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(71) Applicant: **JOHNSON MATTHEY PUBLIC LIMITED COMPANY** [GB/GB]; 5th Floor, 25 Farringdon Street, London EC4A 4AB (GB).

(72) Inventors: **BUIST, Amanda**; c/o Johnson Matthey, Unit 250 Science Park, Milton Road, Cambridge CB4 0WE (GB). **EBERLIN, Alex**; c/o Nuformic plc, 153 Cambridge Science Park, Milton Road, Cambridge CB4 0GN (GB).

(74) Agent: **WHITCOMBE, Nicole**; c/o Johnson Matthey PLC, Group Intellectual Property Department, Gate 20, Orchard Road, Royston Hertfordshire SG8 5HE (GB).

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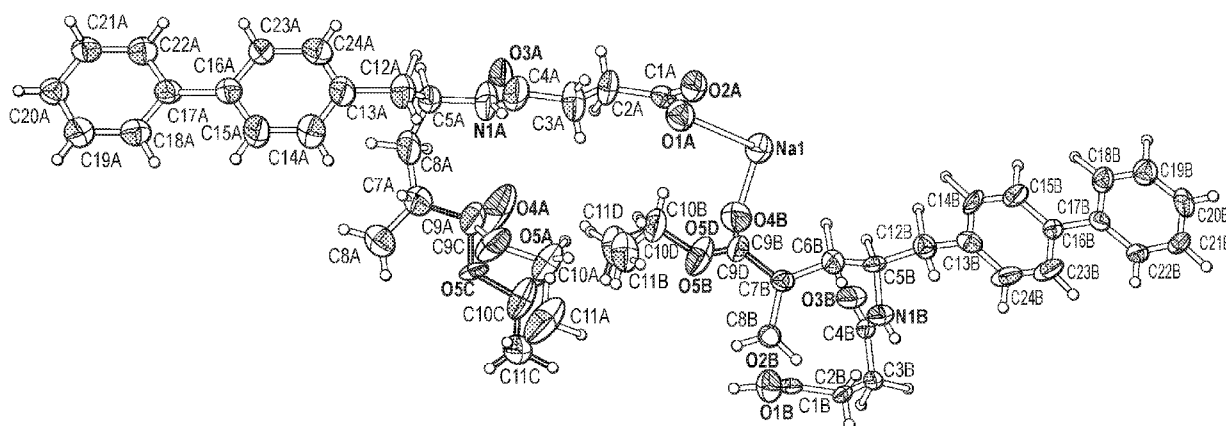


FIG. 7

(57) Abstract: The present disclosure relates to a hybrid salt/co-crystal of sacubitril. The present disclosure is also related to processes for the preparation of the hybrid salt/co-crystal of sacubitril. In addition, the present disclosure is related to the use of the hybrid salt/co-crystal of sacubitril for preparing a pharmaceutical composition.



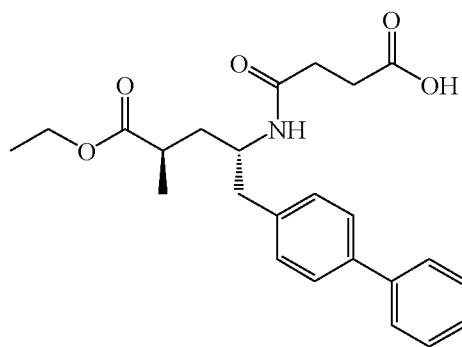
CRYSTALLINE FORM OF SACUBITRIL, ITS PREPARATION AND USE

FIELD OF THE DISCLOSURE

The present disclosure relates to a hybrid salt/co-crystal of sacubitril. The present disclosure is also related to processes for the preparation of the hybrid salt/co-crystal of sacubitril. In addition, the present disclosure is related to the use of the hybrid salt/co-crystal of sacubitril for preparing a pharmaceutical composition.

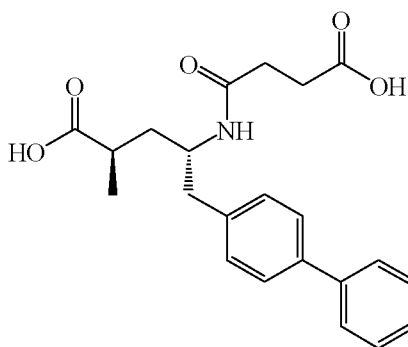
BACKGROUND OF THE DISCLOSURE

Sacubitril (SAC), having the chemical designation 4- {[(2S,4R)-1-(4-biphenyl)-



SAC

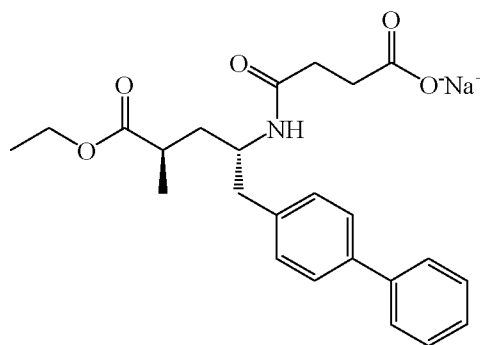
5-ethoxy-4-methyl-5-oxo-2-pentanyl]amino} -4-oxobutanoic acid, is an ethyl ester prodrug of sacubitrilat (SAT) that inhibits the enzyme neprilysin, which is responsible for



SAT

the degradation of atrial and brain natriuretic peptide, two blood pressure-lowering peptides that work mainly by reducing blood volume.

