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(71) Applicants *(for all designated States except US):* **DR. REDDY'S LABORATORIES LTD.** [IN/IN]; 7-1-27 Ameerpet, Hyderabad, 500 016, Andhra Pradesh (IN). **DR. REDDY'S LABORATORIES, INC.** [US/US]; 200 Somerset Corporate Boulevard 7th Floor, Bridgewater, NJ 08807 (US).

(72) Inventors; and

(75) Inventors/ Applicants *(for US only):* **KATKAM, Srinivas** [IN/IN]; H. No. 13-1/32/3, Saipuri Colony, Malkajgiri, Hyderabad, 500 047, Andra Pradesh (IN). **SAGYAM, Rajeshwar, Reddy** [IN/IN]; Plot No. 1322 & 1323, Flat No.204,Vindhya Hills, Pragathi Nagar, Hyderabad, 500 072, Andra Pradesh (IN). **BUCHIKONDA, Ravinder** [IN/IN]; H. No. 12-7-64, Moosapet (Muskipet), Hyderabad, 500 018, Andra Pradesh (IN). **MUTTAVARAPU, Murali, Mohan** [IN/IN]; Nawabupet (Post), Penuganchi Prolu (Mandal), Krishna District, Andhra Pradesh (IN). **MUNAGALA, Sridhar** [IN/IN]; H. No. 2-2-22/180/2/ A/G1, Plot No. 96, Gudavalli Residency Jayanager, Kukatpally, Hyderabad, 500 072, Andra Pradesh (IN). **CHIKKA, Rambabu** [IN/IN]; H. No. 2-1-21/67/E, Saicharan Colony, Shashiguda, Kukatpally, Hyderabad, 500 072, Andra Pradesh (IN).

(74) Agent: **McKENZIE, Thomas, Charles;** Dr. Reddy's Laboratories, Inc., 200 Somerset Corporate Boulevard - 7th floor, Bridgewater, NJ 08807 (US).

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(54) Title: ESLICARBAZEPINE ACETATE AND ITS POLYMORPHS

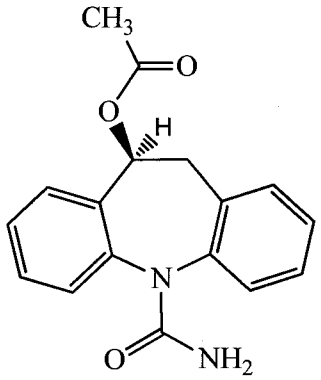
(57) Abstract: Processes for the preparation of eslicarbazepine acetate and intermediates thereof. Also provided are polymorphic forms of eslicarbazepine acetate and methods for their preparation.

ESLICARBAZEPINE ACETATE AND ITS POLYMORPHS

INTRODUCTION

Aspects of the present application relate to processes for the preparation of eslicarbazepine acetate and intermediates thereof. Aspects of the present application also relate to polymorphic forms of eslicarbazepine acetate and methods for their preparation.

Eslicarbazepine acetate is chemically described as (S)-10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide. It has the structure of Formula (I).

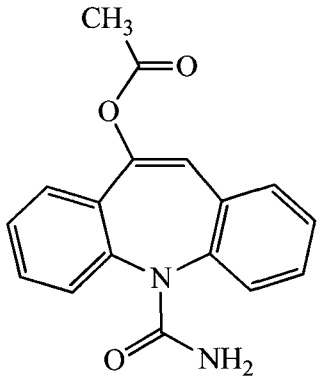


(I)

Eslicarbazepine acetate is a voltage gated sodium channel blocker and is Zebinix™ or Exalief™ by Eisai Co. in Europe and will be marketed as Stedesa™ by Sepracor in America. Eslicarbazepine acetate is indicated as adjunctive therapy in adults with partial-onset seizures with or without secondary generalization.

U.S. Patent No. 5,753,646 discloses 10-acetoxy-10,11-dihydro-5H-dibenz[b,f]azepine-5-carboxamide, or a stereoisomer thereof and processes for their synthesis. U.S. Patent No. 7,119,197 discloses a process for preparing eslicarbazepine acetate by formation of diastereomeric 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide with di-0,0'-substituted-tartaric acid anhydride, separation of the diastereomers, followed by hydrolysis of the corresponding diastereomer to form a compound of Formula (I). U.S. Patent Application Publication No. 2008/0293934 A1 discloses a method for the chiral inversion and esterification of optically pure or optically enriched (R)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (here in after referred as (R)-licarbazepine) and eslicarbazepine. International Application Publication

No. WO 2007/1 17166 A1 discloses a method for the preparation of eslicarbazepine acetate by asymmetric hydrogenation of a compound of Formula (II).

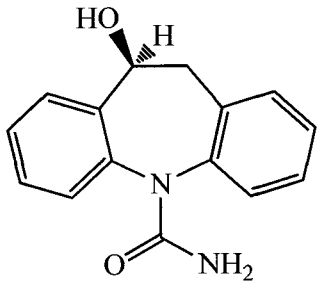


(II)

There remains a need to provide improved process for the preparation of eslicarbazepine acetate and its intermediates that are cost-effective and environment friendly.

SUMMARY OF THE INVENTION

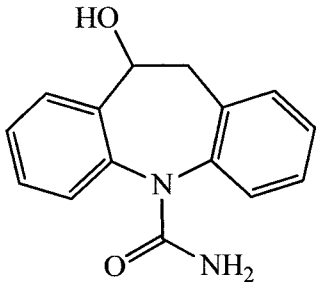
In an aspect, the present application provides an improved process for the preparation of eslicarbazepine of Formula (III):



(III)

which includes one or more of the following steps, individually or in the sequence recited:

(a) reacting racemic 10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (IV):



(IV)

with a reagent capable of forming an ester to provide mixture of diastereomeric esters of 10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide;

(b) separating the diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide into individual diastereomers;

(c) isolating the diastereomeric ester of eslicarbazepine;

(d) hydrolyzing the diastereomeric ester of eslicarbazepine to provide optically pure (S)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide; and

(e) optionally recovering the diastereomeric ester of (R)-licarbazepine.

BRIEF DESCRIPTION OF THE DRAWING

Fig. 1 is an illustration of a powder X-ray diffraction (PXRD) pattern of a crystalline form of eslicarbazepine acetate prepared according to Example 5.

Fig. 2 is an illustration of an infrared absorption spectrum of a crystalline form of eslicarbazepine acetate prepared according to Example 5.

Fig. 3 is an illustration of a differential scanning calorimetry (DSC) thermogram of a crystalline form of eslicarbazepine acetate prepared according to Example 5.

Fig. 4 is an illustration of a thermogravimetric analysis (TGA) curve of a crystalline form of eslicarbazepine acetate prepared according to Example 5.

Fig. 5 is an illustration of a powder X-ray diffraction (PXRD) pattern of an amorphous form of eslicarbazepine acetate prepared according to Example 8.

Fig. 6 is an illustration of an infrared absorption spectrum of an amorphous form of eslicarbazepine acetate prepared according to Example 8.

Fig. 7 is an illustration of a thermogravimetric analysis (TGA) curve of an amorphous form of eslicarbazepine acetate prepared according to Example 8.

Fig. 8 is an illustration of a powder X-ray diffraction (PXRD) pattern of an amorphous form of eslicarbazepine acetate prepared according to Example 9.

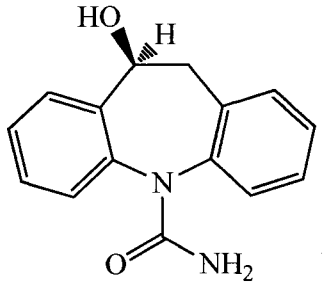
Fig. 9 is an illustration of an infrared absorption spectrum of an amorphous form of eslicarbazepine acetate prepared according to Example 9.

Fig. 10 is an illustration of a thermogravimetric analysis (TGA) curve of an amorphous form of eslicarbazepine acetate prepared according to Example 9.

Fig. 11 is an illustration of a powder X-ray diffraction (PXRD) pattern of a crystalline form of eslicarbazepine acetate prepared according to Example 14.

DETAILED DESCRIPTION

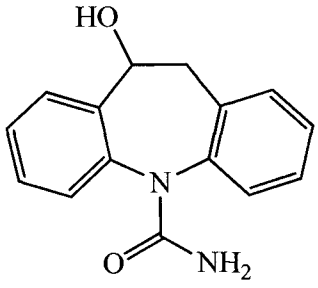
In an aspect, the present application provides an improved process for the preparation of eslicarbazepine of Formula (III):



(III)

which includes one or more of the following steps, individually or in the sequence recited:

(a) reacting racemic 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (IV):



(IV)

with a reagent capable of forming an ester to provide mixture of diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide;

(b) separating the diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide into individual diastereomers;

(c) isolating the diastereomeric ester of eslicarbazepine;

(d) hydrolyzing the diastereomeric ester of eslicarbazepine to provide optically pure (S)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide; and

(e) optionally recovering the diastereomeric ester of (R)-licarbazepine.

Step (a) involves reacting racemic 10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula IV with a chiral reagent capable of forming an ester to provide a mixture of diastereomeric esters of 10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Suitable chiral reagents capable of forming an ester that may be used in step (a) include, but are not limited to, (+)-naproxen, (+)-mandelic acid, (-)-camphor sulphonic acid, lactic acid, (+)-ibuprofen or the like, or any other suitable reagents.

The quantities of reagent that may be used in (a) may be less than about 6 molar equivalents, less than about 5 molar equivalents, less than about 3 molar equivalents, less than about 1 molar equivalent, less than about 0.05 molar equivalents, or any other suitable quantity with respect to the moles of the compound of Formula (IV).

Step (a) may be carried out in the presence of one or more suitable coupling agents. Suitable coupling agents that may be used in step (a) include, but are not limited to, dicyclohexylcarbodiimide **("DCC);** 1-hydroxybenzotriazole ("HOBT"); cyanuric chloride; 2-chloro n-methyl pyridinium iodide; boronic acids; chloroformates, such as, for example, C_6-C_{14}aryl chloroformates, substituted C_6-C_{14}aryl chloroformates, or the like; benzoyl chloride; sulfonyl chlorides such as methanesulfonyl chloride, benzenesulfonyl chloride, trifluoromethanesulfonyl chloride, p-toluenesulfonyl chloride, or the like; or any other suitable coupling agent.

The quantities of coupling agent that may be used in step (a) may be less than about 4 molar equivalents, less than about 3 molar equivalents, less than about 2 molar equivalents, less than about 1 molar equivalent, less than about 0.05 molar equivalents, less than about 0.01 molar equivalents, or any other suitable quantity with respect to the moles of the compound of formula (IV).

Step (a) may be carried out in the presence of one or more suitable bases. Suitable bases that may be used in step (a) include, but are not limited to, organic

bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethyl amino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 1,8-diazabicyclo[5.4.0]undec -7-ene ("DBU"), or the like; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (a) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1, 4-dioxane, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

Suitable temperatures for the reaction of step (a) may be less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or any other suitable temperatures.

If desired, the reaction mixture obtained in step a) may be optionally filtered to remove any insoluble solids, or particles may be removed by other methods such as decantation, centrifugation, gravity filtration, suction filtration or any other technique for the removal of solids.

Step (b) involves separating the diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide into individual diastereomers. Step (b) may be effected by methods including removal of solvent, concentrating the reaction mass, or any other suitable techniques. Suitable techniques that may be

used for the removal of solvent include and are not limited to rotational distillation using a device, such as, for example, a BUchi® Rotavapor®, spray drying, agitated thin film drying, freeze drying (lyophilization), or the like, optionally under reduced pressure. In one embodiment, step (b) may be effected by methods including filtration, centrifugation, or decantation.

Step (c) involves isolating the diastereomeric ester of eslicarbazepine. Thus isolated diastereomeric ester of eslicarbazepine may carry some amount of occluded mother liquor and have undesired isomers. The solid may be washed with a suitable solvent or a mixture of solvents, such as, for example, those used in step (a), to remove the undesired isomers. Thus isolated diastereomeric ester of eslicarbazepine may be subjected to slurring or leaching with a suitable solvent or a mixture of solvents, such as, for example, water; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; organic acid solvents such as acetic acid, formic acid, trifluoroacetic acid, chloroacetic acid, propionic acid, butanoic acid, isobutyric acid, valeric acid, isovaleric acid, benzoic acid, salicylic acid, phthalic acid, p-toluenesulphonic acid, o-toluenesulphonic acid, benzenesulphonic acid, methanesulphonic acid, ethanesulphonic acid or the like; or any mixtures thereof.

The diastereomeric ester of eslicarbazepine may be crystallized from a suitable solvent or a mixture of solvents, such as, alcohol solvents, including, for example, methanol, ethanol, propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

Suitable temperatures for the isolation of diastereomeric ester of eslicarbazepine may be less than about 60°C, less than about 40°C, less than

about 20°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures. Suitable times for the isolation may be less than about 5 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or longer times may be used. The exact temperature and time required for complete isolation may be readily determined by a person skilled in the art and will also depend on parameters, such as, for example, concentration and temperature of the solution or slurry.

As the diastereomers differ in their properties, such as solubility, they may be recovered based on the differences in their properties. The isolated diastereomeric ester of eslicarbazepine may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids. The diastereomeric ester of eslicarbazepine thus isolated may carry some amount of occluded mother liquor and thus have higher than desired levels of impurities. If desired, the solid may be washed with a suitable solvent or a mixture of solvents such as those used in step c) to remove the impurities.

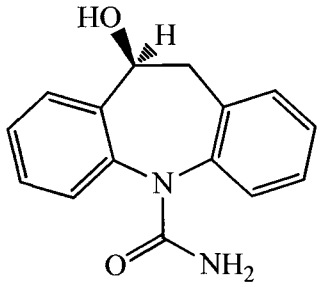
Step (d) involves hydrolyzing the diastereomeric ester of eslicarbazepine to provide optically pure (S)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Step (d) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (d) include, but are not limited to, water; alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene,

tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

Step (d) may be carried out in the presence of one or more suitable bases. Suitable bases that may be used in step (d) include, but are not limited to, inorganic bases, such as, for example, alkali metal hydroxides, including, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; or any other suitable bases.

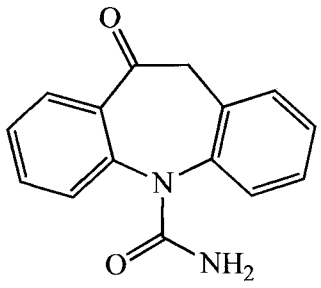
Step (e) optionally involves recovering the diastereomeric ester of (R)-licarbazepine according to methods known in the art.

In an aspect, the present application provides a process for the preparation of (S)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

comprising asymmetrically reducing the compound of formula (V):



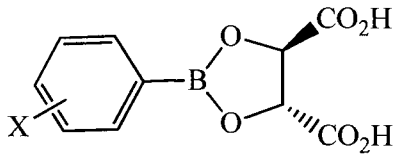
(V)

to form (S)-1 0,11-dihydro-1 0-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III).

Asymmetric reduction of the compound of Formula (V) may be carried out using suitable reduction methods, for example, catalytic hydrogenation, or reduction in the presence of a chiral catalyst or bioreduction.

Suitable reducing agents that may be used for reduction of the compound of Formula (V) include, but are not limited to, lithium aluminum hydride, sodium borohydride, lithium borohydride, potassium borohydride, $NaCNBH_3$, diisobutyl aluminium hydride (DIBAL), borane-dimethyl sulfide (BMS), borane-tetrahydrofuran (BTHF), a combination thereof, or any other suitable reducing agent known in the art.

Asymmetric reduction of the compound of Formula (V) may be carried out in the presence of one or more chiral catalysts. Suitable chiral catalysts that may be used for asymmetric reduction include, but are not limited to, chiral oxazaborolidine catalysts, such as (R)- or (S)-MeCBS (tetrahydro-1-methyl-3, 3-diphenyl-1 H, 3H-pyrrolo [1, 2-c] [1, 3, 2] oxazaborole, or the like; (-)-DIP-chloride [(-)-diisopinocampheylchloroborane] ; L- or K-Selectride®; binol-metal complexes, or the like; a complex of C_6-C_{14}aryl or C_6-Ci_4aryl substituted boronic acid with tartaric acid, such as chiral boronic esters, including, for example, TarB-X of Formula (VIII):



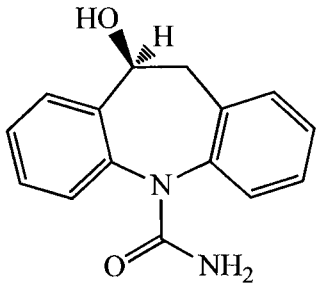
(VIII)

wherein X is H, halo, CrC_6alkyl, or nitro.

Asymmetric reduction of the compound of formula (V) may be carried out in one or more suitable solvents. Suitable solvents that may be used include, but are not limited to, water; alcohol solvents such as methanol, ethanol, 1-propanol, 1-butanol, t-butyl alcohol, ethylene glycol, or the like; ether solvents such as diethyl ether, diisopropyl ether, t-butyl methyl ether, tetrahydrofuran, methyl t-butyl ether, cyclopentyl methyl ether, or the like; aliphatic or alicyclic hydrocarbon solvents such as hexanes, heptane, pentane, cyclohexane, or the like; halogenated hydrocarbon solvents such as dichloromethane, chloroform, or the like; aromatic hydrocarbon solvents such as toluene, xylenes, or the like; polar aprotic solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, pyridine, dimethylsulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or any mixtures thereof.

