyanide (TosMIC) (7.36 g) at 15 °C and stirred 2 hours. The reaction mixture is then cooled to 10 °C and quenched with ice cold water (320 mL). Organic and aqueous layers were separated. Aqueous layer is extracted with toluene (2000 mL). Combined organic layers were washed with water (3.2 L) and brine solution (4 L). Organic layer is separated and proceed to the next step.

Example-9: Preparation of diethyl 2,2,14,14-tetramethyl-8-oxopentadecanedioate

Organic layer as obtained in example 6 is taken in 10 L reactor and added hydrochloric acid (2 L, 32%) at a temperature about 15 °C. The temperature of the reaction mixture is slowly raised to about 25 ° and stirred for 3 hours at the same temperature. The reaction mixture is then quenched with water (2 L) and layers were separated. Aqueous layer is extracted with toluene (1 L). The combined organic layers were washed with a saturated solution of sodium bicarbonate (4.2 L) and brine solution (2.1 L). Organic layer is separated and proceed to the next step.

Example-10: Preparation of diethyl 8-hydroxy-2,2,14,14-tetramethylpentadecanedioate

To a portion of organic layer as obtained in the example 7 (64 g) was added sodiumborohydride (6 g) at temperature 10 °C. Methanol (160 mL) was added to the above reaction mass and stirred for 3 hours at the same temperature. The reaction mixture is then treated with aqueous hydrochloric acid (96 mL). The temperature of the reaction mixture was raised to 30 °C and stirred for 1 hour. Organic and aqueous layers were separated. Organic layer is washed with

aqueous sodium bicarbonate solution (800 mL) followed by aqueous sodium chloride solution (800 mL). Organic layer is treated with activated carbon (30 g). The reaction mixture is then filtered and washed with toluene (120 mL). The resulting filtrate is concentrated under vacuum to obtain title compound (42 g).

Example-11: Preparation of diethyl 8-isocyano-2,2,14,14-tetramethyl-8-tosyl pentadecanedioate.

Sodium hydride (18.45 g) and toluene (400 mL) were charged in to the reactor under nitrogen atmosphere. The reaction mass was cooled to -10°C. Dimethyl acetamide (800 mL) was added to the reaction mass at -10°C and stirred for 5 minutes. 1-((isocyanomethyl)sulfonyl)-4-methylbenzene (66.3 g) and dimethyl acetamide (400 mL) were slowly added to the reaction mass at -10°C and maintained for 60 minutes at -10°C. Ethyl 7-iodo-2,2-dimethylheptanoate (200 g) and toluene (400 mL) were slowly added to the reaction mass -10°C and maintained for 6 hours. Water (1600 mL) was added to the reaction mass and the reaction mass temperature was raised to 25°C and maintained for 60 minutes. Toluene (800 mL) was added to the reaction mass and stirred for 10 minutes. Both layers were separated. Aqueous layer was extracted with toluene (400 mL). Combine the organic layers and washed with 10% brine solution (1000mL) and proceed to the next step.

Example-12: Preparation of diethyl-2,2,14,14-tetramethyl-8-oxopentadecanedioate.

Organic layer as obtained in example 11 (200 g equivalent) is taken into the reactor and cooled to 12 °C and stirred for 10 minutes. Con Hydrochloric acid (160 mL) was added to the reaction mass at 12 °C and maintained for 4 hours. Water (1000 mL) was added to the reaction mass and stirred for 10 minutes. Both layers were separated. 5% NaOH solution (1000 mL) was charged in to the organic layer at 25°C and stirred for 5 minutes. 10% brine solution (1000 mL) was added to the reaction mass and stirred for 10 minutes. Both layers were separated. Carbon (20 g) was added to the organic layer and maintained for 2 hours at 30°C. Filtered the reaction mass through hyflow and washed with toluene (1000 mL). The solvent from organic layer was evaporated under vacuum at 50°C to give title compound as a crude material.

Yield: 150 g

Example-13: Preparation of piperazine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (IIA).