The sodium salt of SAC (Na SAC; sodium 4-{[(2S,4R)-1-(4-biphenyl)-5-



Na SAC

5 ethoxy-4-methyl-5-oxo-2-pentanyl]amino}-4-oxobutanoate) is combined with another drug, valsartan (VAL) as a disodium salt, to yield a Na₃SAC-VAL combined composition that is commercially marketed under the name Entresto[®] for the treatment of patients with heart failure. The Na₃SAC-VAL composition is present as a hemipentahydrate co-crystal of sodium salt of SAC and disodium salt of VAL that is described in U.S. Patent
 10 Nos. 9388134. However, there is no reference that describes an anhydrous hybrid salt/co-crystal of sacubitril (Na SAC-SAC) wherein one of the components, SAC, co-crystallizes with one other component, Na SAC.

15 SUMMARY OF THE DISCLOSURE

The present disclosure relates to Na SAC-SAC. The present disclosure is also related to processes for the preparation of Na SAC-SAC. In addition, the present disclosure is related to the use of Na SAC-SAC for preparing a composition containing amorphous Na SAC.

20

BRIEF DESCRIPTION OF THE DRAWINGS

Figure I is an XRPD pattern of Form I of *t*-butylamine (TBA) salt of SAC (TBA SAC).

Figure II is a ¹H NMR spectrum of Form I of TBA SAC.

25 Figure III is an XRPD pattern of Form I of Na SAC-SAC.

Figure IV is TGA plot of Form I of Na SAC-SAC.

Figure V is DSC plot of Form I of Na SAC-SAC.

Figure VI is a ^1H NMR spectrum of Form I of Na SAC-SAC.

Figure VII shows the asymmetric unit of Form I of Na SAC-SAC.

5 Figure VIII shows a view down the *b*-axis of the unit cell of Form I of Na SAC-SAC and perpendicular to the axis of propagation of the sodium oxygen channel hydrogen bonded chain.

Figure IX shows that the calculated XRPD pattern of Form I of Na SAC-SAC.

10

DETAILED DESCRIPTION OF THE DISCLOSURE

The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles described herein may be applied to other examples and applications without
15 departing from the spirit and scope of the various embodiments. Therefore, the various embodiments are not intended to be limited to the examples described herein and shown, but are to be accorded the scope consistent with the claims.

As used herein and unless otherwise specified, the terms “about” and
20 “approximately,” when used in connection with a numeric value or a range of values which is provided to characterize a particular solid form, e.g., a specific temperature or temperature range, such as, e.g., that describing a DSC or TGA thermal event, including, e.g., melting, dehydration, desolvation or glass transition events; a mass change, such as, e.g., a mass change as a function of temperature or humidity; a solvent or water content,
25 in terms of, e.g., mass or a percentage; or a peak position, such as, e.g., in analysis by IR or Raman spectroscopy or XRPD; indicate that the value or range of values may deviate to an extent deemed reasonable to one of ordinary skill in the art while still describing the particular solid form.

As used herein and unless otherwise specified, “co-crystal” refer to solid materials
30 composed of two or more different molecules and/or ionic compounds in a stoichiometric ratio which interact through non-covalent interactions.

As used herein and unless otherwise specified, the term “pharmaceutical composition” is intended to comprise a pharmaceutically effective amount of active pharmaceutical ingredients and a pharmaceutically acceptable excipient. As used herein, the term “pharmaceutical composition” includes a pharmaceutical composition such as a tablet, pill, powder, liquid, suspension, emulsion, granule, capsule, suppository, or injection preparation, preferably a tablet.

As used herein and unless otherwise specified, the term “crystalline” and related terms used herein, when used to describe a compound, substance, modification, material, component or product, unless otherwise specified, mean that the compound, substance, modification, material, component or product is substantially crystalline as determined by X-ray diffraction. See, e.g., Remington: The Science and Practice of Pharmacy, 21st edition, Lippincott, Williams and Wilkins, Baltimore, Md. (2005); The United States Pharmacopeia, 23rd ed., 1843-1844 (1995).

As used herein and unless otherwise specified, the term “excipient” refers to a pharmaceutically acceptable organic or inorganic carrier substance. Excipients may be natural or synthetic substances formulated alongside the active ingredient of a medication, included for bulking-up formulations that contain potent active ingredients (thus often referred to as "bulking agents," "fillers," or "diluent"), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption or solubility. Excipients can also be useful in the manufacturing process, to aid in the handling of the active substance, such as by facilitating powder flowability or non-stick properties, in addition to aiding in vitro stability such as prevention of denaturation over the expected shelf life.

As used herein and unless otherwise specified, the term “patient” refers to an animal, preferably a mammal, most preferably a human, who has been the object of treatment, observation or experiment. Preferably, the patient has experienced and/or exhibited at least one symptom of the disease or disorder to be treated and/or prevented. Further, a patient may not have exhibited any symptoms of the disorder, disease or condition to be treated and/prevented, but has been deemed by a physician, clinician or other medical professional to be at risk for developing said disorder, disease or condition.

As used herein and unless otherwise specified, the terms “polymorph,” “polymorphic form” or related term herein, refer to a crystal form of one or more molecules, or solvate or salt thereof that can exist in two or more forms, as a result of different arrangements or conformations of the molecule(s), or solvate molecule or salt ion thereof in the crystal lattice of the polymorph.

As used herein and unless otherwise specified, the terms “treat,” “treating” and “treatment” refer to the eradication or amelioration of a disease or disorder, or of one or more symptoms associated with the disease or disorder. In certain embodiments, the terms refer to minimizing the spread or worsening of the disease or disorder resulting from the administration of one or more therapeutic agents to a patient with such a disease or disorder. In some embodiments, the terms refer to the administration of a compound provided herein, with or without other additional active agents, after the onset of symptoms of a disease.