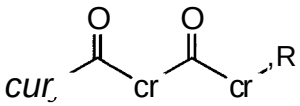
In an aspect, the present application provides a process for the preparation of eslicarbazepine acetate of Formula (I), which includes one or more of the following steps, individually or in the sequence recited:

a) reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

with the compound of Formula (VI):



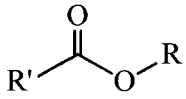
(VI)

wherein R is an optionally substituted C_6-Ci_4aryl group; and

b) isolating eslicarbazepine acetate of Formula (I).

Step (a) involves reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of formula (III) with the compound of formula (VI).

The compound of Formula (VI) of the present application may be prepared by a suitable method known in the art. For example, an embodiment of a process for the preparation of the compound of Formula VI includes reacting an alkali or alkaline earth metal acetate with the compound of formula (VII):



(VII)

in the presence of a base.

wherein R is an optionally substituted C_6-Ci_4aryl group and R' is halo;

Suitable bases that may be used in step (a) as well as for the preparation of the compound of formula (VI) include, but are not limited to, organic bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-

diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethylamino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU"), or the like; inorganic bases, such as, for example, alkali metal hydrides, such as, for example, sodium hydride, potassium hydride, or the like; sodamide; n-butyl lithium; lithium diisopropylamide; alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline 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; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Optionally, Step (a) may be carried out in the presence of acid catalyst. Suitable acid catalysts used in step (a) include, but are not limited to, p-toluene sulfonic acid, sulfamic acid, or the like; Lewis acids such as $Cu(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $HfCl_4 \cdot (THF)_2$, $InCl_3$, or the like; ionic liquids, such as tetraalkylammonium, trialkylsulphonium, tetraalkylphosphonium, 1,3-dialkylimidazolium, N-alkyl-pyridinium, N,N-dialkylpyrrolidinium, N-alkylthiazolium, N,N-dialkyltriazolium, N,N-dialkyloxazolium, and N,N-dialkylpyrazolium cations combined with anions such as BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $MeSO_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO_2)_2^-$, $N(FSO_2)_2^-$, $C(CF_3SO_2)_3^-$, $CF_3CO_2^-$, or CF_3SCv which lead to neutral and stoichiometric ionic liquids; imidazolium-based ionic liquids, or the like; or any other suitable catalyst.

Step (a) may be carried out in a suitable solvent. Suitable solvents that may be used in step (a) include, but are not limited to, ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether,

tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1, 4-dioxane, glyme, diglyme, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

If desired, step a) may be carried out under phase transfer catalyzed conditions in presence of a phase transfer catalyst. Such phase transfer catalyzed conditions may include, but are not limited to, solid-liquid phase transfer catalyzed conditions, and liquid-liquid phase transfer catalyzed conditions.

Suitable temperatures that may be used in step (a) may be less than about 200°C less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or any other suitable temperature.

The isolation in step (b) may be effected by methods including removal of solvent, cooling, concentrating the reaction mass, adding an anti-solvent, adding seed crystals, or the like. Suitable temperatures for isolation may be less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures. Suitable times for isolation may be less than about 5 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or longer times may be used. The exact temperature and time required for complete isolation may be readily determined by a person skilled in the art and will also depend on parameters, such as, for example, concentration and temperature of the solution or slurry. Stirring or other alternate methods, such as, for example, shaking, agitation, or the like, that mix the contents may also be employed for isolation.

Suitable techniques that may be used for the removal of solvent include, but are not limited to, rotational distillation using a device, such as, for example, a Biichi® Rotavapor®, spray drying, agitated thin film drying, freeze drying (lyophilization), or the like, optionally under reduced pressure.

The isolated eslicarbazepine acetate of Formula (I) may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids. The eslicarbazepine acetate of Formula (I) thus isolated may carry some amount of occluded mother liquor and have higher than desired levels of impurities. The solid may be washed with a suitable solvent or a mixture of solvents, such as, for example, those used in step (a), to remove the impurities.

The isolated eslicarbazepine acetate of Formula (I) may be further purified by recrystallization from a suitable solvent or a mixture of solvents, such as, for example, those used in step (a), to provide eslicarbazepine acetate of Formula (I) having a purity by HPLC which is essentially pure, substantially pure, or even pure.

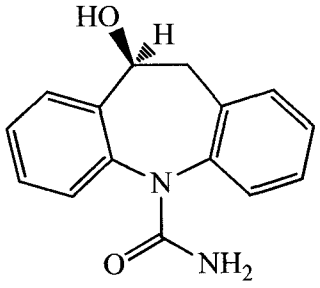
The recovered solid may be optionally further dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under a reduced pressure at temperatures of less than about 150°C, less than about 120°C, less than about 100°C, less than about 80°C, less than about 60°C, or any other suitable temperature as long as the eslicarbazepine acetate of Formula (I) is not degraded in quality. The drying may be carried out for any desired time until the required purity is achieved. For example, it may vary from about 1 to about 10 hours or longer.

The dried product may be optionally milled to get the required particle size. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation sifting; milling using mills, such as, for example, ball, roller and hammer mills, and jet mills, including, for example, air jet mills; or any other conventional technique. The desired particle size may also be achieved directly from the reaction mixture by selecting equipment that is able to provide eslicarbazepine acetate with the desired particle size.

In an aspect, the present application provides a process for the preparation of eslicarbazepine acetate of Formula (I), which includes one or more of the following steps, individually or in the sequence recited:

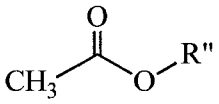
In an aspect, the present application provides a process for the preparation of eslicarbazepine acetate of Formula (I), which includes one or more of the following steps, individually or in the sequence recited:

(a) reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

with a compound of Formula (IX):



(IX)

wherein R" is an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_6-C_{14}aryl, C_7-C_{10}(ar)alkyl group, C_1-C_6alkyl-sulfonyl group or C_6-C_{14}aryl-sulfonyl group; and

(b) isolating eslicarbazepine acetate of formula (I).

Step (a) involves reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of formula (III) with the compound of formula (IX). Step (a) may be carried out in the presence of acid catalyst. Suitable acid catalysts used in step (a) include, but are not limited to, methane sulfonic acid, p-toluene sulfonic acid, sulfamic acid, or the like; Lewis acids such as for example, $Cu(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $HfCl_4 \bullet (THF)_2$, $InCl_3$, or the like; ionic liquids, such as for example, tetraalkylammonium, trialkylsulphonium, tetraalkylphosphonium, 1,3-dialkylimidazolium, N-alkyl-pyridinium, N,N-dialkylpyrrolidinium, N-alkylthiazolium, N,N-dialkyltriazolium, N,N-dialkyloxazolium, or N,N-dialkylpyrazolium cations combined with anions such as for example, BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $MeSO_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO_2)_2^-$,

$N(FSO_2)_2^-$, $C(CF_3SO_2)_3^-$, CF3CO2-, or CF3SO3-, which lead to neutral and stoichiometric ionic liquids; imidazolium-based ionic liquids, or the like; or any other suitable catalyst.

Step (a) may be carried out in a suitable solvent. Suitable solvents that may be used in step (a) include, but are not limited to, ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1, 4-dioxane, glyme, diglyme, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

If desired, step a) may be carried out under phase transfer catalyzed conditions in presence of a phase transfer catalyst. Such phase transfer catalyzed conditions may include, but are not limited to, solid-liquid phase transfer catalyzed conditions, and liquid-liquid phase transfer catalyzed conditions.

Suitable temperatures that may be used in step (a) may be less than about 200°C less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or any other suitable temperature.

The isolation in step (b) may be effected by methods including removal of solvent, cooling, concentrating the reaction mass, adding an anti-solvent, extraction with a solvent, crystallization from a suitable solvent or a mixture of solvents, adding seed crystals, or the like. Stirring or other alternate methods such as shaking, agitation or the like, may also be employed for isolation.

Suitable temperatures for isolation may be less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 5°C, less than about 0°C, less than about -10°C, less than about -20°C, or any other suitable temperatures. Suitable times for isolation may be less than about 5 hours, less than about 3 hours, less than about 2 hours, less than about 1 hour, or longer times may be used. The exact temperature and time required for complete isolation may be readily determined by a person skilled in the art and will also depend on parameters, such as, for example, concentration and temperature of the solution or slurry. Stirring or other alternate methods, such as, for example, shaking, agitation, or the like, that mix the contents may also be employed for isolation.

Suitable techniques that may be used for the removal of solvent include, but are not limited to, rotational distillation using a device, such as, for example, a Buchi® Rotavapor®, spray drying, agitated thin film drying, freeze drying (lyophilization), or the like, optionally under reduced pressure.

The isolated eslicarbazepine acetate of Formula (I) may be recovered by methods including decantation, centrifugation, gravity filtration, suction filtration, or any other technique for the recovery of solids. The eslicarbazepine acetate of Formula (I) thus isolated may carry some amount of occluded mother liquor and have higher than desired levels of impurities. The solid may be washed with a suitable solvent or a mixture of solvents, such as, for example, those used in step (a), to remove the impurities.

The isolated eslicarbazepine acetate of Formula (I) may be further purified by recrystallization from a suitable solvent or a mixture of solvents, to provide eslicarbazepine acetate of Formula (I) having a purity by HPLC which is essentially pure, substantially pure, or even pure. Suitable solvents that may be used for crystallization or recrystallization of eslicarbazepine acetate of Formula (I) include, but are not limited to, alcohol solvents such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, neopentyl alcohol, amyl alcohol, 2-methoxyethanol, 2-ethoxyethanol, ethylene glycol, glycerol or the like; ketone solvents such as acetone, butanone; 2-pentanone, 3-pentanone, methyl butyl ketone, methyl iso-butyl ketone or the like; ester solvents such as ethyl formate, methyl acetate, ethyl acetate, propyl acetate,

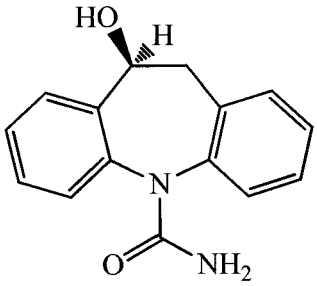
t-butyl acetate, isobutyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate or the like; aliphatic or alicyclic hydrocarbon solvents such as hexanes, heptane, pentane, cyclohexane, methylcyclohexane, nitromethane or the like; halogenated hydrocarbon solvents such as dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene or the like; aromatic hydrocarbon solvents such as toluene, xylenes, chlorobenzene, tetralin or the like; nitrile solvents such as acetonitrile, propionitrile or the like; or mixtures thereof.

The recovered solid may be optionally further dried. Drying may be carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under a reduced pressure at temperatures of less than about 150°C, less than about 120°C, less than about 100°C, less than about 80°C, less than about 60°C, or any other suitable temperature as long as the eslicarbazepine acetate of Formula (I) is not degraded in quality. The drying may be carried out for any desired time until the required purity is achieved. For example, it may vary from about 1 to about 10 hours or longer.

The dried product may be optionally milled to get the required particle size. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation sifting; milling using mills, such as, for example, ball, roller and hammer mills, and jet mills, including, for example, air jet mills; or any other conventional technique. The desired particle size may also be achieved directly from the reaction mixture by selecting equipment that is able to provide eslicarbazepine acetate with the desired particle size.

In an aspect, the present application provides a process for the preparation of eslicarbazepine acetate of formula (I), which includes one or more of the following steps, individually or in the sequence recited:

(a) reacting the (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

with an acetylating agent selected from acetic anhydride, acetyl chloride, or acetic acid; and

(b) isolating eslicarbazepine acetate of Formula (I).

Suitable bases that may be used in step (a) as well as for the preparation of the compound of formula (VI) include, but are not limited to organic bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethylamino) pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU"), or the like; inorganic bases, such as, for example, alkali metal hydrides, such as, for example, sodium hydride, potassium hydride, or the like; sodamide; n-butyl lithium; lithium diisopropylamide; alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline 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; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; and mixtures thereof.

Optionally, Step (a) may be carried out in the presence of acid catalyst. Suitable acid catalysts used in step (a) include, but are not limited to, p-toluene sulfonic acid, sulfamic acid, or the like; Lewis acids such as $Cu(OTf)_2$, $Yb(OTf)_3$, $Sc(OTf)_3$, $In(OTf)_3$, $HfCl_4 \cdot (THF)_2$, $InCl_3$, or the like; ionic liquids, such as tetraalkylammonium, trialkylsulphonium, tetraalkylphosphonium, 1,3-

dialkylimidazolium, N-alkyl-pyridinium, N,N-dialkylpyrrolidinium, N-alkylthiazolium, N,N-dialkyltriazolium, N,N-dialkyloxazolium, and N,N-dialkylpyrazolium cations combined with anions such as BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $MeSO_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO2)2^-$, $N(FSO_2)2^-$, $C(CF_3SO_2)_3^-$, $CF_3CO_2^-$, or $CF_3SO_3^-$' which lead to neutral and stoichiometric ionic liquids; imidazolium-based ionic liquids, or the like; and any other suitable catalyst.

Step (a) may be carried out in a suitable solvent. Suitable solvents that may be used in step (a) include, but are not limited to, ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1, 4-dioxane, glyme, diglyme, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

If desired, step a) may be carried out under phase transfer catalyzed conditions in presence of a phase transfer catalyst. Such phase transfer catalyzed conditions may include, but are not limited to, solid-liquid phase transfer catalyzed conditions, and liquid-liquid phase transfer catalyzed conditions.

Suitable temperatures that may be used in step (a) may be less than about 200°C less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or any other suitable temperature.

In an aspect, the present application provides a crystalline form of eslicarbazepine acetate characterized by a powder X-ray diffraction pattern having peak locations substantially as listed in Table 1.

Table 1

2θ (degrees) ± 0.2	d-spacing (Å)± 0.02
5.6	15.50
10.0	8.78
11.2	7.87
12.8	6.88
16.9	5.22
17.9	4.94
19.0	4.66
19.5	4.53
20.0	4.41
20.3	4.35
21.2	4.17
22.0	4.02
22.6	3.92
24.1	3.68
25.9	3.43
27.1	3.27
27.9	3.19
28.1	3.16
30.0	2.97
30.7	2.90
32.3	2.76

In an aspect, the present application provides crystalline form of eslicarbazepine acetate characterized by a powder X-ray diffraction (PXRD) pattern, an infrared absorption spectrum, differential scanning calorimetry (DSC) thermogram, and/or thermal gravimetric analysis (TGA) curve substantially as illustrated by Figs. 1, 2, 3 and 4, respectively.

For example, eslicarbazepine acetate of Formula (I) prepared according to a process described in the present application has a PXRD pattern substantially as illustrated in Fig. 1.

For example, eslicarbazepine acetate of Formula (I) prepared according to a process described in the present application has an infrared absorption spectrum substantially as illustrated in Fig. 2.

For example, eslicarbazepine acetate of Formula (I) prepared according to a process described in the present application has a DSC thermogram substantially as illustrated in Fig. 3.

For example, eslicarbazepine acetate of Formula (I) prepared according to a process described in the present application has a TGA curve corresponding to a weight loss of less than about 1% w/w. For example, eslicarbazepine acetate of Formula (I) prepared according to a process described in the present application has a TGA curve substantially as illustrated in Fig. 4.

In an aspect, the present application provides an amorphous form of eslicarbazepine acetate.

In an aspect, the present application provides a process for the preparation of an amorphous form of eslicarbazepine acetate, comprising:

a) providing a solution of eslicarbazepine acetate in a solvent or mixture of solvents; and

b) isolating an amorphous form of eslicarbazepine acetate.

Step a) involves providing a solution of eslicarbazepine acetate in a solvent or mixture of solvents.

Providing a solution in step a) includes:

i) direct use of a reaction mixture containing eslicarbazepine acetate that is obtained in the course of its synthesis; or

ii) dissolving eslicarbazepine acetate in a suitable solvent or mixture of solvents.

Any physical form of eslicarbazepine acetate, such as crystalline, amorphous or their mixtures may be utilized for providing the solution of eslicarbazepine acetate in step a). Suitable solvents that may be used in step a) include, but are not limited to, water; alcohol solvents such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, t-butyl alcohol, 1-pentanol, 2-pentanol, neopentyl alcohol, amyl alcohol, 2-methoxyethanol, 2-ethoxyethanol, ethylene glycol, glycerol or the like; ketone solvents such as acetone, butanone; 2-pentanone, 3-pentanone, methyl butyl ketone, methyl isobutyl ketone or the like; ester solvents such as ethyl formate, methyl acetate, ethyl acetate, propyl acetate, t-butyl acetate, isobutyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate or the like; halogenated hydrocarbon solvents such as dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene or the like; nitrile solvents such as acetonitrile, propionitrile or the like; polar aprotic solvents such as N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone,

pyridine, dimethylsulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

The dissolution temperatures may range from about -20°C to about the reflux temperature of the solvent, depending on the solvent used for dissolution, as long as a clear solution of eslicarbazepine acetate is obtained without affecting its quality. The solution may optionally be treated with carbon, flux-calcined diatomaceous earth (Hyflow) or any other suitable material to remove color and/or to get clarity of the solution. Optionally, the solution obtained above may be filtered to remove any insoluble particles. The insoluble particles may be removed suitably by filtration, centrifugation, decantation, or any other suitable techniques. The solution may be filtered by passing through paper, glass fiber, or other membrane material, or a bed of a clarifying agent such as Celite® or Hyflow. Depending upon the equipment used and the concentration and temperature of the solution, the filtration apparatus may need to be preheated to avoid premature crystallization.