Diethyl-2,2,14,14-tetramethyl-8-oxopentadecanedioate (92 g) and methanol (920 mL) were charged into the reactor at 28 °C. Sodium hydroxide solution (60 g in 460 mL water) was added to the reaction mass at 28°C. The reaction mass was heated to 58°C and maintained for 14 hours. The solvent from the reaction mass was distilled completely under vacuum at 40°C. methyl tertiary butyl ether (460 mL) and water (460 mL) were charged to the crude at 28 °C and stirred for 10 minutes. Both layers were separated. Methyl tertiary butyl ether (460 mL) was charged to the aqueous layer and cooled to 15°C. The pH of the reaction mass was adjusted to acidic by using con hydrochloric acid. Both layers were separated. Methyl tertiary butyl ether (460 mL) was charged to the aqueous layer at 15°C. Both layers were separated and combined the organic layer and washed with 5% sodium chloride solution. The solvent form the organic layer was evaporated completely under vacuum at below 45°C.

1,4-dioxane (750 mL) was added to the obtained crude at 28°C and the reaction mass was heated to 51°C. Piperazine (18.96 g) was added to the reaction mass at 51°C. The reaction mass was heated to 65°C and maintained for 3 hours. The reaction mass was cooled to 45 °C and maintained for 4 hours. The reaction mass was further cooled to 35°C and maintained for 6-8 hours. The obtained solid was filtered and washed with 1,4-dioxane (250 mL), dried under vacuum to obtain the title compound.

Yield: 41 g

Purity by HPLC: 96.29%

Mass spectrometry value (m/z) = 429.25[M+1].

Piperazine content: 19.8 %

^{1}H-NMR (DMSO, 400 MHz): δ 3.06 (s, 8H), δ 2.43(t, 4H, J=7.3), δ 1.54(m, 4H), 1.46(m, 4H), 1.27 (m, 8H), 1.12 (s, 12H).

^{13}C-NMR: δ 214.5 (1C), 185.57 (2C), 43.78 (2C), 43.56(2C), 42.36 (2C), 31.04 (2C), 26.29 (2C), 24.96 (2C), 26.4 (4C), 44.41(4C).

Example-14: Preparation of Bempedoic acid (I).

DM-Water (12 L) was charged into the reactor at 20°C. Caustic soda flakes (0.23 Kg) was added to the reactor at 20°C and stirred for 30 minutes. Piperazine salt of 2,2,14,14-

tetramethyl-8-oxopentadecanedioic acid (1 Kg) was slowly added to the reactor at 20°C and maintained for 30 minutes. The reaction mass was cooled to 5 °C. Sodium borohydride (0.097 Kg) was added lot wise at 10 °C and maintained the reaction mass at same temperature for 6 hours. Methyl tert-butyl ether (8 L) was added to the reactor at 10 °C. Aqueous hydrochloric solution (1.5 L HCl in 1.5 L DM-water) was added to the reaction mass at below 20 °C and stirred for 3-4 hours at 10-20 °C. Settle the reaction mass for 45 minutes. Separate the bottom aqueous layer was charged in to another reactor. Methyl tert-butyl ether (4 L) was added to the reactor at 10-20 °C and stirred for 30 minutes at same temperature. Organic and aqueous layers were separated. Combine the organic layers. DM-water (2X 5 L) was added to the organic layer at 25-35 °C and stirred the reaction mass for 30 minutes. Organic and aqueous layers were separated. The solvent from the organic layer was evaporated under vacuum at below 45°C. The reaction mass was cooled to 30 °C. Ethyl acetate (2.4 L) and cyclohexane (8 L) were charged in to the reactor at 30 °C. The reaction mass was heated to 55 °C and maintained for 60 minutes. The reaction mass was cooled to 35-45 °C and maintained for 3 hours. The reaction mass was cooled to 25-35 °C and maintained for 5 hours. The solid was filtered, washed with ethyl acetate (0.35 L) and cyclohexane (1.25 L) mixture to obtain the wet material.