As used herein and unless otherwise specified, the term “room temperature” refers to the working laboratory temperature range, about 15 – 25 °C.

As used herein and unless otherwise specified, the term “overnight” refers to the period of time between the end of one working day to the subsequent working day in which a time frame of about 12 – 18 hours has elapsed between the end of one procedural step and the instigation of the following step in a procedure.

20

Embodiments

Compound and process, and composition

Na SAC-SAC (an anhydrous hybrid salt/co-crystal of sacubitril) according to the invention has an asymmetric unit formed by a sodium salt of sacubitril, Na SAC (single positively charged sodium ion and single negatively charged molecule of sacubitril due to the deprotonation of the carboxylic acid moiety thereof) and a molecule of neutral SAC, wherein the two charged constituents of the Na SAC form one of the components of the co-crystal, and the neutral molecule of sacubitril forms the other component of the co-crystal.

The present disclosure is also related to a number of processes for the preparation of Na SAC-SAC. The processes involve the preparation by a variety of reactants and conditions.

One embodiment for the preparation of Na SAC-SAC comprises

- 5 a) reacting *t*-butylamine (TBA) salt of SAC (TBA SAC) in ethyl acetate (EtOAc) with sodium 2-ethylhexanoate while stirring;
- b) removing solvent to yield oil; and
- c) suspending oil in *t*-butyl methyl ether (TBME) with stirring to yield Na SAC-SAC.

10 A particular embodiment of the instant preparation is wherein the ratio of TBA SAC:sodium 2-ethylhexanoate is about 1 mol eq:1 mol eq. Yet another embodiment of the preparation is wherein the ratio of TBA SAC_{mol}:EtOAc_{vol(L)} is about 1:50. Yet another embodiment of the preparation is wherein the stirring in step a) occurs at about room temperature (RT) for about 4 d. Still another embodiment of the preparation is wherein
 15 the solvent removal is undertaken at reduced pressure. Yet another embodiment of the preparation is wherein the ratio of TBA SAC_{mol}:TBME_{vol(L)} is about 1:100. Still another embodiment of the preparation is wherein the stirring in step c) occurs at RT overnight.

The process for preparing the TBA SAC used in the aforesaid process comprises

- a) reacting a calcium salt of SAC (CaSAC₂) in water with HCl to form SAC;
- 20 b) adding to the aqueous mixture with stirring dichloromethane (DCM) to extract SAC;
- c) separating the DCM from the water and isolating SAC from DCM by concentration at reduced pressure;
- d) adding the isolated SAC in EtOAc with stirring to form a biphasic mixture of
 25 the SAC and EtOAc;
- e) adding *t*-butylamine (TBA) with stirring to the biphasic mixture to form a solution;
- f) adding portions of acetone (ACE) with stirring until a suspension forms of TBA SAC;
- 30 g) isolating the TBA SAC.

The instant aforesaid preparation wherein the CaSAC_2 is Form I hemi calcium salt of SAC. The preparation wherein the ratio of $\text{CaSAC}_2:\text{HCl}$ is about 1 mol eq:2 mol eq. The preparation wherein about 1 M HCl is used. The preparation wherein the ratio of $\text{HCl}_{\text{vol(L)}}:\text{water}_{\text{vol(L)}}$ is about 1:12. The preparation wherein the ratio of $\text{CaSAC}_{2\text{weight(g)}}:\text{water}_{\text{vol(L)}}$ is about 33.3:1. The preparation wherein the stirring in step b) occurs at about room temperature (RT) for about 30 min. The preparation wherein the ratio of water used in step a) to EtOAc used in step d) ($\text{water}_{\text{vol}}:\text{EtOAc}_{\text{vol}}$) is about 1.5:1. The preparation wherein step d) is carried out at about room temperature (RT) for about 0.5 h. The preparation wherein the ratio of TBA: CaSAC_2 is about 1 mol eq:1 mol eq. The preparation wherein the stirring in step e) occurs at RT for about 7 d. The preparation wherein the ratio of EtOAc used in step d) to the ACE used in step f) ($\text{EtOAc}_{\text{vol}}:\text{ACE}_{\text{vol}}$) is about 1:2. The preparation wherein the stirring in step f) occurs at RT for about 3 h. The preparation wherein the isolating is carried out by filtration. The preparation further comprising drying the TBA SAC after its isolation.

An alternative process for preparing the TBA SAC comprises carrying out step d) at about room temperature (RT) for about 1 h. The alternative process also comprises treating the biphasic mixture with TBA until a suspension develops in about 5 min. That suspension is further stirred overnight, before filtering the TBA SAC and drying it under reduced pressure for about 25 min. The alternative process also provides for the TBA SAC being washed with TBME and dried under reduced pressure.

Another embodiment for preparing Na SAC-SAC comprises

- a) dissolving CaSAC_2 in mixture of aqueous HCl and EtOAc with stirring;
- b) separating the EtOAc layer from the aqueous layer;
- c) drying the EtOAc with MgSO_4 ;
- d) concentrating the dried EtOAc to yield SAC as an oil;
- e) dissolving SAC is dissolved in EtOAc; and
- f) treating the SAC in EtOAc as follows:

SAC conversion 1

- i) treating with NaOH with stirring at RT overnight;
- ii) cooling the mixture of step i) to about 5 °C for about 3 days until a suspension appears;

- iii) filtering the suspension to collect the filtrate; and
- iv) drying the filtrate under air for about 1 h before drying under vacuum for about 1 h to yield Na SAC-SAC;

SAC conversion 2

- 5 i) treating with NaOMe in methanol (MeOH) with stirring at RT overnight to form a suspension;
- ii) filtering the suspension to collect the filtrate;
- iii) washing the filtrate with EtOAc; and
- iv) drying the washed filtrate under air for about 2 hours before drying
- 10 under vacuum for about 1 h to yield Na SAC-SAC; or

SAC conversion 3

- i) treating with NaOMe in MeOH;
- ii) adding seeds of Na SAC-SAC to mixture of step i);
- 15 iii) stirring the mixture of step ii) at RT for about 20 h to yield a precipitate;
- iv) cooling the precipitate mixture of step iii) to about 10 °C for 36 h;
- v) filtering the precipitate;
- vi) drying the precipitate under air for about 1 h before drying under vacuum for about 1 h to yield Na SAC-SAC.