Step b) involves isolation of an amorphous form of eslicarbazepine acetate from the solution of step a).

In one embodiment, the isolation may be effected by removing solvent. Suitable techniques which may be used for the removal of solvent include using a rotational distillation device such as a Buchi® Rotavapor®, spray drying, agitated thin film drying, freeze drying (lyophilization), or the like, or any other suitable technique.

The solvent may be removed, optionally under reduced pressures, at temperatures less than about 200°C, less than about 150°C, less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C, less than about -60°C, less than about -80°C, or any other suitable temperatures.

Freeze drying (lyophilization) may be carried out by freezing a solution of eslicarbazepine acetate at low temperatures and reducing the pressure as required to remove the solvent from the frozen solution of eslicarbazepine acetate. Temperatures that may be required to freeze the solution, depending on the solvent chosen to make the solution of eslicarbazepine acetate, may range from about -80°C to about 0°C, or up to about 40°C. Temperatures that may be

required to remove the solvent from the frozen solution may be less than about 20°C, less than about 0°C, less than about -20°C, less than about -40°C, less than about -60°C, less than about -80°C, or any other suitable temperatures.

Alternatively, isolation may also be effected by adding a suitable anti-solvent to the solution obtained in step a), optionally after concentrating the solution obtained in step a). Suitable anti-solvents that may be used include, but are not limited to, ether solvents such as diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 1,4-dioxane, 2-methoxyethanol, 2-ethoxyethanol, anisole or the like; aliphatic or alicyclic hydrocarbon solvents such as hexanes, heptane, pentane, cyclohexane, methylcyclohexane, nitromethane or the like; aromatic hydrocarbon solvents such as toluene, xylenes, chlorobenzene, tetralin or the like; or mixtures thereof.

The compound obtained from step b) may be collected using techniques such as by scraping, or by shaking the container, or other techniques specific to the equipment used.

The product thus isolated may be optionally further dried to afford an amorphous form of eslicarbazepine acetate.

Drying may be suitably carried out in a tray dryer, vacuum oven, Buchi® Rotavapor®, air oven, fluidized bed dryer, spin flash dryer, flash dryer, or the like. The drying may be carried out at atmospheric pressure or under reduced pressures at temperatures of less than about 200°C, less than about 150°C, less than about 100°C, less than about 60°C, less than about 40°C, less than about 20°C, less than about 0°C, less than about -20°C, or any other suitable temperatures. The drying may be carried out for any time period required for obtaining a desired quality, such as from about 15 minutes to several hours.

The dried product may be optionally milled to get desired particle sizes. Milling or micronization may be performed before drying, or after the completion of drying of the product. Techniques that may be used for particle size reduction include, without limitation, ball, roller and hammer mills, and jet mills.

In an aspect, the present application provides an amorphous form of eslicarbazepine acetate characterized by a powder X-ray diffraction (PXRD) pattern, infrared absorption spectrum and/or thermal gravimetric analysis (TGA) curve substantially as illustrated by Figs. 8, 9 and 10, respectively.

All PXRD data reported herein were obtained using a Bruker AXS D8 Advance Powder X-ray Diffractometer with copper Ka radiation. Infrared absorption (IR) spectrum analyses reported herein were carried out using Perkin Elmer System Spectrum 1 model spectrophotometer, between 450 cm-1 and 4000 cm-1 , with a resolution of 4 cm-1 in a potassium bromide pellet, the test compound being at the concentration of 1% by mass. Differential scanning calorimetric analyses reported herein were carried out using a DSC Q1000 model from TA Instruments with a ramp of 10°C/minute up to 200°C. The starting temperature was 20°C and ending temperature was 200°C. Thermogravimetric analysis analyses reported herein were carried out using a TGA Q500 V6.4 Build 193 from TA Instruments, with a ramp of 10°C/minute up to 200°C.

In an aspect, the present application provides eslicarbazepine acetate having maximum particle sizes less than about 300 μm, less than about 250 pm, less than about 200 pm, less than about 150 pm, less than about 100 pm, less than about 50 μιη , less than about 20 μιη , or less than about 10 pm.

Particle size distributions of eslicarbazepine acetate particles may be measured by any technique known in the art. For example, particle size distributions of eslicarbazepine acetate particles may be measured using light scattering equipment, such as, for example, a Malvern Master Sizer 2000 from Malvern Instruments Limited, Malvern, Worcestershire, United Kingdom (helium neon laser source, eslicarbazepine acetate suspended in light liquid paraffin, size range: 0.02 μm to 2000 μιτι).

In an aspect, the present application provides pharmaceutical compositions prepared using eslicarbazepine acetate having maximum particle sizes less than about 300 pm, less than about 250 pm, less than about 200 pm, less than about 150 pm, less than about 100 pm, less than about 50 pm, less than about 20 pm, or less than about 10 pm, together with one or more pharmaceutically acceptable excipients.

A pharmaceutical composition comprising eslicarbazepine acetate and one or more pharmaceutically acceptable excipients may be formulated as solid oral dosage forms, such as, for example, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms, such as, for example, syrups, suspensions, dispersions, and emulsions; and injectable preparations, such as, for example,

solutions, dispersions, and freeze dried compositions. Immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations. Modified release compositions may comprise hydrophilic and/or hydrophobic release rate controlling substances to form matrix and/or reservoir systems. The pharmaceutical compositions may be prepared by direct blending, dry granulation, or wet granulation or by extrusion and spheronization. Compositions may be uncoated, film coated, sugar coated, powder coated, enteric coated, or modified release coated.

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

DEFINITIONS

The following definitions are used in connection with the present invention unless the context indicates otherwise. In general, the number of carbon atoms present in a given group is designated "C_x-C_y", where x and y are the lower and upper limits, respectively. For example, a group designated as "Ci-C_6" contains

from 1 to 6 carbon atoms. The carbon number as used in the definitions herein refers to carbon backbone and carbon branching, but does not include carbon atoms of the substituents, such as alkoxy substitutions or the like. Unless indicated otherwise, the nomenclature of substituents that are not explicitly defined herein are arrived at by naming from left to right the terminal portion of the functionality followed by the adjacent functionality toward the point of attachment. "KF" means Karl Fischer, a method to determine trace amounts of water in a sample. Naproxen is (+)-(S)-2-(6-methoxynaphthalen-2-yl) propanoic acid.

"Alkenyl-" refer to a straight or branched chain unsaturated hydrocarbon containing at least one double bond. Where E- and/or Z-isomers are possible, the term "alkenyl" is intended to include all such isomers. Examples of a C_2-C_6alkenyl-group include, but are not limited to, ethylenyl, prop-1-en-1-yl, allyl, butyl-1-en-1-yl, butyl-2-en-1-yl, 2-methylprop-1-en-1-yl, 2-methylallyl, pent-1-en-1-yl, pent-2-en-1-yl, 3-methylbut-3-en-1-yl, 3-methylbut-2-en-1-yl, 3-methylbut-1-en-1-yl, penta-1 ,4-dien-1-yl, hex-1-en-1-yl, hex-2-en-1-yl, hex-3-en-1-yl, and 4-methylpent-3-en-1-yl. An alkenyl-group can be unsubstituted or substituted with one or more of the following groups: halogen, H_2N-, **(Ci**-C_6alkyl)amino-, di(C_1-C_6alkyl)amino-, **(CrC $_6$alkyl**)C(0)N **(Ci**-C_3alkyl)-, **(C_1**-C_6alkyl)carboxyamido-, HC(0)NH-, H_2NC(0)-, **(Ci**-C_6alkyl)NHC(0)-, di**(C_1**-C_6alkyl)NC(0)-, NC-, hydroxyl, **C_1**-C_6alkoxy-, **C_1**-C_6alkyl-, H0 $_2$C-, (C_1-C_6alkoxy)carbonyl-, **(CrC** $_6$alkyl)C(0)-, C_6-C_{14}aryl-, **C_1**-C_9heteroaryl-, C_3-C_8cycloalkyl-, **CrC** $_6$haloalkyl-, amino(C_1-C_6alkyl)-, **(CrC** $_6$alkyl)carboxyl-, C_1-C_6carboxyamidoalkyl-, or 0 $_2$N-.

An "alcohol solvent" is an organic solvent containing a carbon bound to a hydroxyl group. "Alcohol solvents" include, but are not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, glycerol, **C_{1-6}**alcohols, or the like.

An "aliphatic or alicyclic hydrocarbon solvent" refers to a liquid, non-aromatic, hydrocarbon, which may be linear, branched, or cyclic. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of a

hydrocarbon solvent include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, C_5-C_8aliphatic hydrocarbons, petroleum ethers, or mixtures thereof.

"Alkyl-" refers to a hydrocarbon chain that may be a straight chain or branched chain, containing the indicated number of carbon atoms, for example, a Ci-C|$_0$alkyl- group may have from 1 to 10 (inclusive) carbon atoms in it. In the absence of any numerical designation, "alkyl" is a chain (straight or branched) having 1 to 6 (inclusive) carbon atoms in it. Examples of Ci-C $_6$alkyl- groups include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, or isohexyl. An alkyl- group can be unsubstituted or substituted with one or more of the following groups: halogen, H_2N-, (C_1-C_6alkyl)amino-, di(d-C $_6$alkyl)amino-, (Ci-C $_6$alkyl)C(0)N(d-C_3alkyl)-, (C_1-C_6alkyl)carboxyamido-, HC(0)NH-, $H_2NC(0)$-, (d-C $_6$alkyl)NHC(0)-, di(d-C $_6$alkyl)NC(0)-, NC-, hydroxyl, Ci-C $_6$alkoxy-, CrC $_6$alkyl-, H0 $_2$C-, (d-C_6alkoxy)carbonyl-, (d-C $_6$alkyl)C(0)-, C_6-Ci $_4$aryl-, Ci-Cgheteroaryl-, C_3-C_8cycloalkyl-, d-C $_6$haloalkyl-, amino(Ci-C $_6$alkyl)-, (d-C $_6$alkyl)carboxyl-, Ci-C_6carboxyamidoalkyl-, or 0 $_2$N-.

"Alkyl-sulfonyl" refers to the group R-S(0) $_2$- where R is an alkyl group, as defined above and linked to the rest of the molecule through the sulfur atom of the S0 $_2$ group. Examples of d-C $_6$alkyl-sulfonyl groups include, but are not limited to, methanesulfonyl, ethanesulfonyl, propanesulfonyl, butanesulfonyl, pentanesulfonyl, hexanesulfonyl, isopropanesulfonyl, isobutanesulfonyl, sec-butanesulfonyl, tert-butanesulfonyl, isopentanesulfonyl, neopentanesulfonyl, or isohexanesulfonyl.

"(Ar)alkyl-" refers to an alkyl group, as defined above, wherein one or more of the alkyl group's hydrogen atoms have been replaced with an aryl group as defined above. C_7-C_{10}(Ar)alkyl- moieties include benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 2-phenylpropyl, or the like. An (ar)alkyl group can be unsubstituted or substituted with one or more of the following groups: halogen,

H_2N-, hydroxyl, (Ci-C_6alkyl)amino-, di(Ci-C_6alkyl)amino-, (C_1-C_6alkyl)C(0)N(C_1-C_3alkyl)-, (CrC_6alkyl)carboxyamido-, HC(0)NH-, H_2NC(0)-, (Ci-C_6alkyl)NHC(0)-, di(Ci-C_6alkyl)NC(0)-, NC-, hydroxyl, C_1-C_6alkoxy-, C_1-C_6alkyl-, H0$_2$C-, (C_1-C_6alkoxy)carbonyl-, (C-i-C_6alkyl)C(0)-, C_6-Ci$_4$aryl-, CrCgheteroaryl-, C_3-C_8cyclo alkyl-, C_1-C_6haloalkyl-, amino(C_1-C_6alkyl)-, (CrC_6alkyl)carboxyl-, Ci-C_6carboxyamido alkyl-, or 0$_2$N-.

"Aromatic hydrocarbon solvent" refers to a liquid, unsaturated, cyclic, hydrocarbon containing one or more rings which has at least one 6-carbon ring containing three double bonds. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of an aromatic hydrocarbon solvent include, but are not limited to, benzene toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, indane, naphthalene, tetralin, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C_6-C_{10}aromatic hydrocarbons, or mixtures thereof.

"Aryl-" refers to an aromatic hydrocarbon group. Examples of a C_6-C_{14}aryl-group include, but are not limited to, phenyl, 1-naphthyl, 2-naphthyl, 3-biphen-1-yl, anthryl, tetrahydronaphthyl, fluorenyl, indanyl, biphenylenyl, or acenaphthenyl. An aryl group can be unsubstituted or substituted with one or more of the following groups: CrC_6alkyl-, halogen, haloalkyl-, hydroxyl, hydroxyl(C_1-C_6alkyl)-, H_2N-, amino(Ci-C_6alkyl)-, di(Ci-C_6alkyl)amino-, H0$_2$C-, (CrC_6alkoxy)carbonyl-, (C-i-C_6alkyl)carboxyl-, di(Ci-C_6alkyl)amido-, H_2NC(0)-, (C_1-C_6alkyl)amido-, or 0$_2$N-.

"Aryl-sulfonyl" refers to the group R-S(0)$_2$- where R is an aryl, as defined above and linked to the rest of the molecule through the sulfur atom of the S0$_2$ group. Examples of a C_6-C_{14}aryl-sulfonyl group include, but are not limited to, benzenenesulfonyl, 1-naphthenesulfonyl, 2-naphthenesulfonyl, 3-biphen-1-enesulfonyl, anthrenesulfonyl, tetrahydronaphthenesulfonyl, fluorenenesulfonyl, indanenesulfonyl, biphenenesulfonylenenesulfonyl, or acenaphthenenesulfonyl.

An "ester solvent" is an organic solvent containing a carboxyl group -(C=0)-0- bonded to two other carbon atoms. "Ester solvents" include, but are not limited to, ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, C_{3-6}esters, or the like.

An "ether solvent" is an organic solvent containing an oxygen atom -O- bonded to two other carbon atoms. "Ether solvents" include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C_{2-6}ethers, or the like.

A "halogenated hydrocarbon solvent" is an organic solvent containing a carbon bound to a halogen. "Halogenated hydrocarbon solvents" include, but are not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride, or the like.

An "ionic liquid" is a salt in which the ions are poorly coordinated, which results in these solvents being liquid below 100°C, or even at room temperature. At least one ion of the ionic liquid has a delocalized charge and one component is organic, which prevents the formation of a stable crystal lattice. "Ionic liquids" include, but are not limited to, 2-hydroxyethyl-trimethylammonium L-(+)-lactate, benzyldimethyltetradecylammonium chloride, benzyltrimethylammonium tribromide, butyltrimethylammonium bis(trifluoromethylsulfonyl)imide, diethylmethyl(2-methoxyethyl)ammonium bis(trifluoromethylsulfonyl)imide, ethyldimethylpropylammonium bis(trifluoromethylsulfonyl)imide, methyl-trioctylammonium bis(trifluoromethylsulfonyl)imide, methyltrioctadecylammonium bromide, methyltrioctylammonium hydrogen sulfate, methyltrioctylammonium thiosalicylate, tetrabutylammonium benzoate, tetrabutylammonium bis-trifluoromethanesulfonimidate, tetrabutylammonium heptadecafluoro octanesulfonate, tetrabutylammonium hydroxide 30-hydrate, tetrabutylammonium methanesulfonate, tetrabutylammonium nitrite, tetrabutylammonium nonafluorobutanesulfonate, tetrabutylammonium succinimide, tetrabutyl ammonium thiophenolate, tetrabutylammonium triiodide, tetradodecylammonium bromide, tetradodecylammonium chloride, tetraethylammonium acetate tetrahydrate, tetraethylammonium trifluoroacetate, tetraethylammonium trifluoromethanesulfonate, tetraheptylammonium bromide, tetraheptylammonium chloride, tetrahexylammonium hydrogensulfate, tetrahexylammonium iodide, tetrahexylammonium tetrafluoroborate, tetrakis(decyl)ammonium bromide, tetramethylammonium hydroxide pentahydrate, tetraoctylammonium chloride,