The obtained wet material, ethyl acetate (2 L) and cyclohexane (4 L) were charged in to the reactor at 25-35 °C and stirred for 10 minutes. The reaction mass was heated to 50-60 °C and maintained for 60 minutes. The reaction mass was cooled to 35-45 °C and maintained for 2 hours. The reaction mass was cooled to 25-35 °C and maintained for 5 hours. The solid was filtered, washed with ethyl acetate (0.33 L) and cyclohexane (1 L) mixture to obtain the wet material.

The obtained wet material and ethyl acetate (2.4 L) were charged in to the reactor at 25-35 °C and stirred for 10 minutes. The reaction mass was heated to 55-65 °C and maintained for 20 minutes. The reaction mass was cooled to 25-35 °C and maintained for 3 hours. The reaction mass further cooled to 5-15 °C and maintained for 3 hours. The solid was filtered, washed with chilled ethyl acetate (0.6 L) to obtain the title compound.

Yield: 0.55 Kg

Purity by HPLC: 99.95%

Example-15: Preparation of n-butyl amine salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (IIB).

2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (**III**) (1 g) and 1,4-dioxane (10 mL) were charged in to RBF at 27°C and stirred for 10 minutes. The reaction mixture was heated 54°C and the reaction mixture was cooled to 27°C and stirred for 10 minutes. n-butyl amine (0.45 g) was added to the reaction mass at 27°C and stirred for 10 minutes. 1,4-dioxane (10 mL) was added to the reaction mass at 27°C and maintained for 4 hours. Filtered and washed with 1,4-dioxane (3 mL) and dried under vacuum to obtain the title compound.

Yield: 1.2 g

Example-16: Preparation of L-proline salt of 2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (IIC).

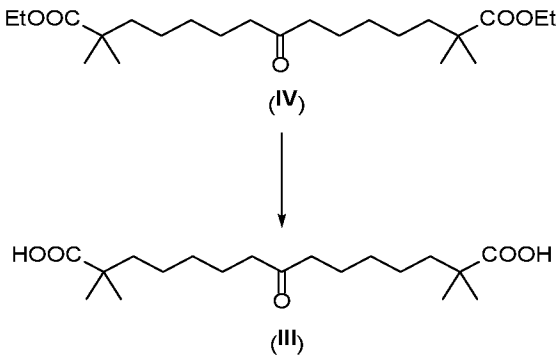
2,2,14,14-tetramethyl-8-oxopentadecanedioic acid (**III**) (1 g) and 1,4-dioxane (10 mL) were charged in to RBF at 28°C and stirred for 10 minutes. The reaction mixture was heated 52°C and the reaction mixture was cooled to 27°C and stirred for 10 minutes. L-proline (0.70 g) was added to the reaction mass at 27°C and stirred for 10 minutes. 1,4-dioxane (5 mL) was added to the reaction mass at 27°C and maintained for 4 hours. Filtered and washed with 1,4-dioxane (3 mL) and dried under vacuum to obtain the title compound.

Yield: 0.6 g

WE CLAIM:

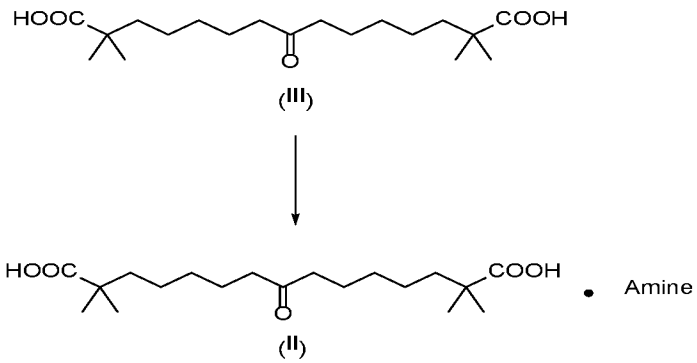
1. A process for preparation of compound of formula (**II**) comprising;

a) reacting compound of formula (**IV**) with suitable hydrolyzing agent to form compound of formula (**III**)



(IV) (III) ;

b) converting the compound of Formula (**III**) to compound of formula (**II**)



(III) (II)

2. The process according to claim 1, wherein suitable hydrolyzing agent used in step a) is selected from alkali metal hydroxides, alkaline earth metal hydroxides, alkali metal carbonates and alkali metal bicarbonates.