20 A particular embodiment of the instant preparation is wherein the CaSAC_2 is Form I hemi calcium salt of SAC. Another embodiment is wherein in step a) the HCl is provided as about 0.1 M HCl and ratio of $\text{HCl}_{\text{vol}}:\text{EtOAc}_{\text{vol}}$ is about 1:1. Another embodiment is wherein the ratio of $\text{CaSAC}_{2\text{weight(mg)}}:\text{EtOAc}_{\text{vol(mL)}}$ is about 33:1. Yet another embodiment optionally further comprises extracting the separated aqueous layer

25 of step b) with additional EtOAc; and separating the EtOAc layer used for extracting and combining all EtOAc layers before the drying of step c). Another embodiment is wherein in the ratio of volumes of EtOAc used in steps a) and c) are 1:1. Yet another embodiment is wherein in the ratio of volumes of EtOAc used in steps c) and EtOAc used in optional second extraction is 1:1. Yet a further embodiment is wherein the ratio of

30 $\text{SAC}_{\text{mol}}:\text{EtOAc}_{\text{volume(L)}}$ is about 1:5.6.

For SAC conversion 1, a particular embodiment is wherein the ratio of NaOH:SAC is about 1 mol eq:2 mol eq. Another embodiment is wherein in step i) the NaOH is provided as about 5.0 M NaOH.

For SAC conversions 2 and 3, a particular embodiment is wherein the ratio of NaOMe:SAC is about 1 mol eq:2 mol eq. Another embodiment is wherein in step i) the NaOMe is provided as about 2.1 M NaOMe in MeOH.

Yet an additional embodiment of the invention for a method for the preparation of Na SAC-SAC comprises

- a) dissolving CaSAC_2 in mixture of HCl (aq.) and EtOAc with stirring at RT for 1 h;
- b) separating the EtOAc layer from the aqueous layer;
- c) washing the EtOAc with water before separating the EtOAc;
- d) drying the EtOAc with MgSO_4 ;
- e) concentrating the dried EtOAc to yield SAC as an oil; and
- f) dissolving SAC in EtOAc;
- g) adding NaOMe in MeOH to the SAC in EtOAc mixture;
- h) seeding the mixture with Na SAC-SAC with stirring overnight at RT to yield a precipitate;
- i) cooling the mixture to about 5 °C for about 3 days;
- j) filtering the precipitate; and
- k) drying the precipitate under air for about 30 min to yield Na SAC-SAC.

A particular embodiment of the instant preparation is wherein the CaSAC_2 is Form I hemi calcium salt of SAC (CaSAC_2). Another embodiment is wherein in step a) the HCl is provided as about 0.1 M HCl and ratio of $\text{HCl}_{\text{vol}}:\text{EtOAc}_{\text{vol}}$ is about 1.8:1. Another embodiment is wherein the ratio of $\text{CaSAC}_{2\text{weight(mg)}}:\text{EtOAc}_{\text{vol(mL)}}$ is about 59:1. Yet another embodiment optionally further comprises extracting the separated aqueous layer of step b) with additional EtOAc; and separating the EtOAc layer used for extracting and combining all EtOAc layers before the washing of step c). Yet another embodiment is wherein in the ratio of volumes of EtOAc used in steps a) and optional second extraction is 1:1.8. Still another embodiment is wherein the ratio of water for washing to EtOAc (vol:vol) in step c) is about 1:12. Another embodiment is wherein the

ratio of $\text{SAC}_{\text{mol}}:\text{EtOAc}_{\text{volume(L)}}$ in step f) is about 1:6.5. A particular embodiment is wherein the ratio of NaOMe:SAC is about 1 mol eq:2 mol eq. Another embodiment is wherein in step g) the NaOMe is provided as about 2.1 M NaOMe.

5 Still another embodiment of the invention for a method for the preparation of Na SAC-SAC comprises

- a) dissolving CaSAC_2 in mixture of 0.1 M HCl (aq) and dichloromethane (DCM) with stirring at RT for 1.5 h;
- b) separating the DCM layer from the aqueous layer;
- c) washing the combined DCM with water before separating the DCM;
- 10 d) concentrating the DCM to yield SAC as an oil;
- d) dissolving SAC in EtOAc;
- e) adding NaOMe to SAC in EtOAc mixture;
- f) seeding the mixture with Na SAC-SAC with stirring at RT for about 2 h to yield a suspension;
- 15 g) cooling the suspension with stirring at about 5 °C for about overnight;
- h) filtering the precipitate; and
- i) drying the precipitate under suction for about 1.5 h to yield Na SAC-SAC.