tetrapentylammonium thiocyanate, tributylmethylammonium chloride, tributylmethylammonium dibutyl phosphate, tributylmethylammonium methyl carbonate, tributylmethylammonium methyl sulfate, triethylmethylammonium dibutyl phosphate, triethylmethylammonium methyl carbonate, tris(2-hydroxyethyl)methylammonium methylsulfate, cholin acetate, cholin salicylate, 3-(triphenylphosphonio)propane-l -sulfonate, 3-(triphenylphosphonio)propane-1 -sulfonic acid tosylate, tetrabutylphosphonium methanesulfonate, tetrabutyl phosphonium p-toluenesulfonate, tetrabutylphosphonium tetrafluoroborate, tributylmethylphosphonium dibutyl phosphate, tributylmethylphosphonium methyl carbonate, tributylmethylphosphonium methyl sulfate, triethylmethylphosphonium dibutyl phosphate, trihexyltetradecylphosphonium bis(2,4,4-trimethylpentyl) phosphinate, trihexyltetradecylphosphonium bis(trifluoromethylsulfonyl)amide, trihexyltetradecylphosphonium bromide, trihexyltetradecylphosphonium chloride, trihexyltetradecylphosphonium decanoate, trihexyltetradecylphosphonium dicyanamide, triisobutylmethylphosphonium tosylate, 1-(3-cyanopropyl)pyridinium bis(trifluoromethylsulfonyl)imide, 1-(3-cyanopropyl)pyridinium chloride, 1-butyl-3-methylpyridinium bis(trifluormethylsulfonyl)imide, 1-butyl-4-methylpyridinium bromide, 1-butyl-4-methylpyridinium chloride, 1-butyl-4-methylpyridinium hexafluorophosphate, 1-butyl-4-methylpyridinium iodide, 1-butyl-4-methylpyridinium tetrafluoroborate, 1-butylpyridinium bromide, 1-ethylpyridinium tetrafluoroborate, 3-methyl-1-propylpyridinium bis(trifluormethylsulfonyl)imide, 1-butyl-1 -methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, 1-butyl-1 -methylpyrrolidinium bis(trifluoromethylsulfonyl)imide, 1-butyl-1 -methylpyrrolidinium bromide, 1-butyl-1 -methylpyrrolidinium chloride, 1-butyl-1 -methylpyrrolidinium dicyanamide, 1-butyl-1 -methylpyrrolidinium hexafluorophosphate, 1-butyl-1 -methylpyrrolidinium iodide, 1-butyl-1 -methylpyrrolidinium methyl carbonate, 1-butyl-1 -methylpyrrolidinium tetrafluoroborate, 1-butyl-1 -methylpyrrolidinium trifluoromethanesulfonate, 1-ethyl-1 -methylpyrrolidinium bis(trifluoromethyl sulfonyl)imide, 1-ethyl-1-methylpyrrolidinium bromide, 1-ethyl-1-methylpyrrolidinium hexafluorophosphate, 1-ethyl-1 -methylpyrrolidinium tetrafluoroborate, triethylsulfonium bis(trifluoromethylsulfonyl)imide, 1-butyl-1 -methylpiperidinium bis(trifluoromethylsulfonyl)imide, 1-butyl-1 -methylpiperidinium hexafluorophosphate, 1-butyl-1-methylpiperidinium tetrafluoroborate, 1-ethyl-1-

methylpiperidinium methyl carbonate, 4-ethyl-4-methylmorpholinium methyl, bis(pentafluoroethylsulfonyl)imide, 1,2,3-trimethylimidazolium methyl sulfate, 1,2,3-trimethylimidazolium trifluoromethanesulfonate, ,1,2-dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide, 1,2-dimethyl-3-propylimidazolium bis(trifluoromethylsulfonyl)imide, 1,2-dimethyl-3-propylimidazolium tris(trifluoromethylsulfonyl)methide, 1,3-bis(cyanomethyl) imidazolium bis(trifluoromethylsulfonyl)imide, 1,3-bis(cyanomethyl)imidazolium chloride, 1,3-diethoxyimidazolium bis(trifluoromethylsulfonyl)imide, 1,3-diethoxyimidazolium hexafluorophosphate, 1,3-dihydroxyimidazolium bis(trifluoromethylsulfonyl)imide, 1,3-dimethoxyimidazolium bis(trifluoromethylsulfonyl)imide, 1,3-dimethoxyimidazolium hexafluorophosphate, 1,3-dimethylimidazolium dimethyl phosphate, 1,3-dimethylimidazolium hydrogen carbonate, 1,3-dimethylimidazolium methanesulfonate, 1,3-dimethylimidazolium methyl sulfate, 1,3-dimethylimidazolium methyl sulfate, 1,3-bis(3-cyanopropyl)imidazolium bis(trifluoromethylsulfonyl)imide, 1,3-bis(3-cyanopropyl)imidazolium chloride, 1,3-dihydroxy-2-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1,3-dimethoxy-2-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1,3-dimethoxy-2-methylimidazolium hexafluorophosphate, 1-(2-hydroxyethyl)-3-methylimidazolium dicyanamide, 1-(3-cyanopropyl)-3-methylimidazolium bis(trifluoromethylsulfonyl)amide, 1-(3-cyanopropyl)-3-methylimidazolium chloride, 1-(3-cyanopropyl)-3-methylimidazolium dicyanamide, 1-(cyanomethyl)-3-methylimidazolium chloride, 1-allyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-allyl-3-methylimidazolium bromide, 1-allyl-3-methylimidazolium chloride, 1-allyl-3-methylimidazolium dicyanamide, 1-benzyl-3-methylimidazolium chloride, 1-benzyl-3-methylimidazolium hexafluorophosphate, 1-benzyl-3-methylimidazolium tetra fluoroborate, 1-butyl-1-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)imidazolium hexafluorophosphate, 1-butyl-2,3-dimethylimidazolium chloride, 1-butyl-2,3-dimethylimidazolium hexafluorophosphate, 1-butyl-2,3-dimethylimidazolium tetrafluoroborate, 1-butyl-2,3-dimethylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium 2-(2-methoxyethoxy)ethyl sulfate, 1-butyl-3-methylimidazolium acetate, 1-butyl-3-methylimidazolium acetate, 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-butyl-3-methylimidazolium bis(trifluoromethyl

sulfonyl)imide,1-butyl-3-methylimidazolium bromide, 1-butyl-3-methylimidazolium bromide, 1-butyl-3-methylimidazolium chloride, 1-butyl-3-methylimidazolium chloride, 1-butyl-3-methylimidazolium chloride, 1-butyl-3-methylimidazolium chloride, 1-butyl-3-methylimidazolium dibutyl phosphate, 1-butyl-3-methylimidazolium dicyanamide, 1-butyl-3-methylimidazolium hexafluoro antimonate, 1-butyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium hexafluorophosphate, 1-butyl-3-methylimidazolium hydrogen carbonate, 1-butyl-3-methylimidazolium hydrogen sulfate, 1-butyl-3-methylimidazolium iodide, 1-butyl-3-methylimidazolium methanesulfonate, 1-butyl-3-methylimidazolium methyl sulfate, 1-butyl-3-methylimidazolium methyl sulfate, 1-butyl-3-methylimidazolium nitrate, 1-butyl-3-methylimidazolium octyl sulfate, 1-butyl-3-methylimidazolium tetrachloroaluminate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium tetrafluoroborate, 1-butyl-3-methylimidazolium thiocyanate, 1-butyl-3-methylimidazolium thiocyanate, 1-butyl-3-methylimidazolium tosylate, 1-butyl-3-methylimidazolium trifluoroacetate, 1-butyl-3-methylimidazolium trifluoromethanesulfonate, 1-butyl-3-methylimidazolium trifluoromethanesulfonate, 1-butyl-3-methyl-imidazolium methyl carbonate, 1-decyl-3-methylimidazolium chloride, 1-decyl-3-methylimidazolium tetrafluoroborate, 1-dodecyl-3-methylimidazolium iodide, 1-ethyl-2,3-dimethylimidazolium chloride, 1-ethyl-2,3-dimethylimidazolium ethyl sulfate, 1-ethyl-2,3-dimethylimidazolium hexafluorophosphate, 1-ethyl-2,3-dimethylimidazolium methyl carbonate, 1-ethyl-2,3-dimethylimidazolium tetrafluoroborate, 1-ethyl-2,3-dimethylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methylimidazolium 1,1 ,2,2-tetrafluoro ethanesulfonate, 1-ethyl-3-methylimidazolium L-(+)-lactate, 1-ethyl-3-methylimidazolium acetate, 1-ethyl-3-methylimidazolium acetate, 1-ethyl-3-methylimidazolium bis(pentafluoroethylsulfonyl)imide, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-ethyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 1-ethyl-3-methylimidazolium bromide,., 1-ethyl-3-methylimidazolium bromide, 1-ethyl-3-methylimidazolium chloride, 1-ethyl-3-methylimidazolium chloride, 1-ethyl-3-methylimidazolium chloride, 1-ethyl-3-methylimidazolium dibutyl phosphate, 1-ethyl-3-methylimidazolium dicyanamide, 1-ethyl-3-methylimidazolium dicyanamide, 1-ethyl-3-methylimidazolium diethyl

phosphate, 1-ethyl-3-methylimidazolium diethyl phosphate, 1-ethyl-3-methylimidazolium dimethyl phosphate, 1-ethyl-3-methylimidazolium ethyl sulfate, 1-ethyl-3-methylimidazolium ethyl sulfate, 1-ethyl-3-methylimidazolium hexafluorophosphate, 1-ethyl-3-methylimidazolium hydrogen sulfate, 1-ethyl-3-methylimidazolium hydrogen carbonate, 1-ethyl-3-methylimidazolium iodide, 1-ethyl-3-methylimidazolium methanesulfonate, 1-ethyl-3-methylimidazolium methanesulfonate, 1-ethyl-3-methylimidazolium methyl sulfate, 1-ethyl-3-methylimidazolium nitrate, 1-ethyl-3-methylimidazolium tetrachloroaluminate, 1-ethyl-3-methylimidazolium tetrachloroaluminate, 1-ethyl-3-methylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium tetrafluoroborate, 1-ethyl-3-methylimidazolium thiocyanate, 1-ethyl-3-methylimidazolium thiocyanate, 1-ethyl-3-methylimidazolium tosylate, 1-ethyl-3-methylimidazolium trifluoromethane sulfonate, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methylimidazolium trifluoromethanesulfonate, 1-ethyl-3-methyl-imidazolium methyl carbonate, 1-hexyl-3-methylimidazolium bis(trifluormethylsulfonyl)imide, 1-hexyl-3-methylimidazolium chloride, 1-hexyl-S-methylimidazolium chloride, 1-hexyl-3-methylimidazolium hexafluorophosphate, 1-hexyl-3-methylimidazolium iodide, 1-hexyl-3-methylimidazolium tetrafluoroborate, 1-hexyl-3-methylimidazolium trifluoromethansulfonate, 1-methyl-3-(3,3,4,4,5,5,6,6,7,7,8,8,8-tridecafluorooctyl)imidazolium hexafluorophosphate, 1-methyl-3-octylimidazolium chloride, 1-methyl-3-octylimidazolium hexafluorophosphate, 1-methyl-3-octylimidazolium tetrafluoroborate, 1-methyl-3-octylimidazolium trifluoromethanesulfonate, 1-methyl-3-octylimidazolium trifluoromethanesulfonate, 1-methyl-3-propylimidazolium iodide, 1-methyl-3-propylimidazolium methyl carbonate, 1-methyl-3-vinylimidazolium methyl carbonate, 1-methylimidazolium chloride, 1-methylimidazolium hydrogen sulfate, 1-propyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide, 4-(3-butyl-1-imidazolio)-1-butanesulfonate, 4-(3-butyl-1-imidazolio)-1-butanesulfonic acid triflate, or the like.

A "ketone solvent" is an organic solvent containing a carbonyl group -(C=0)- bonded to two other carbon atoms. "Ketone solvents" include, but are not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, C_{3-6}ketones, and the like.

An "organic base" is an organic compound, which acts as a base. Examples of such bases include, but are not limited to, triethylamine, diisopropylamine, Hunig's base, DABCO, triethanolamine, tributylamine, pyridine, lutidine, 4-dimethylaminopyridine (DMAP), N-methylpyrrolidine, diethanolamine, 4-methylmorpholine, dimethylethanolamine, tetramethylguanidine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, tetramethylammonium hydroxide, tetraethylammonium hydroxide, N-methyl-1,5,9-triazabicyclo[4.4.0] decene, 1,8-diazabicyclo[5.4.0]undec-7-ene, dicyclohexylamine, and picoline.

A "nitrile solvent" is an organic solvent containing a cyano -(C≡N) bonded to another carbon atom. "Nitrile solvents" include, but are not limited to, acetonitrile, propionitrile, **C_{2-6}nitriles,** or the like.

A "phase transfer catalyst" is a compound, which will enhance the rate of a reaction between chemical species located in different phases such as immiscible liquids, liquid/solid, or liquid/gas reactions. The phase transfer catalyst extracts one of the reactants, most commonly an anion, across the interface into the other phase so that reaction can proceed. These catalysts are salts of onium ions (e.g. tetraalkyl ammonium salts) or agents that complex inorganic cations *(e.g.* crown ethers). The catalyst cation is not consumed in the reaction although an anion exchange does occur. Such catalysts can be utilized in either stoichiometric or catalytic, *e.g.* less than stoichiometric quantities. Examples of such catalysts include, but are not limited to, benzyltrimethylammonium chloride, benzyltributyl ammonium bromide, benzyltrioctyl ammonium bromide, benzyltriphenyl phosphonium bromide, benzyltriethylammonium chloride, benzyltriethylammonium bromide, hexadecyltributylphosphonium bromide, hexadecyltrimethylammonium bromide, methyltrioctylammonium chloride, methyltrioctyl ammonium bromide, tetrabutyl ammonium bromide, tetrabutylammonium chloride, tetrabutylammonium iodide, tetrabutylammonium hydrogen sulfate, tetramethyl ammonium hydrogen sulfate, tetramethylammonium bromide, tetramethylammonium chloride, tetramethyl ammonium iodide, tetraethylammonium bromide, tetraethyl

ammonium chloride, tetraethylammonium iodide, tetraethylammonium hydrogen sulfate, tetrapropyl ammonium bromide, tetrapropylammonium chloride, tetrapropylammonium iodide, tetrapropylammonium hydrogen sulfate, triethylbutylammonium bromide, trimethylbenzylammonium bromide, triethylbenzyl ammonium chloride, tripropylbenzyl ammonium chloride, dodecyltrimethyl ammonium bromide, tricetylmethyl ammonium chloride, crown ethers such as 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane), and polyethylene glycols.

A "polar aprotic solvent" has a dielectric constant greater than 15 and is at least one selected from the group consisting of amide-based organic solvents, such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP), formamide, acetamide, propanamide, hexamethyl phosphoramide (HMPA), and hexamethyl phosphorus triamide (HMPT); nitro-based organic solvents, such as nitromethane, nitroethane, nitropropane, and nitrobenzene; pyridine-based organic solvents, such as pyridine and picoline; sulfone-based solvents, such as dimethylsulfone, diethylsulfone, diisopropylsulfone, 2-methylsulfolane, 3-methylsulfolane, 2,4-dimethylsulfolane, 3,4-dimethy sulfolane, 3-sulfolene, and sulfolane; and sulfoxide-based solvents such as dimethylsulfoxide (DMSO).

"Suitable coupling agent" refers to a compound, molecule, or substance, capable of activating carboxylic acids with respect to nucleophilic attack. In some embodiments, the suitable coupling agents are capable of activating carboxylic acids where the attacking nucleophile is an alcohol, resulting in ester formation. Non-limiting examples of such suitable coupling agents include carbodiimide compounds *(e.g.* N,N'-dicyclohexylcarbodiimide (DCC), N,N'-diisopropylcarbodiimide (DIC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl), or the like). Carbodiimide compounds may be either used alone or in combination with HOAt, HOBt, or HODhbt. Further examples of suitable coupling agents include alkyl chloroformate compounds *(e.g.* ethyl chloroformate, isobutyl chloroformate, or the like) that are generally used with a tertiary amine like triethyl amine, diethyl azodicarboxylate (DEAD) with triphenyiphosphine (the Mitsunobu reaction), various chlorosilanes, chlorosulfonyl isocyanate, N,N'-carbonyldiimidazole (CDI), phosphonium reagents (e.g. BOP, AOP, PyBOP, PyAOP, BroP, PyBroP, CF_3-$N0_2$-PyBOP or the like), *in situ* acid

fluoride generators *(e.g.* TFFH, BTFFH, DAST, cyanuric fluoride, or the like), aminium reagents **(e.g.** HBTU, HATU, HBPyU, HAPyU, or the like) phosphinyls (**e.g.** DPPA, DEPC, or the like), pentafluorophenyl active ester generators **(e.g.** PfTU, PfPyU, FDPP, PFP-trifluoroacetate, FPFOH plus DCC, or the like), mixed carbon anhydrides **(e.g.** EEDQ, IIDQ, or the like), CIP, or BOP-Cl.

An "ether solvent" is an organic solvent containing an oxygen atom -O- bonded to two other carbon atoms. "Ether solvents" include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C_{2-6}ethers, or the like.

All percentages and ratios used herein are by weight of the total composition and all measurements made are at 25° C and normal pressure unless otherwise designated. All temperatures are in degrees Celsius unless specified otherwise. As used herein, "comprising" means the elements recited, or their equivalent in structure or function, plus any other element or elements that are not recited. The terms "having" and "including" are also to be construed as open ended unless the context suggests otherwise. As used herein, "consisting essentially of means that the invention may include ingredients in addition to those recited in the claim, but only if the additional ingredients do not materially alter the basic and novel characteristics of the claimed invention. All ranges recited herein include the endpoints, including those that recite a range "between" two values. The terms "about," "generally," "substantially,", and the like are to be construed as modifying a term or value such that it is not an absolute, but does not read on the prior art. Such terms will be defined by the circumstances and the terms that they modify as those terms are understood by those of skill in the art. This includes, at very least, the degree of expected experimental error, technique error and instrument error for a given technique used to measure a value.