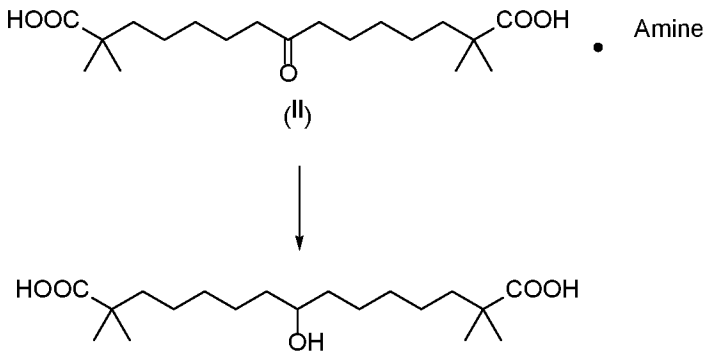
3. The process according to claim 1, wherein the suitable amine in step b) is selected from a group of L-proline, n-butylamine and piperazine.

4. The process according to claim 3, wherein the suitable amine in step b) is piperazine.

5. The process according to claim 1, wherein the compound of formula (**III**) is proceeded to next step without purification.

6. The process according to claim 1, further comprising:

a) converting compound of formula (**II**) to Bempedoic acid of formula (**I**)



Bempedoic acid (I)

;

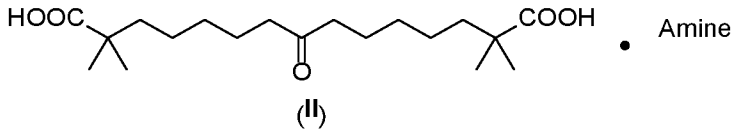
b) optionally purifying Bempedoic acid of formula (**I**).

7. The process according to claim 6, wherein step a) is carried out in presence of suitable reducing agent.

8. The process according to claim 7, wherein the suitable reducing agent is selected from Lithium Borohydride, Sodium Borohydride ($NaBH_4$), Lithium Aluminum hydride ($LiAlH_4$), Sodium triacetoxyborohydride, and sodium cyanoborohydride.

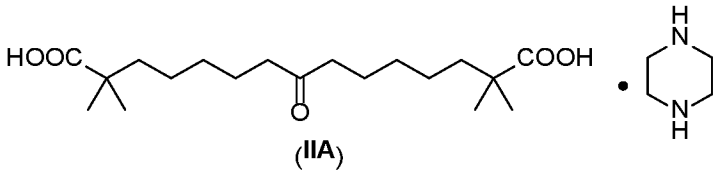
9. The process according to claim 8, wherein the suitable reducing agent is Sodium Borohydride ($NaBH_4$).

10. A compound of formula (**II**)



.

11. The compound of formula (II) according to claim 10, wherein amine is piperazine (IIA).



12. The use of compound of formula (**II**) according to claim 10, for the preparation of Bempedoic acid.

13. The compound of formula (**IIA**) according to claim 11, wherein the compound is crystalline.

14. The crystalline form of compound of formula (**IIA**) according to claim 13, characterized by its powder X-ray diffraction (PXRD) pattern having peaks at about 10.5, 15.2, 15.7 and 16.3 ± 0.2 degrees 2θ.

15. The crystalline form of compound of formula (**IIA**) according to claim 13, wherein the powder X-ray diffraction (PXRD) pattern having peaks located substantially as illustrated in the pattern of Figure 1.