A particular embodiment of the instant preparation is wherein the CaSAC_2 is Form I hemi calcium salt of SAC (CaSAC_2). Another embodiment is wherein in step a) 20 the HCl is provided as about 0.1 M HCl and ratio of $\text{HCl}_{\text{vol}}:\text{DCM}_{\text{vol}}$ is about 1:1. Another embodiment is wherein the ratio of $\text{CaSAC}_{2\text{weight(mg)}}:\text{DCM}_{\text{vol(mL)}}$ is about 33.3:1. Yet another embodiment optionally further comprises extracting the separated aqueous layer of step b) with additional DCM; and separating the DCM layer used for extracting and combining all DCM layers before the washing of step c). Yet another embodiment is 25 wherein in the ratio of volumes of DCM used in steps a) and optional second extraction is 1:1. Still another embodiment is wherein the ratio of water for washing to DCM (vol:vol) in step c) is about 1:6. Another embodiment is wherein the ratio of $\text{SAC}_{\text{mol}}:\text{EtOAc}_{\text{volume(L)}}$ in step d) is about 1:6.5. A particular embodiment is wherein the ratio of NaOMe:SAC is about 1 mol eq:2 mol eq. Another embodiment is wherein in step e) the NaOMe is 30 provided as about 2.1 M NaOMe in MeOH.

In addition, the present disclosure is related to the use of the anhydrous hybrid salt/co-crystal form of sacubitril (Na SAC-SAC) for preparing a composition with VAL, wherein the composition is amorphous Na₃SAC-VAL.

In one embodiment of the invention amorphous Na SAC is formed from Form I of Na SAC-SAC, which method comprises

- a) dissolving in methanol Form I of Na SAC-SAC and adding NaOMe in MeOH thereto; and
- b) removing the solvent under reduced pressure to yield amorphous Na SAC.

A particular embodiment of the instant preparation is wherein the ratio of Na SAC-SAC:NaOMe is about 1:1.2. Another embodiment is wherein the NaOMe is provided as about 1 M NaOMe and ratio of Na SAC-SAC_{weight(g)}:MeOH_{vol(L)} is about 5:1.

As Form I of Na SAC-SAC is convertible to amorphous NaSAC, such can be used in combination with VAL to prepare Na₃SAC/VAL by the method that comprises

- a) dissolving Form I of Na SAC-SAC and VAL in MeOH and NaOMe;
- b) removing the solvent under pressure to give a white viscous oil;
- c) dissolving the oil in water (20 mL);
- d) treating the solution of step b) with about NaOMe (5 drops of 1 M); and
- e) lyophilizing the mixture of step c) to yield amorphous Na₃SAC/VAL combination.

A particular embodiment of the instant preparation is wherein the ratio of Na SAC-SAC:VAL:NaOMe is about 1:2.3:2.5. Another embodiment is wherein in step a) the NaOMe is provided as about 1 M NaOMe and ratio of Na SAC-SAC_{weight(g)}:MeOH_{vol(L)} is about 24:1.

An alternative method according to the invention for preparing Na₃SAC/VAL comprises

- a) dissolving Form I of Na SAC-SAC, VAL and NaOMe in *t*-BuOH:H₂O; and
- b) lyophilizing the mixture of step a) to yield amorphous Na₃SAC/VAL combination.

A particular embodiment of the instant preparation is wherein the ratio of Na SAC-SAC:VAL:NaOMe is about 1:2:2.5. Another embodiment is wherein the *t*-

BuOH:H₂O is 18% v/v; 10 mL) in step a) the NaOMe is provided as about 1 M NaOMe and ratio of Na SAC-SAC_{weight(g)}: *t*-BuOH:H₂O_{vol(L)} is about 12:1.

Another embodiment of the present invention is directed to pharmaceutical compositions comprising a combination, a linked pro-drug or a dual-acting compound; in particular the complex as described herein and at least one pharmaceutically acceptable additive. The details regarding the combination and the complex, including the ARB and the NEPi, are as described above.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal, and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of the combination or dual-acting compound; in particular the complex, alone or in combination with at least one pharmaceutically acceptable carrier, especially suitable for enteral or parenteral application. Typical oral formulations include tablets, capsules, syrups, elixirs and suspensions. Typical injectable formulations include solutions and suspensions.

Pharmaceutically acceptable additives suitable for use in the present invention include, without limitation and provided they are chemically inert so that they do not adversely affect the combination or the dual-acting compound; in particular the complex of the present invention, diluents or fillers, disintegrants, glidants, lubricants, binders, colorants and combinations thereof. The amount of each additive in a solid dosage formulation may vary within ranges conventional in the art. Typical pharmaceutically acceptable carriers for use in the formulations described above are exemplified by: sugars, such as lactose, sucrose, mannitol and sorbitol; starches, such as cornstarch, tapioca starch and potato starch; cellulose and derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and methyl cellulose; calcium phosphates, such as dicalcium phosphate and tricalcium phosphate; sodium sulfate; calcium sulfate; polyvinylpyrrolidone; polyvinyl alcohol; stearic acid; alkaline earth metal stearates, such as magnesium stearate and calcium stearate; stearic acid; vegetable oils, such as peanut oil, cottonseed oil, sesame oil, olive oil and corn oil; non-ionic, cationic and anionic surfactants; ethylene glycol polymers; .beta.-cyclodextrin; fatty alcohols; and hydrolyzed cereal solids, as well as other non-toxic compatible fillers, binders, disintegrants, buffers,

preservatives, antioxidants, lubricants, flavoring agents and the like commonly used in pharmaceutical formulations.

Pharmaceutical preparations for enteral or parenteral administration are, e.g., in unit dose forms, such as coated tablets, tablets, capsules or suppositories, and also
5 ampoules. These are prepared in a manner which is known per se, e.g., using conventional mixing, granulation, coating, solubilizing or lyophilizing processes. Thus, pharmaceutical compositions for oral use can be obtained by combining the linked pro-drug, combination or dual-acting compound; in particular the complex with solid excipients, if desired, granulating a mixture which has been obtained, and, if required or
10 necessary, processing the mixture or granulate into tablets or coated tablet cores after having added suitable auxiliary substances.