Where this document refers to a material, such as, for example, in this instance, eslicarbazepine acetate, and the unique solid and/or crystalline forms, salts, solvates, and/or optical isomers thereof by reference to patterns, spectra, or other graphical data, it may do so by qualifying that they are "substantially" shown or depicted in a figure, or by one or more data points. It will be appreciated that patterns, spectra, and other graphical data may be shifted in their positions,

relative intensities, or other values due to a number of factors known to those of skill in the art. For example, in the crystallographic and powder X ray diffraction arts, shifts in peak positions, or the relative intensities of one or more peaks of a pattern can occur because of, without limitation: the equipment used, the sample preparation protocol, preferred packing and orientations, the radiation source, operator error, method and length of data collection, and the like. However, those of ordinary skill in the art will be able to compare the figures herein with a pattern generated of an unknown form of, in this case, eslicarbazepine acetate, and confirm its identity as one of the forms disclosed and claimed herein. The same holds true for other techniques which may be reported herein, as well as for distinguishing between amorphous forms.

In addition, where a reference is made to a figure, it is permissible to select any number of data points illustrated in the figure that uniquely define that crystalline form, salt, solvate, and/or optical isomer, within any associated and recited margin of error, for purposes of identification. Again, by way of example, it is permissible to select any number of PXRD peaks represented in Figure 1 to uniquely identify a crystalline form of eslicarbazepine acetate.

Unless specified otherwise, the word "pure" as used herein means that the material is at least about 99% pure. In general, this refers to purity with regard to unwanted residual solvents, reaction by-products, impurities, and unreacted starting materials. In the case of stereoisomers, "pure" as used herein also means 99% of one enantiomer or diastereomer, as appropriate. "Substantially pure" as used herein means at least about 98% pure and, likewise, "essentially pure" as used herein means at least about 95% pure.

The phrase "substantially free of one or more of its corresponding impurities" as used herein, unless otherwise defined, means comprising less than about 7%, less than about 5%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, less than about 0.3%, less than about 0.1%, or less than about 0.05% by weight, of one or more of the corresponding impurities as measured by HPLC.

Certain specific aspects and embodiments of the present application will be explained in more detail with reference to the following examples, which are

provided for purposes of illustration only and should not be construed as limiting the scope of the present application in any manner.

EXAMPLES

Example 1: Preparation of racemic (+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Oxcarbazepine (200 g), ethanol (800 mL) and water (200 mL) are charged into a round-bottom flask and stirred for 5 minutes. Sodium borohydride (24.1 g) is charged slowly to the mixture at 25-35°C and stirred for 10 minutes. The mixture is heated to 40-45°C and maintained for 2-3 hours. The solvent from the reaction mixture is evaporated completely at 45-50°C. Water (2000 mL) is added to the mass and stirred at 30°C for 1-2 hours. The obtained solid is collected by filtration, washed with water (200 mL), and dried at 70°C, to afford 190.0 g of the title compound. Purity by HPLC: 99.1%

Example 2: Preparation of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Dichloromethane (200 mL) and borane dimethyl sulfide complex (34.1 mL) are charged into a round-bottom flask and stirred for 10 minutes. The mixture is cooled to -10°C to 0°C. R-MeCBS (methyl oxazaborolidine) (47.0 mL) is added to the mixture at -9°C to -8°C and stirred for 5 minutes. A solution of oxcarbazepine (20 g) in dichloromethane (100 mL) is added to the mixture. The reaction mixture is heated to 0-10°C and maintained for 3-4 hours. Methanol (40 mL) is added to the reaction mixture, followed by 5% H_2O_2 (100 mL) solution and 10% HCl solution (100 mL). The mixture is stirred for 15-20 minutes. Both layers are separated and the organic layer is washed with 10% $NaHCO_3$ solution (100 mL), followed by 10% NaCl solution (100 mL). The solvent from the organic layer is evaporated completely at 60°C. Water (40 mL) is added to the mass at 30°C and stirred for 1 hour. Dichloromethane (100 mL) is added to the mixture and stirred for 45 minutes. The obtained solid is collected by filtration, washed with water (10 mL), and dried at 60-68°C, to afford 11.2 g of the title compound. Purity by HPLC: 96.6%; chiral purity by HPLC: 93.6% water content by KF method: 0.29% (w/w).

Example 3: Preparation of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Racemic (±)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (100 g), dichloromethane (500 mL) and naproxen (108.69 g) are charged into a round-bottom flask and stirred for 5

minutes. Dicyclohexylcarbodiimide ("DCC", 105.7 g) and 1-hydroxybenzotriazole ("HOBT, 5.5 g) are added to the mixture. The reaction mixture is maintained at 30°C for 7-8 hours, then filtered and the solid washed with dichloromethane (300 mL). The filtrate is evaporated completely under reduced pressure. Ethyl acetate (1800 mL) is added to the mass and stirred at 29°C for 15-20 minutes. The mixture is heated to reflux temperature and maintained for 50-60 minutes. The solid obtained is collected by filtration, washed with ethyl acetate (360 mL) and dried at 70°C to afford 24.9 g of naproxen ester of (S)-(+)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Purity by HPLC: 91.8%; choral purity by HPLC: 93.9%.

The naproxen ester of (S)-(+)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (15 g) and methanol (150 mL) are charged into a round-bottom flask and stirred for 5 minutes. A 10% solution of sodium hydroxide (150 mL), followed by dichloromethane (200 mL) are added to the mixture. The mixture is heated to reflux temperature and maintained for 1-2 hours. The solvent from the reaction mixture is evaporated at 40-41 °C. Dichloromethane (75 mL) and water (75 mL) are added to the mass and stirred for 5-10 minutes. Both layers are separated and the aqueous layer is extracted with dichloromethane (75 mL). The organic layer is washed with water (75 mL) and the solvent from the organic layer is evaporated completely at 40-41 °C under reduced pressure to afford 7.3 g of the title compound. Purity by HPLC: 96.7%; chiral purity by HPLC: 92.3%; specific optical rotation=+1 13.3° (c=1 .1, pyridine).

Example 4: Preparation of (S)-(-)-10-acetoxy-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (Eslicarbazepine acetate).

(S)-(+)-1 0,11-Dihydro-1 0-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (7 g) and dichloromethane (70 mL) are charged into a round-bottom flask and stirred for 5 minutes. Triethylamine (7.6 mL) and acetic anhydride (4.0 mL) are added to the mixture. The reaction mixture is heated to reflux and maintained for 6-7 hours. Water (35 mL) is added to the reaction mixture and stirred for 10-20 minutes. Both layers are separated and the aqueous layer is extracted with dichloromethane (35 mL). The organic layer is washed with water (35 mL) and the solvent from the organic layer is evaporated completely at 38-41 °C. Ethyl acetate (25 mL) is added to the reaction mass and stirred at 29°C for 15 minutes. The reaction mass is

cooled to 10-15°C and stirred for 45-60 minutes. The solid is collected by filtration, washed with ethyl acetate (8 ml_), and dried at 70-72°C, to afford 4.5 g of the title compound. Purity by HPLC: 98.8%; chiral purity by HPLC: 95.0%; specific optical rotation = -18.78° (c=1 , pyridine); water content by KF method: 0.24% (w/w). Particle size distribution: D_{10}: 2.541 μm; D_{50}: 16.192 μηη; D_{90}: 107.933 pm.

Example 5: Preparation of (S)-(-)-10-acetoxy-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (Eslicarbazepine acetate).

Dichloromethane (30 ml_), potassium acetate (3 g) and tetrabutylammonium bromide (0.8 g) are charged in to a round-bottom flask and stirred for 5 minutes. The mixture is cooled to -5°C under nitrogen atmosphere and a solution of 4-nitrophenyl chloroformate (3.1 g) in dichloromethane (30 ml.) is added to the mixture under nitrogen atmosphere at -5 to 0°C. The reaction mixture temperature is raised to 25°C and stirred for 50-60 minutes. The reaction mixture temperature is heated to reflux temperature and stirred for 20-30 minutes. The mixture is cooled to 25-35°C, filtered to remove unwanted solids from the mixture, and washed with dichloromethane (5 mL) under nitrogen atmosphere to obtain a filtrate. Eslicarbazepine (3 g), dichloromethane (30 mL), pyridine (1 g) and dimethylaminopyridine (3 g) are stirred for 10-15 minutes in another round-bottom flask at 28°C under nitrogen atmosphere. The above-obtained filtrate is slowly added to the mixture at 28°C and stirred for 40 minutes. The reaction mixture is heated to reflux temperature and maintained for 14-16 hours. The reaction mixture is cooled to 25-35°C, water (150 mL) is added, and both layers are separated. The organic layer is washed with water (150 mL) and the solvent from the organic layer is evaporated completely at 40°C. Ethyl acetate (15 mL) is added to the mass and stirred for 5 minutes. The mixture is cooled to 10-15°C and stirred for 45 minutes. The obtained solid is collected by filtration, washed with ethyl acetate (10 mL), and dried at 65-70°C to afford 1.6 g of the title compound. Purity by HPLC: 98.7%; chiral purity by HPLC: 99%.

Example 6: Preparation of (S)-(-)-10-acetoxy-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (Eslicarbazepine acetate).

Eslicarbazepine (3.0 g), isopropenyl acetate (8.3 g), tetrabutylammonium bromide (0.3 g), and para-toluenesulfonic acid (0.2 g) are charged into round bottom flask and stirred. The mixture is heated to 60°C and the reaction is maintained at 60-

65°C for 3 hours. The mixture is cooled to 28°C and charged with dichloro methane (30 mL) and washed with water. The dichloromethane is evaporated completely from the organic layer. Ethyl acetate (15 mL) is added and stirred to dissolve. The solution is cooled to 15° C and stirred. The separated solid is collected by filtration and washed with ethyl acetate to obtain a wet solid, which is then dried at 70°C under reduced pressure to obtain 2.0 g of eslicarbazepine acetate. Purity by HPLC: 95.5%; chiral purity by HPLC: 99%.

Example 7: Preparation of (S)-(-)-10-acetoxy-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (Eslicarbazepine acetate). Potassium acetate (3.0 g) and dichloromethane (30.0 mL) are charged in to a round bottom flask at 25-35°C and stirred for 5 minutes. Methanesulfonyl chloride (2.0 g) is added to the mixture at 25-35°. The reaction mixture is heated to reflux temperature and maintained at reflux for 1-2 hours. The mixture is cooled to 25-35°C, filtered, and the solid washed with dichloromethane (9.0 mL) under nitrogen atmosphere to provide a filtrate.

Eslicarbazepine (3.0 g) and dichloromethane (30.0 mL) are charged in to another round bottom flask at room temperature and stirred for 5 minutes. Dimethylaminopyridine (2.8 g) is added to the mixture at 29°C and stirred for 5-10 minutes. The above obtained filtrate is added to the reaction mixture at 29°C. The reaction mixture is stirred at 25-35°C for 2-3 hours. Water (15.0 mL) is added to the mixture and stirred the mixture at 28°C for 10-15 minutes. Both layers are separated and the organic layer is washed with water (15.0 mL). The solvent from the organic layer is evaporated completely at 40°C. Ethyl acetate (18.0 mL) is added to the obtained mass and stirred at 29°C for 30-45 minutes. The obtained solid is collected by filtration, washed with ethyl acetate (6.0 mL), and dried at 65-70°C to afford 2.0 g of the title compound. Purity by HPLC: 97.7%.

Example 8: Preparation of amorphous form of Eslicarbazepine acetate. Eslicarbazepine acetate (2 g) and methanol (20 mL) are charged into a round-bottom flask and stirred at 29°C for 5 minutes. The mixture is heated to 60-65°C and maintained for 1 hour. Carbon (0.2 g) is added to the reaction solution and stirred at 64°C for 5-10 minutes. The solution is filtered, washed with methanol (4 mL) and the filtrate evaporated completely under reduced pressure at 65°C to afford 1.9 g of the title compound. Purity by HPLC: 97.4%; choral purity

by HPLC: 97.3%; water content by KF method: 0.26% (w/w); particle size distribution: D_{10}: 12.807 μm; D_{50}: 83.402 μm; D_{90}: 256.628 μm.

Example 9: Preparation of amorphous form of Eslicarbazepine acetate. Eslicarbazepine acetate (2 g) and dichloromethane (80 mL) are charged into a round-bottom flask and stirred at 29°C for 5 minutes. The mixture is heated to reflux temperature and stirred for 10 minutes. Carbon (0.2 g) is added to the resultant solution and stirred for 10 minutes. The solution is filtered, washed with dichloromethane (6 mL), and the filtrate evaporated completely under reduced pressure at 40-41 °C to afford 1.9 g of the title compound. Purity by HPLC: 97.5%; chiral purity by HPLC: 97.2%; water content by KF method: 1.65% (w/w); particle size distribution: D_{10}: 3.949 μm; D_{50}: 38.172 μm; D_{90}: 139.341 μm.

Example 10: Preparation of racemic (+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Oxcarbazepine (29 Kg), methanol (87 L) and water (29 L) are charged into the reactor at 25-35°C and stirred for 10-20 minutes. Sodium borohydride (1.16 Kg) is added to the reaction mass at 25-35°C and maintained for 10-20 minutes. Again sodium borohydride (1.16 Kg) is added to the reaction mass at 25-35°C and maintained for 10-20 minutes. Again sodium borohydride (1.16 Kg) is added to the reaction mass at 25-35°C and maintained for 10-20 minutes. The reaction mixture is heated to 60-65°C and maintained for 1-2 hours. The reaction mixture is cooled to 25-35°C and rinsed the walls of the reactor with a mixture of methanol (7 L) and water (7 L). Sodium borohydride (1.74 Kg) is added to the reaction mass at 25-35°C and maintained for 10-20 minutes. The reaction mixture is heated to 60-65°C within one hour and maintained for 1-2 hours. The reaction mass is cooled to 25-35°C and water (174 L) is added to the reaction mass. Reaction mass is further cooled to 0-10°C and maintained for 30-60 minutes. The obtained solid is collected by filtration, washed with a mixture of methanol (9 L) and water (20 L), and dried at 65-70°C, to afford 24.4 Kg of the title compound. Purity by HPLC: 99.96%

Example 11: Preparation of [10(S)-5-carbamoyl-10,11-dihydro-5H-dibenz[b,f]azepin-10-yl]-2(S)-methyl-(6-methoxynaphthalen-2-yl)ethanoate. Dichloromethane (200 L) and S-(+)-naproxen (27.25 Kg) are charged in to the reactor at 25-30°C and stirred for 5-10 minutes under nitrogen atmosphere. The reaction mixture is cooled to 10-15°C. 4-Dimethylaminopyridine (1.25 Kg) and

N,N-diisopropylethylamine (19 Kg) are charged in to the reaction mixture at 10-15°C under nitrogen atmosphere and stirred for 5-10 minutes under the same conditions. (±)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (25 Kg) is charged to the reaction mass at 10-15°C under nitrogen atmosphere and stirred for 5-10 minutes under same conditions. Benzoyl chloride (16.5 Kg) is added to the reaction mass at 10-20°C in 30-60 minutes. The reaction mass is maintained at 25-30°C for 4 hours under nitrogen atmosphere. The reaction mass is cooled to 10-15°C and maintained for 20-30 minutes. The obtained solid is collected by filtration and washed with prechilled dichloromethane (at 10-15°C; 50 L). The obtained wet material (36.70 Kg) and dichloromethane (200 L) are charged in to the reactor at 25-30°C and maintained for 30-60 minutes. The reaction mass is cooled to 10-15°C and maintained for 20-30 minutes. The resultant solid is collected by filtration and washed with prechilled dichloromethane (at 10-15°C; 50 L). The obtained wet material (29.90 Kg), acetic acid (175 L) are charged in to the reactor at 25-35°C and maintained for 1-2 hours. The solid is collected by filtration and washed with acetic acid (50 L). The obtained wet material (23.20 Kg) and water (175 L) are charged in to the reactor 25-35°C and maintained for 30-60 minutes. The solid is collected by filtration, washed with water (50 L), and dried at 65-70°C, to afford 17.65 Kg of the title compound. Purity by HPLC: 99.0%

Example 12: Preparation of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide. Water (13 L) and sodium hydroxide (1.43 Kg) are charged in to the reactor at 25-35 °C and maintained for 20-30 minutes. Isopropyl alcohol (195 L) is charged to the reaction mixture at 25-35°C and maintained for 20-30 minutes. [10(S)-5-carbamoyl-10,11-dihydro-5H-dibenz[b,f]azepin-10-yl]-2(S)-methyl-(6-methoxynaphthalen-2-yl)ethanoate (13 Kg) is charged to the reaction mixture at 25-35°C and maintained for 20-30 minutes. The reaction mixture is heated to 65-70°C and maintained for 3 hours. The reaction mass is cooled to 25-35°C and maintained for 2 hours. The reaction mass is filtered and the solid washed with isopropyl alcohol (52 L). The solvent from the filtrate is evaporated completely under reduced pressure at below 45°C. Water (91 L) is charged to the reaction mass at below 45°C. Again the solvent from the resultant mass is evaporated at below 55°C under reduced pressure until

5 to 6 volumes of the reaction mass is retained. The reaction mass is cooled to 25-35°C and maintained for 15-30 minutes. The reaction mass is further cooled to 10-15°C and maintained for 2 hours. The obtained solid is collected by filtration, washed with water (13 L), and dried at 65-70°C, to afford 5.2 Kg of the title compound. Purity by HPLC: 99.5%