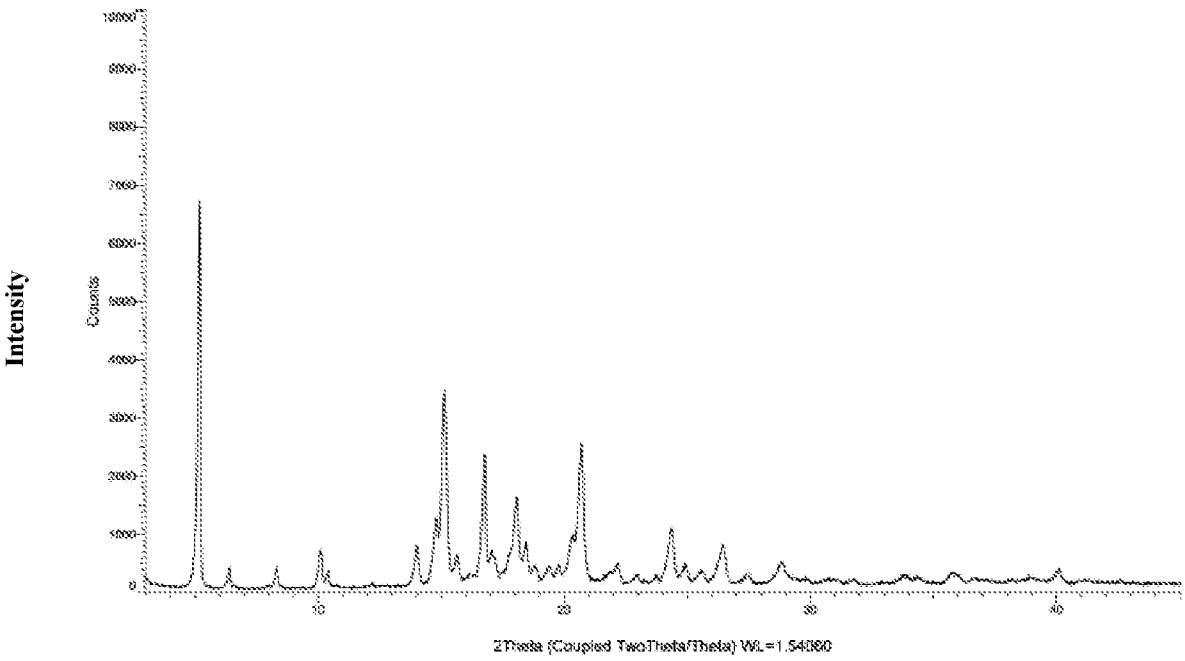


Figure 1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2022/050007

A. CLASSIFICATION OF SUBJECT MATTER
C07C51/09,C07C59/245 Version=2022.01

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)

C07C

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)

STN, 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.
Y	WO 2004067489 A2 (ESPERION THERAPEUTICS, INC) 12 AUGUST 2004 (12.08.2004) *examples 6.19, 6.20*	1-15
Y	WO 2020141419 A2 (LUPIN LIMITED) 09 JULY 2020 (09.07.2020) *pg. 4, formula DD*	1-15
Y	WO 2020257573 A1 (ESPERION THERAPEUTICS, INC) 24 DECEMBER 2020 (24.12.2020) *pg.4, lines 18-20; pg. 30*	1-15
Y	WO 2021255180 A1 (SYNTHON B.V.) 23 DECEMBER 2021 (23.12.2021) *pg. 2 lines 20-21; example 2* FAMILY: [NONE]	1-15

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

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
07-04-2022	07-04-2022
Name and mailing address of the ISA/ Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Authorized officer Vishakha Gupta Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2022/050007

Citation	Pub.Date	Family	Pub.Date
WO 2004067489 A2	12-08-2004	EP 2404890 A1	11-01-2012
		US 20050043278 A1	24-02-2005
WO 2020141419 A2	09-07-2020	EP 3906231 A2	10-11-2021
		JP 2022516530 A	28-02-2022
WO 2020257573 A1	24-12-2020	US 20210139405 A1	13-05-2021