The dosage of the active compounds in the combination or dual-acting compound; in particular the complex can depend on a variety of factors, such as mode of administration, homeothermic species, age and/or individual condition. The projected
15 efficacy in animal disease models ranges from about 0.1 mg/kg/day to about 1000 mg/kg/day given orally, and the projected dose for human treatment ranges from about 0.1 mg/day to about 2000 mg/day. Preferred ranges are from about 40 mg/day to about 960 mg/day of the linked pro-drug, preferably about 80 mg/day to about 640 mg/day. The ARB component is administered in a dosage of from about 40 mg/day to about 320
20 mg/day and the NEPi component is administered in a dosage of from about 40 mg/day to about 320 mg/day. More specifically, the dosages of ARB/NEPi, respectively, include 40 mg/40 mg, 80 mg/80 mg, 160 mg/160 mg, 320 mg/320 mg, 40 mg/80 mg, 80 mg/160 mg, 160 mg/320 mg, 320 mg/640 mg, 80 mg/40 mg, 160 mg/80 mg and 320 mg/160 mg, respectively. These dosages are "therapeutically effective amounts". Preferred dosages
25 for the linked pro-drug, combination or dual-acting compound, in particular the complex of the pharmaceutical composition according to the present invention are therapeutically effective dosages.

Examples, which follow herein, are directed to embodiments of the invention. The examples are presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles described herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Therefore, the various embodiments are illustrative of the present disclosure and the disclosure is not intended to be limited to the examples described herein and shown.

Analytical Techniques

XRPD patterns are obtained using a Bruker D8 diffractometer equipped with a Cu K α radiation source (40 kV, 40 mA, $\lambda=1.54 \text{ \AA}$), and a θ -2 θ goniometer fitted with a Ge monochromator. The incident beam passes through a 2.0 mm divergence slit followed by a 0.2 mm anti-scatter slit and knife edge. The diffracted beam passes through an 8.0 mm receiving slit with 2.5° Soller slits followed by LYNXEYE super speed detector. Samples are placed on zero-background, silicon plate holders for analysis. *Diffraction Plus* XRD Commander and *Diffraction Plus* EVA software are used respectively for data collection and analysis. One skilled in the art would recognize that the 2 θ values and the relative intensity values are generated by performing a peak search on the measured data and the *d*-spacing values are calculated from the 2 θ values using Bragg's equation. One skilled in the art would further recognize that the relative intensity for the measured peaks may vary because of sample preparation, orientation and instrument used, for example.

SCXRD Data is collected on a Rigaku Oxford Diffraction SuperNova, Dualflex, Cu at Zero, Atlas S2 CCD diffractometer equipped with an Oxford Cryosystems Cobra cooling device. The data were collected using $\lambda=1.54 \text{ \AA}$ Cu K α radiation. Structures are solved and refined using the Bruker AXS SHELXD-2014/6 crystallographic software.

DSC data are collected using a TA Instruments Q2000 DSC. Approximately, samples (0.5-3 mg of each sample, is placed in a pin-holed aluminium pan, and heated at 10 °C/min from 25 °C to 300 °C under a nitrogen purge of about 50 mL/min at a rate of about 50 mL/min.

TGA measurements are recorded using TA Q500 instrument. Typically, 5-10 mg of samples are weighed in aluminum pans. TGA investigations are performed at a heating rate of 10 °C/min over a temperature range of from about 25 to about 350 °C, with purging with nitrogen at a flow rate of 60 mL/min. Advantage for Q Series and Thermal Advantage is the instrument control software that is used and the data is analyzed using Universal Analysis or TRIOS.

¹H-NMR data is collected using a Bruker 400 MHz instrument equipped with TopSpin software. Samples are prepared by dissolving the compound in deuterated dimethylsulfoxide or deuterated MeOH. Spectra are collected at ambient temperature.

The number of scans are either 16, 64 or 128 for ¹H-NMR. Automated experiments are acquired using ICON-NMR configuration within Topspin software, using standard Bruker-loaded experiments (¹H). Off-line analysis is performed using ACD Spectrus Processor.

Experimental

Examples below provide embodiments of the preparation of hybrid salt/co-crystal of sacubitril.

Example I

Preparation of Form I of *t*-Butylamine Salt of SAC (TBA SAC)

Method 1

Form I hemi calcium salt of SAC (CaSAC₂) (~ 100 mg) (which can be prepared as described in WO2016074651, more particularly as is described in Example 16, which is incorporated herein by reference) is suspended in water (3 mL) and 1 M HCl (250 µL).

Dichloromethane (DCM) (3 mL) is added to solubilize the material. The solution is stirred at room temperature (RT) for about 1.5 h. The DCM layer is extracted and concentrated at reduced pressure to give an oil (SAC).

EtOAc (1.5 mL) is added to the oil with stirring for 30 min, with the sample remaining as an oil in EtOAc biphasic mixture. Then additional EtOAc (0.5 mL) is added to the mixture with stirring for about 5 min at about 19-25 °C. There is no change in appearance in the mixture after the second addition. That biphasic mixture is then treated

with 1 eq. of *t*-butylamine and stirred at RT. After 7 days, the mixture is a solution. The solution is treated with stirring at RT with increasing aliquots of anti-solvent (4 mL of acetone). After about 5 min, a thin suspension is obtained. The sample is further stirred at RT for about 3 h.