Example 13: Preparation of Eslicarbazepine acetate. Dichloromethane (24 L), isopropenyl acetate (2.59 Kg) are charged in to the reactor at 25-35°C and stirred for 10 minutes. The reaction mixture is cooled to 10-20°C, methane sulphonic acid (2.68 Kg) is charged to the reaction mixture and maintained for 10-20 minutes. The reaction mixture is cooled to 10-15°C, (S)-(+)-10,1 1-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (4.7 Kg) is charged to the reaction mixture and maintained for 4 hours. A solution of sodium bicarbonate (1.18 Kg) in water (24 L) is charged to the reaction mixture at 10-15°C. The reaction mixture temperature is raised to 25-35°C and maintained for 10-15 minutes. Both layers are separated and the organic layer is washed with water (2X14 L). The solvent from the organic layer is evaporated at below 43°C under reduced pressure until 2 volumes of reaction mass retained. Isopropyl alcohol (47 L) is charged to the reaction mass at below 43°C. Again the solvent from the reaction mass is evaporated under atmospheric pressure at below 75°C and maintained for 30 minutes. The reaction mass is cooled to 25-35°C. The reaction mass is further cooled to 10-15°C and maintained for 30-60 minutes. The obtained solid is collected by filtration, washed with isopropyl alcohol (5 L), and dried at 65-70°C for 6 hours, to afford 4.25 Kg of the title compound. Purity by HPLC: 99.96%

Example-14: Purification of Eslicarbazepine acetate. Methanol (32 L) and eslicarbazepine acetate (4 Kg) are charged in to the reactor at 25-35°C. Rinsed the walls of the reactor with methanol (8 L). The reaction mixture is heated to 50-55°C and maintained for 10-15 minutes. Activated carbon (0.4 Kg) is added to the reaction mixture at 50-55°C and maintained for 10-15 minutes. The reaction mixture is filtered through the candy and micro filters at 50-55°C and washed with methanol (8 L). The solvent from the filtrate is evaporated under reduced pressure at below 55°C. The reaction mass is cooled to below 45°C and isopropyl alcohol (16 L) is charged to the reaction mass. The reaction mass is heated to 50-55°C and maintained for 30-60 minutes. The reaction mass is cooled to 25-30°C. The

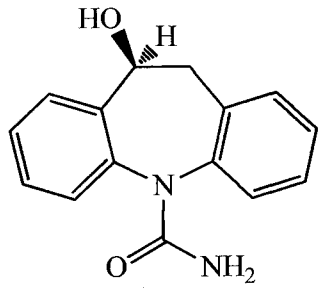
reaction mass is further cooled to 0-5°C and maintained for 30-60 minutes. The obtained solid is collected by filtration, washed with prechilled isopropyl alcohol (4 L), and dried at 25-30°C for 1 hour ± 15 minutes under reduced pressure. The material is dried again at 65-70°C for 10 hours, to afford 3.18 Kg of the title compound. Purity by HPLC: 99.99%; particle size distribution: D_{10}: 10.201 µm; D_{50}: 54.336 µm; D_{90}: 100.866 pm.

Throughout this application, various publications are referenced. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art as known to those skilled therein as of the date of the application described and claimed herein.

While particular embodiments of the present application have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the application. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

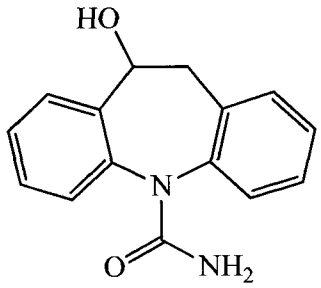
CLAIMS:

1. A process for the preparation of eslicarbazepine of Formula (III), comprising:



(III)

(a) reacting racemic 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (IV):



(IV)

with a reagent capable of forming an ester to provide mixture of diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide;

(b) separating the diastereomeric esters of 10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide into individual diastereomers;

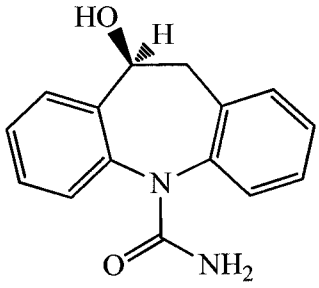
(c) isolating the diastereomeric ester of eslicarbazepine;

(d) hydrolyzing the diastereomeric ester of eslicarbazepine to provide optically pure (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide; and

(e) optionally recovering the diastereomeric ester of (R)-licarbazepine.

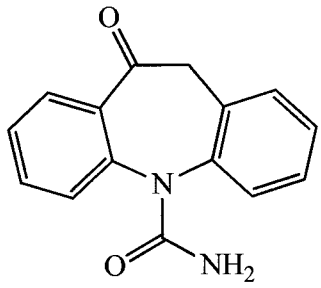
2. The process of claim 1, wherein the reagent comprises one or more of (+)-naproxen, (+)-mandelic acid, (-)-camphor sulphonic acid, lactic acid, and (+)-ibuprofen.

3. A process for the preparation of (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

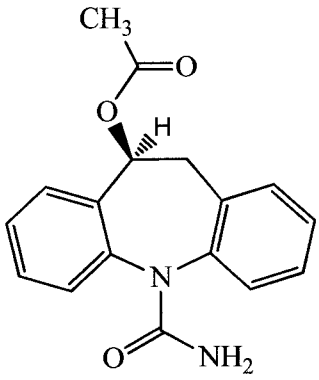
comprising asymmetrically reducing the compound of formula (V):



(V)

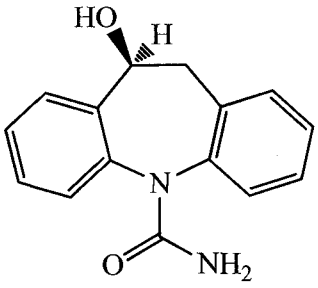
to form (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III).

4. A process for the preparation of eslicarbazepine acetate of Formula (I), comprising:



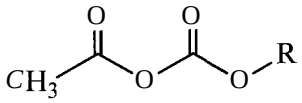
(I)

a) reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

with the compound of Formula (VI):

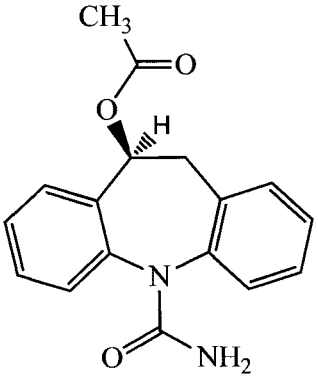


(VI)

wherein R is an optionally substituted C_6-C_{14}aryl group; and

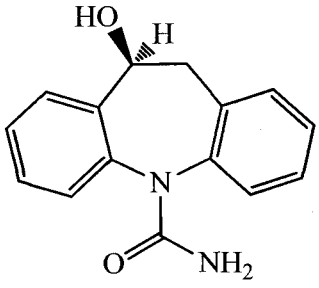
b) isolating eslicarbazepine acetate of Formula (I).

5. A process for the preparation of eslicarbazepine acetate of Formula (I), comprising:



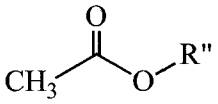
(I)

a) reacting (S)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide of Formula (III):



(III)

with the compound of Formula (IX):



(IX)

wherein R" is an optionally substituted C_1-C_6alkyl, C_2-C_6alkenyl, C_6-C_{14}aryl, C_7-C_{10}(ar)alkyl group, C_1-C_6alkyl-sulfonyl group, or C_6-C_{14}aryl-sulfonyl group; and

b) isolating eslicarbazepine acetate of formula (I).

6. An amorphous form of eslicarbazepine acetate.

7. The amorphous form of eslicarbazepine acetate of claim 6, characterized by a powder X-ray diffraction (PXRD) pattern, infrared absorption spectrum, and/or thermal gravimetric analysis (TGA) curve substantially as illustrated by Figs. 8, 9 and 10, respectively.

8. A process for preparing amorphous form of eslicarbazepine acetate of claim 6, comprising:

(a) providing a solution of eslicarbazepine acetate in a solvent or mixture of solvents; and

(b) isolating an amorphous form of eslicarbazepine acetate.

9. Eslicarbazepine acetate having maximum particle sizes less than about 300 pm.

10. Eslicarbazepine acetate having maximum particle sizes less than about 250 pm.

11. Eslicarbazepine acetate having maximum particle sizes less than about 200 pm.

12. Eslicarbazepine acetate having maximum particle sizes less than about 150 μm.

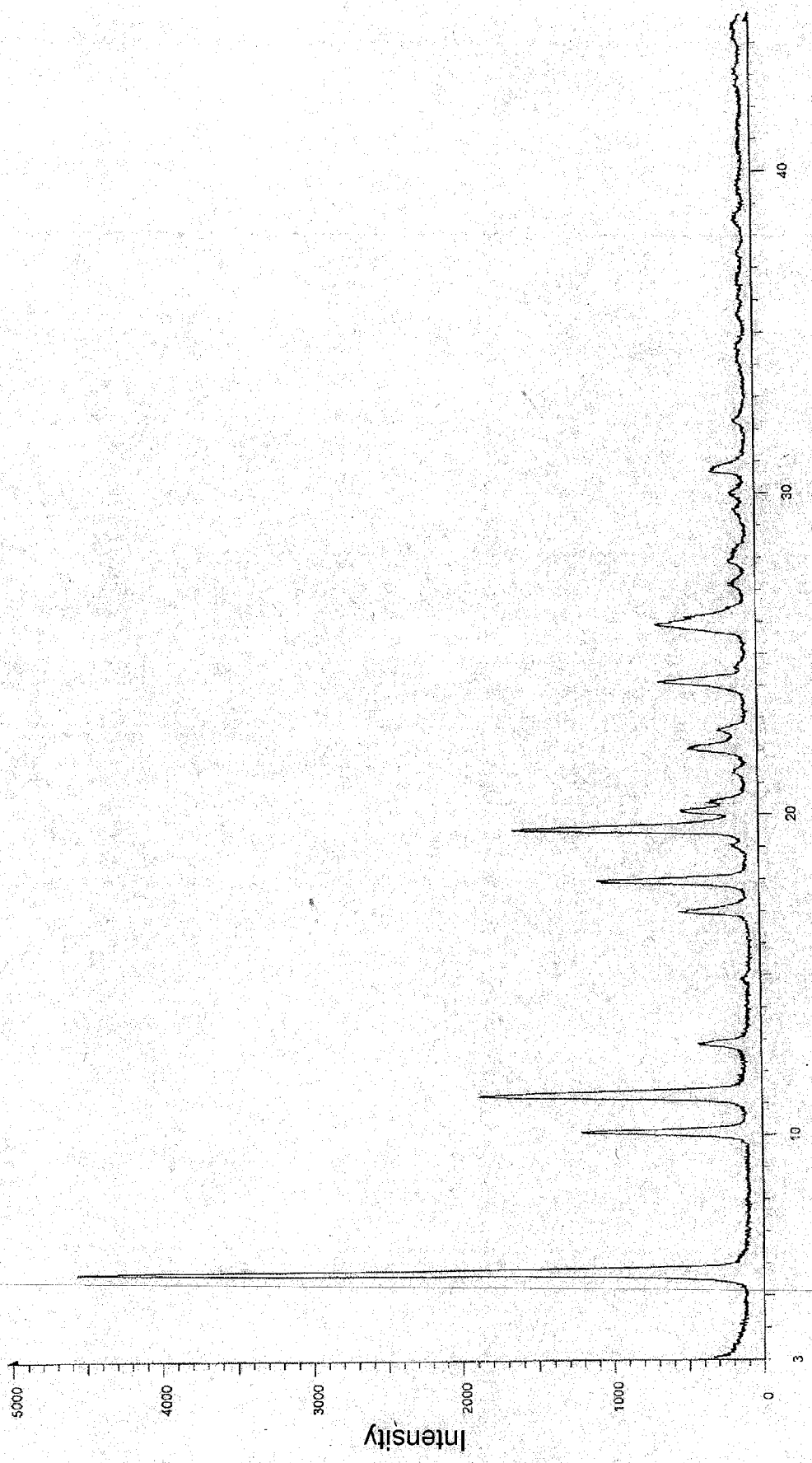
13. Eslicarbazepine acetate having maximum particle sizes less than about 100 pm.

14. Eslicarbazepine acetate having maximum particle sizes less than about 50 pm.

15. Eslicarbazepine acetate having maximum particle sizes less than about 20 μm.

16. Eslicarbazepine acetate having maximum particle sizes less than about 10 μm.

Fig 1


Intensity
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3000
2000
1000
0
3
10
20
30
40
2-theta (Degrees)

Fig 2

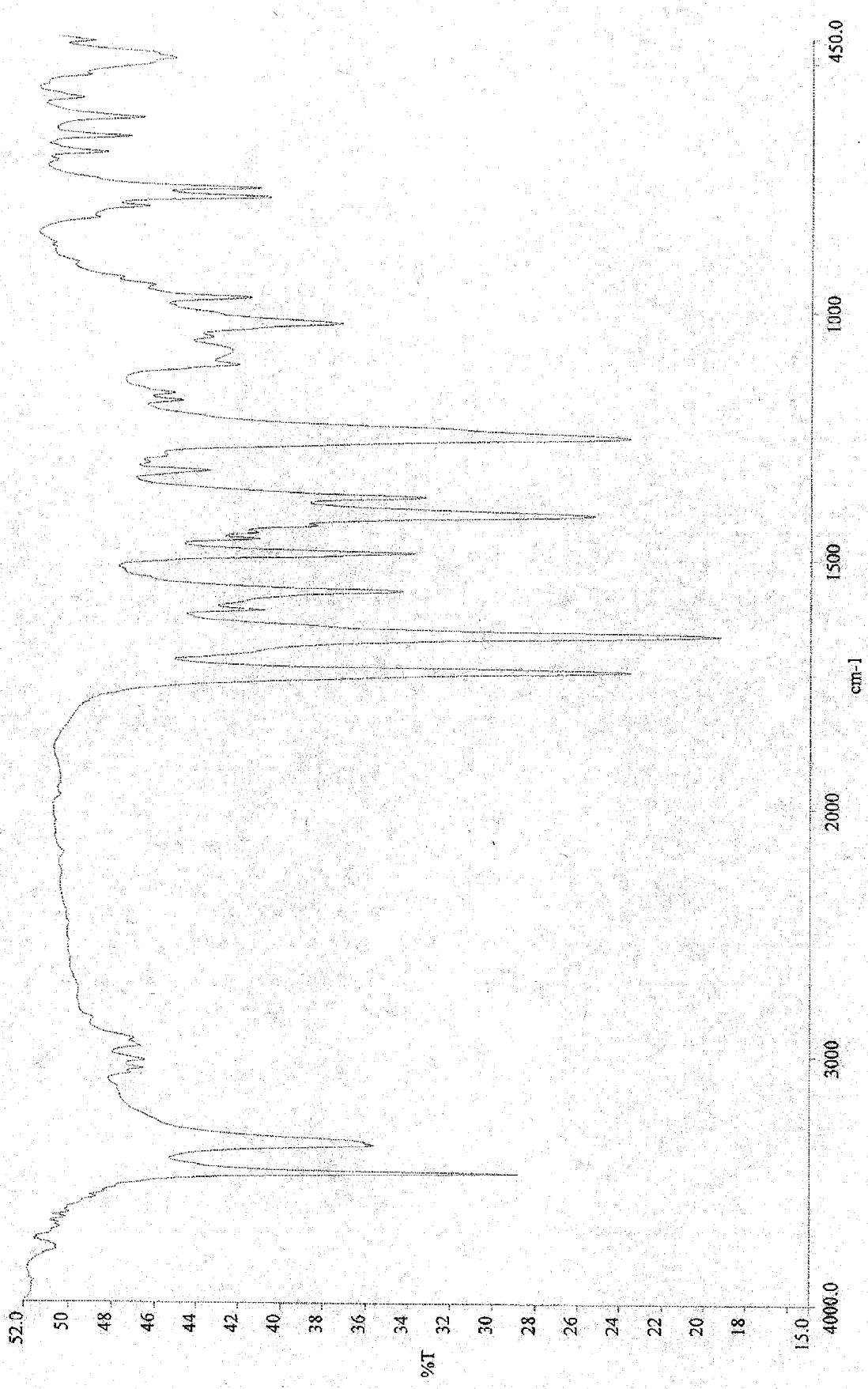
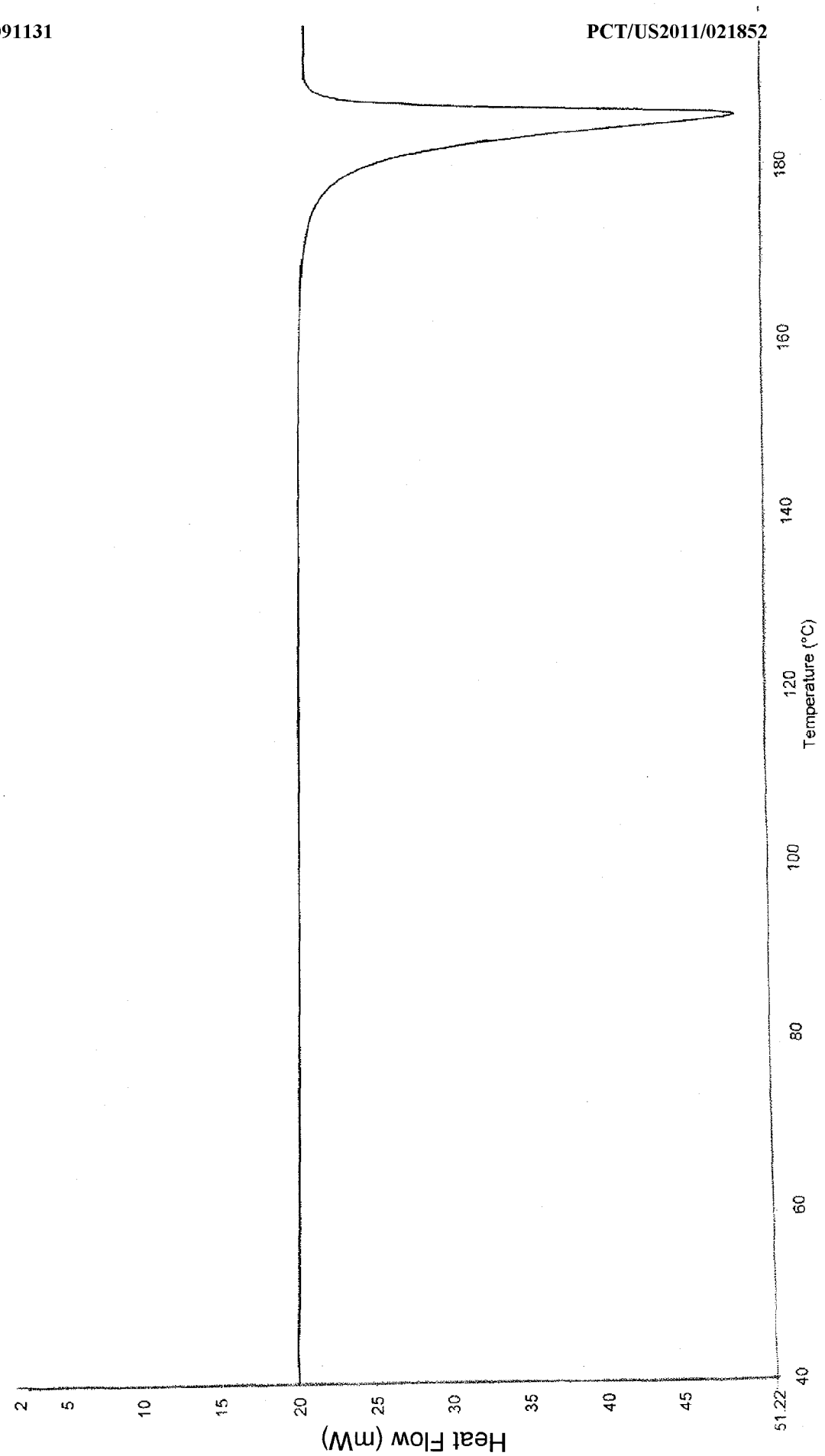