5 The sample is filtered and dried under suction for about 25 min to yield Form I of TBA SAC.

Method 2

The procedure of Example I method 1 is repeated to form the oil of SAC in EtOAc biphasic mixture, and stirred at RT for about 1 h. The biphasic mixture is treated
10 with *t*-butylamine and a suspension develops after stirring at RT for about 5 minutes. The suspension is stirred overnight, filtered and dried under reduced pressure for 20 min. The filtered material is washed with 2 mL of TBME and dried under reduced pressure to yield TBA SAC.

Method 3

15 Form I CaSAC₂ (10.4 g) is suspended in water (300 mL) and HCl (23 mL, 1 M HCl). DCM (300 mL) is added to solubilize the material and the solution is stirred at RT for about 30 min. The DCM layer is extracted and the solvent removed at reduced pressure to give SAC as an oil.

EtOAc (200 mL) is added to the oil with stirring at RT. After about 5 min, partial
20 dissolution is observed. 1.0 eq. of *t*-butylamine is added to the EtOAc mixture. A small quantity of solid remains and the mixture is stirred for a further 5 min. Seeds of TBA SAC are added to the sample. After stirring for a few minutes, precipitation is observed. The sample is stirred at RT for about 3 days. The sample is filtered, and resultant cake is briefly agitated. The sample is dried for one hour, and then the transferred to a vacuum
25 oven and dried under vacuum at RT overnight to yield TBA SAC.

Figure I is the XPRD pattern for Form I of TBA SAC that is made according to Example 1, Method 3.

30

Figure II is directed to the ¹H NMR for the Form I of TBA SAC.

Example II

Preparation of Form I of anhydrous hybrid
sodium salt/co-crystal form of sacubitril (Na SAC-SAC)

5

Method 1

TBA SAC (22 mg, 0.04 mmol) is dissolved in ethyl acetate (2 mL) with agitation at 50 °C overnight. The solution is treated with sodium 2-ethylhexanoate (7.4 mg, 0.04 mmol, added as a solid) and stirred at RT for 4 days. The solution is then treated with
10 anti-solvent (5 mL of acetone) and stirred overnight. A solution is observed and treated with further anti-solvent (4 mL of acetone) and stirred overnight. Precipitation does not occur, so the solvent and anti-solvent are removed at reduced pressure to give an oil. The oil is suspended in TBME (4 mL) and the resulting suspension is stirred at RT overnight). The sample is filtered and dried under suction for 15 min to yield Na SAC-SAC.

15

Method 2

TBA SAC (500 mg, 1.03 mmol) is suspended in EtOAc (10 mL) and stirred at RT for 1 h. To the suspension, water (10 mL) and 1.0 eq. of 1 M HCl (a stock solution) are added at RT. The resultant biphasic mixture is extracted to obtain the organic layer
20 that is concentrated under reduced pressure to yield an oil. The oil is treated with THF (10 mL) and of NaOMe in methanol (0.5 M, 176 µL, 3.09 mmol). The methanolic solution is stirred at about 50 °C for 1 hour and cooled to 25 °C at a rate of 0.1 °C per minute. After stirring at 25 °C overnight, the solution is treated with heptane (15mL) and stirred at RT for 2 h. The solution is treated with methyl ethyl ketone (MEK) (10 mL) and
25 stirred at RT overnight. The solution is stirred at 50 °C for 1 hour, then cooled to 25 °C at a rate of 0.1 °C/min, and then cooled to 5 °C at a rate of 0.1 °C/min and held at 5 °C overnight. Seeds of Na SAC are added to the solution and the sample is stirred at RT. After 4 days, a suspension is obtained. The sample is filtered and dried under suction for 5 minutes prior to yield Na SAC-SAC.

30

Method 3

CaSAC₂ (2.8 g, 3.22 mmol) is dissolved in 0.1 M HCl (aq., 85 mL) and EtOAc (85 mL) with stirring at RT for about 30 min. The aqueous layer is extracted and washed with additional EtOAc (85 mL). The organic layer is extracted and the combined organic layers dried with MgSO₄. The solution is concentrated *in-vacuo* to give a viscous oil (recovery = 2.86 g, about 15% w/w EtOAc). The SAC oil is dissolved in EtOAc (36 mL) and dispensed into 3 vials (containing 0.72, 0.72 and 1.44 mmol respectively).

- i. SAC in EtOAc (0.72 mmol) is treated with 0.5 eq of NaOH (5 M aq.) and stirred at RT overnight. The sample remains a solution and is cooled to 5 °C. After 3 days, a suspension appears. The suspension is filtered, air dried for about 1 h before drying under vacuum (25 °C) for about 1 hour prior to yield Na SAC-SAC (53 mg).
- ii. SAC in EtOAc (0.72 mmol) is treated with 0.5 eq NaOMe (2.1 M in MeOH) and stirred at RT overnight whereby a suspension is formed. The suspension is filtered and washed with EtOAc (1 mL). The filtered material is recovered, air dried for about 2 hours and then dried under vacuum (25 °C) for about 1 hour prior to yield Na SAC-SAC (530 mg).
- iii. SAC in EtOAc (1.44 mmol) was treated with 0.5 eq NaOMe (2.1 M in MeOH) and seeds of Na SAC-SAC of Method 3 ii) are added. A white precipitate is formed and stirred at 20 °C for 20 h and then cooled to 10 °C at rate of 0.1 °C per min. After stirring at 10 °C for 36 h the sample is filtered, air dried for about 1 h before drying under vacuum (25 °C) for about 1 h prior to yield Na SAC-SAC (830 mg).

Figure III is the XPRD pattern for Form I of Na SAC-SAC that is made according to Example 1, Method 3. Form I of Na SAC-SAC is characterized by its XRPD pattern peaks and their corresponding intensities that are listed in Table I below.