52.0
50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20
18
15.0
%T
4000.0
3000
2000
1500
1000
450.0
cm-1

Fig 3


Heat Flow (mW)
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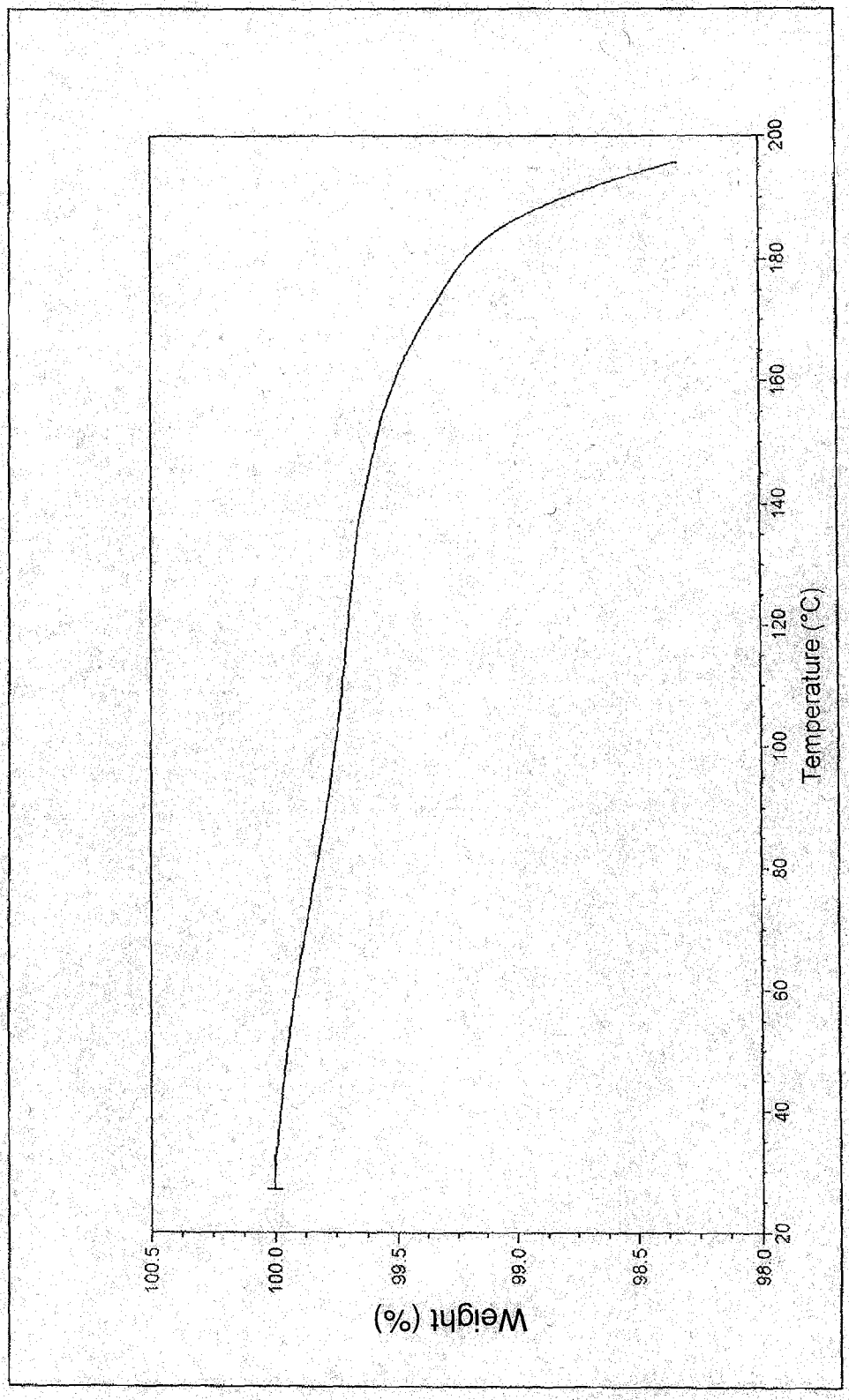
5
10
15
20
25
30
35
40
45
51.22
40
60
80
100
120
140
160
180
Temperature (°C)

Fig 4


Weight (%)
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100.0
99.5
99.0
98.5
98.0
Temperature (°C)
20
40
60
80
100
120
140
160
180
200

Fig 5

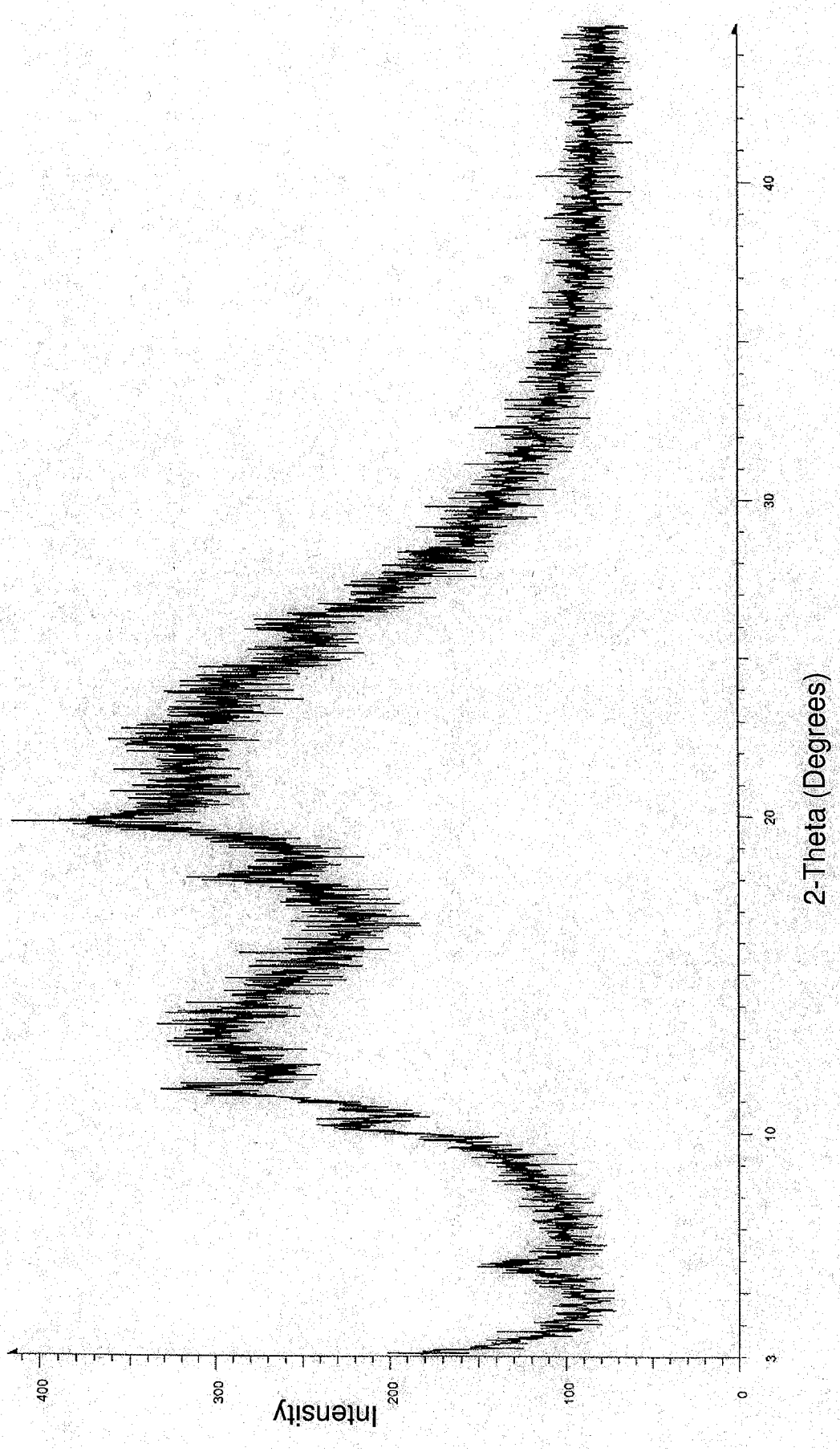


Fig 6

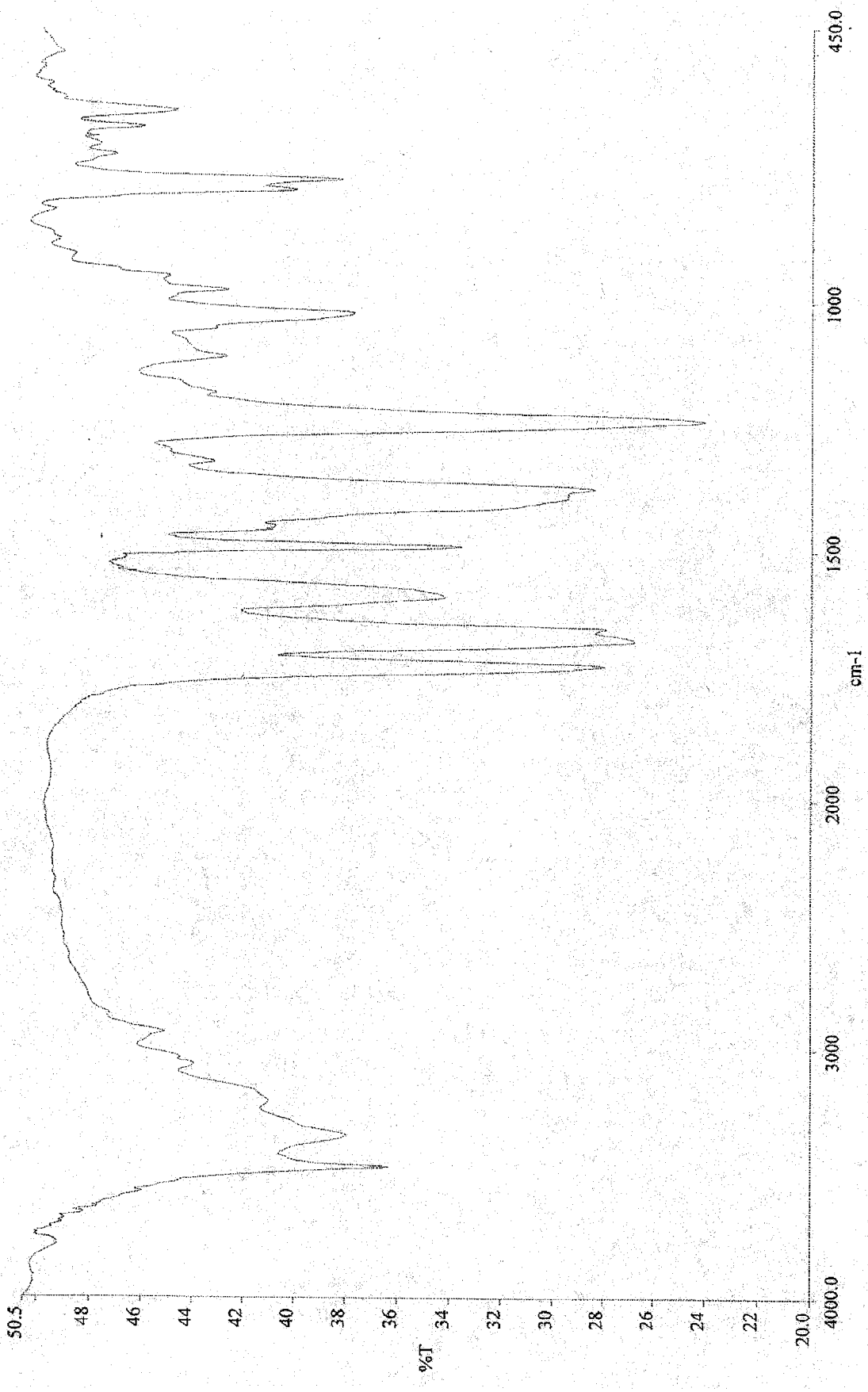
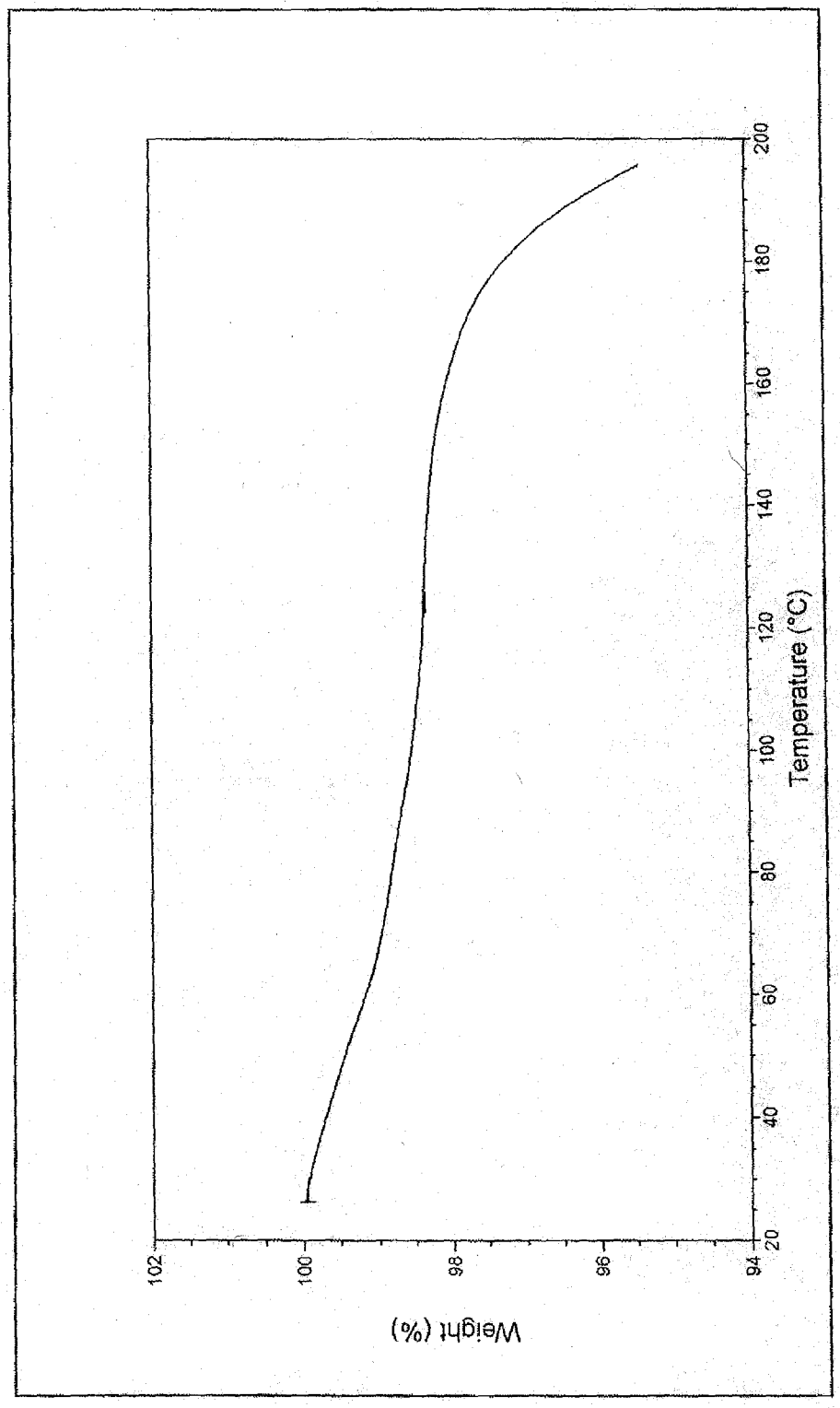

50.5
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20.0
%T
4000.0
3000
2000
1500
1000
450.0
cm-1

Fig 7


Weight (%)
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98
96
94
Temperature (°C)
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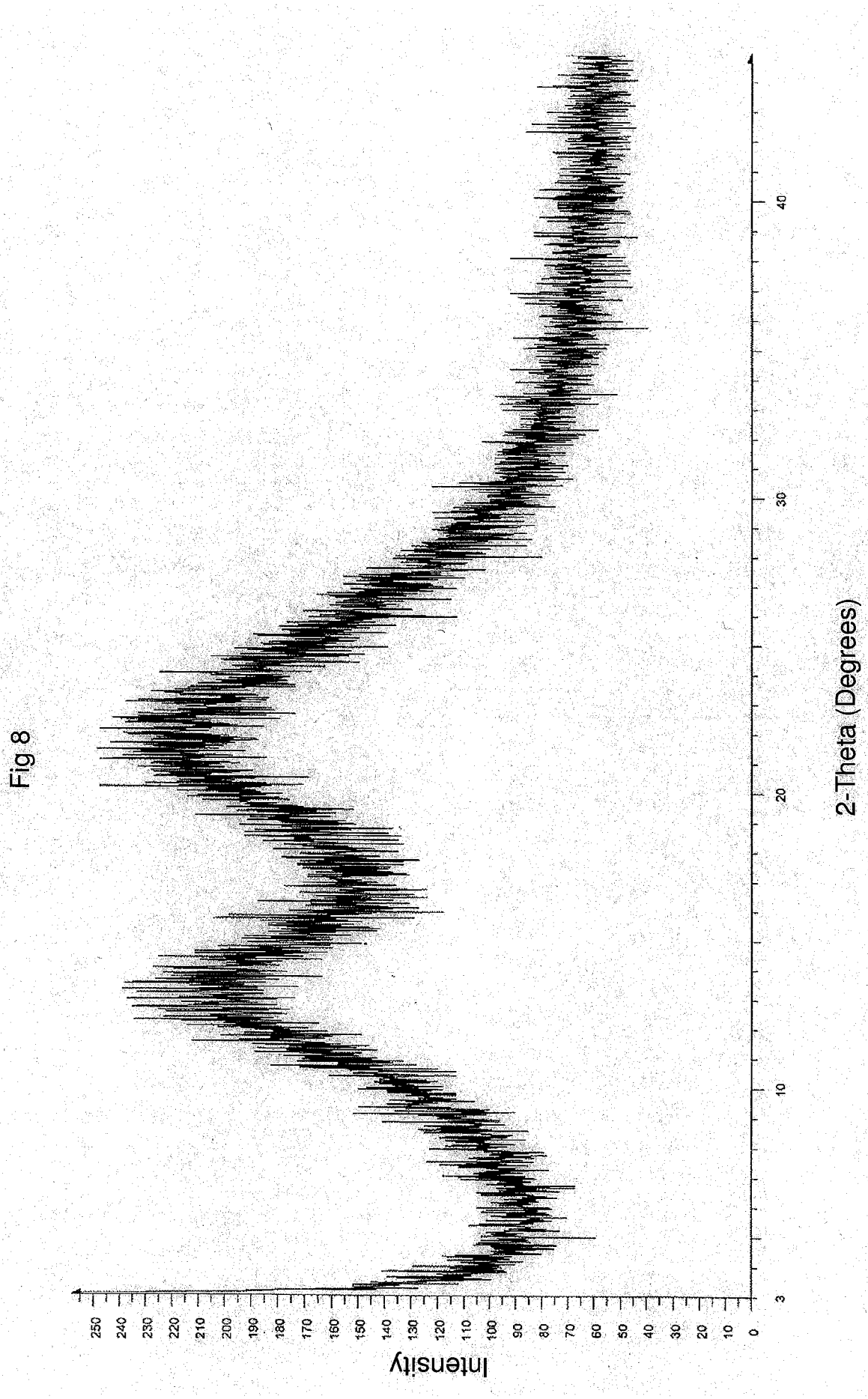
40
60
80
100
120
140
160
180
200


Intensity
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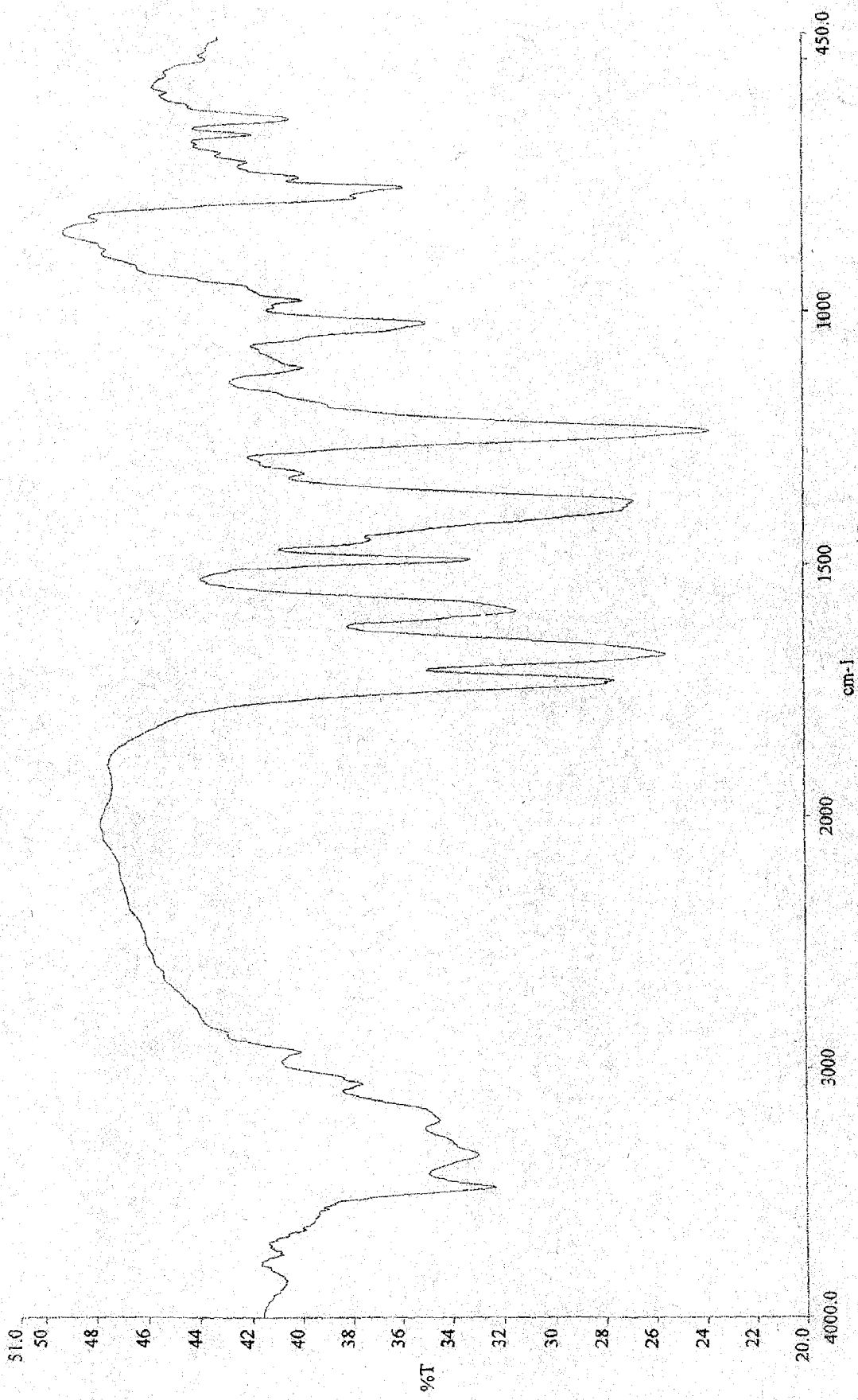
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
220
230
240
250
3
10
20
30
40
2-Theta (Degrees)

Fig 8

Fig 9


%T
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50
48
46
44
42
40
38
36
34
32
30
28
26
24
22
20.0
4000.0
3000
2000
1500
1000
450.0
cm-1

Fig 10

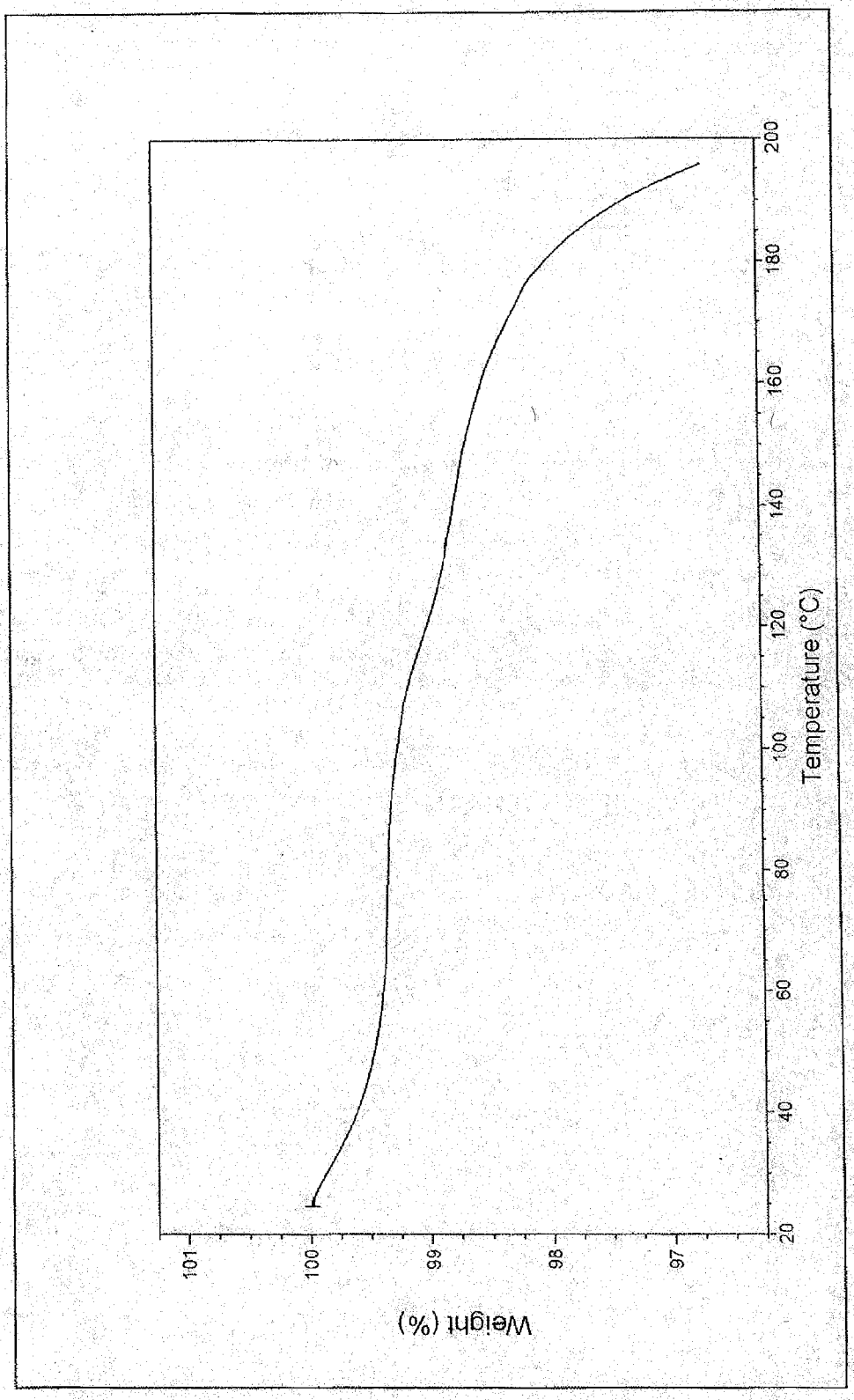
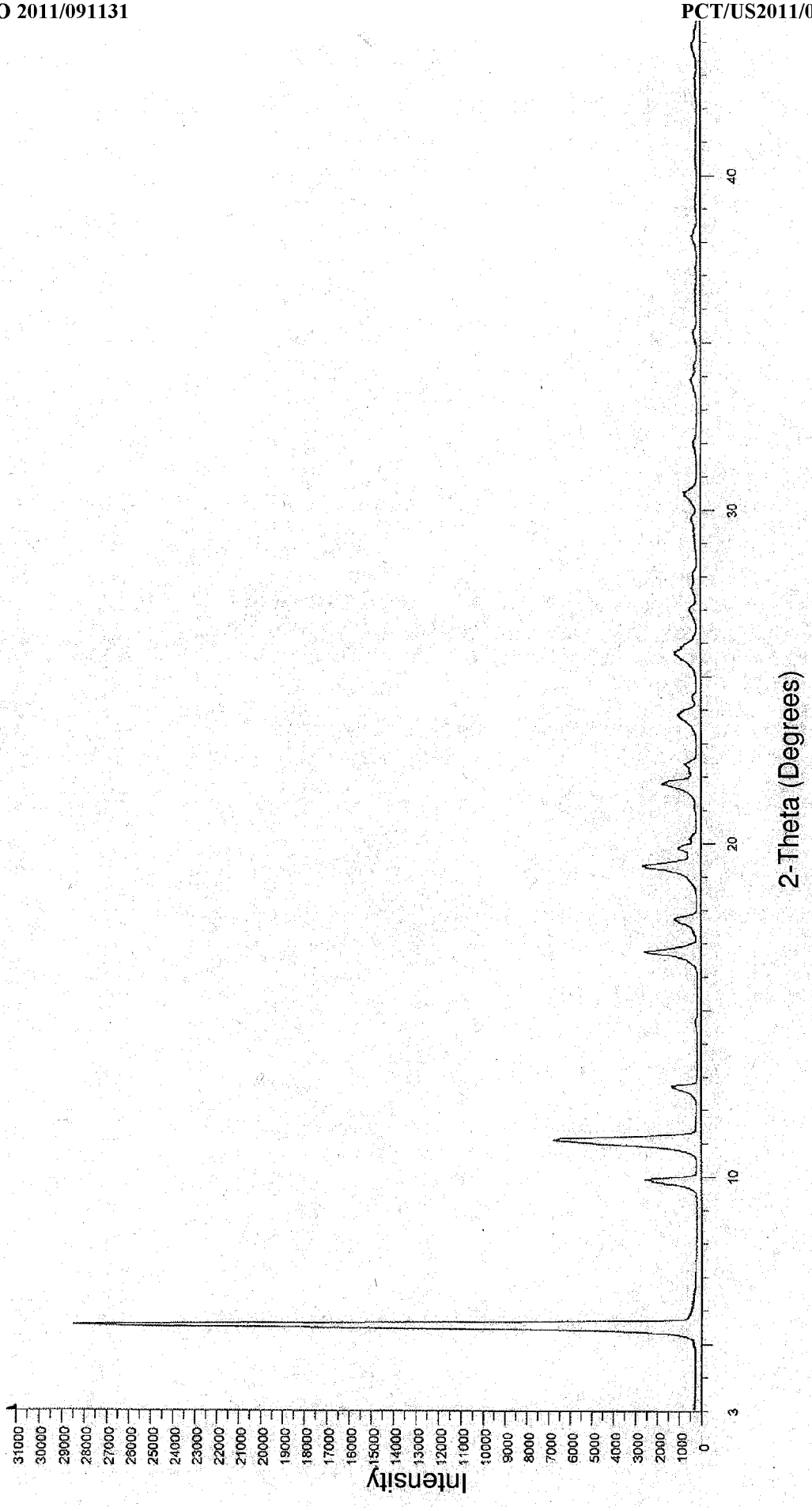

Weight (%)
101
100
99
98
97
Temperature (°C)
20
40
60
80
100
120
140
160
180
200

Fig 11


Intensity
2-Theta (Degrees)
0
1000
2000
3000
4000
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6000
7000
8000
9000
10000
11000
12000
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14000
15000
16000
17000
18000
19000
20000
21000
22000
23000
24000
25000
26000
27000
28000
29000
30000
31000
3
10
20
30
40