Table I:

Angle	Intensity, %
3.6	13.4
5.3	26.9
8.8	15.4

10.6	100.0
11.0	6.0
11.6	2.3
12.3	23.1
14.8	7.7
15.9	22.4
17.0	5.6
17.2	5.3
17.6	14.7
18.8	2.7
19.4	21.7
19.9	15.3
20.5	7.5
20.8	23.5
21.2	12.5
21.6	6.0
22.2	6.3
24.0	3.7
24.8	3.7
26.6	7.1
26.9	6.0
28.4	7.4

The angle measurements are $\pm 0.2^\circ 2\theta$. Key defining peaks for solid-state Form I of Na SAC-SAC include 5.3, 8.8, 10.6, 12.3, 14.8, 15.9, 17.6, 19.4 and $19.9^\circ 2\theta$.

The TGA plot (Figure IV) show TGA weight loss of about 0.4% from about 30
 5 $^\circ\text{C}$ through about 50 $^\circ\text{C}$ for Form I of Na SAC-SAC. The DSC plot (Figure V) shows a thermal event at 135.5 $^\circ\text{C}$ for Form I of Na SAC-SAC.

Figure VI is directed to the ^1H NMR for the Form I of Na SAC-SAC.

Single crystals of Form I of Na SAC-SAC are obtained by Method i), and the single crystal parameters for the Form I of Na SAC-SAC as determined by SCXRD are:

10 Space Group: Monoclinic, $P2_1$
 $a = 5.157(5) \text{ \AA}$
 $b = 8.394(9) \text{ \AA}$
 $c = 50.092(6) \text{ \AA}$
 $\alpha = \gamma = 90^\circ, \beta = 92.282(10)^\circ$
 15 Volume: $2166.7 \text{ \AA}^3$

Figure VII shows the asymmetric unit of Form I of Na SAC-SAC. The asymmetric unit of the hybrid salt/co[crystal has a single positively charged sodium ion and single negatively charged molecule of sacubitril due to the deprotonation of the carboxylic acid moiety thereof, i.e., sodium sacubitril (Na SAC), wherein the two constituent of the Na SAC (Na⁺ and negatively charged molecule of sacubitril), molecule A forms one of the components of the co[crystal, and a fully protonated molecule of sacubitril (molecule B) forms the other component of the co-crystal. Figure VIII shows a view down the *b*-axis of the unit cell of Form I of Na SAC-SAC and perpendicular to the axis of propagation of the sodium oxygen channel hydrogen bonded chain. Figure IX shows that the calculated XRPD pattern of Form I of Na SAC-SAC as determined by SCXRD.

Method 4

i) CaSAC₂ (5.0 g, 5.8 mmol) is dissolved in 0.1 M HCl (aq., 150 ml) and EtOAc (85 mL) with stirring at RT for 1 hour. The EtOAc layer is separated and aqueous layer extracted with additional EtOAc (150 mL). The EtOAc layers are combined, and washed with water (20 mL). The EtOAc layer is separated and dried with MgSO₄. The EtOAc is removed at reduced pressure to give SAC as a viscous oil that is then dissolved in EtOAc (75 mL, 15 volumes) and 0.5 mol. eq. of NaOMe (2.9 mL, 2.1 M in MeOH) is added. The solution is seeded with Na SAC-SAC and stirred at RT overnight. A thin precipitate is observed, and stirred at 5 °C for 3 days. A white precipitate results and is filtered and air-dried for 30 min to yield Form I of Na SAC-SAC (1.7 g).

ii) Calcium Sacubitril (5.0 g, 5.8 mmol) is dissolved in 0.1 M HCl (aq., 150 mL) and DCM (150 mL) with stirring at RT for 1.5 h. The DCM layer is separated and aqueous layer washed with additional DCM (150 mL). The DCM layers are combined, and washed with water (50 mL) and the organic layer was extracted. The DCM is removed at reduced pressure to give a viscous oil. The oil is washed with 15 ml of DCM. The DCM is removed at reduced pressure to give a viscous oil. The oil is dissolved in DCM (15 mL) and removed under reduced pressure to give SAC as an oil.

The oil is dissolved in EtOAc (75 mL) and 0.5 mol. eq. of NaOMe (2.7 mL, 2.1 M in MeOH) is added thereto. The solution is seeded with Na SAC-SAC and stirred at RT. After about 2 hours a suspension is obtained. The sample is cooled and stirred at

about 5 °C. After stirring overnight, the sample is filtered and dried under suction for 1.5 hours to yield Form I of Na SAC-SAC (3.06 g).

Example III

5 Preparation of Amorphous NaSAC via Form I of Na SAC-SAC

Form I of Na SAC-SAC (about 0.1 g) is dissolved in MeOH (20 mL) and 1 M NaOMe (1.26 ml of 1 M NaOMe). The solvent is removed under reduced pressure to yield amorphous NaSAC as a white foam.

10 Example IV

Preparation of Amorphous Na₃SAC/VAL Combination using Form I of Na SAC-SAC

Method 1

A mixture of Form I of Na SAC-SAC (243 mg) and VAL (250 mg) is dissolved 10 ml of MeOH and 1.44 ml of 1 M NaOMe (about 2.5 eq.) The solvent is removed
15 under pressure to give a white viscous oil. The sample is re-constituted in 20 ml of water. The suspension was treated with about 5 drops of 1 M NaOMe to aid dissolution. A milky white suspension is obtained and lyophilized to yield amorphous Na₃SAC/VAL combination.

Method 2

20 A mixture of Form I of Na SAC-SAC (121 mg, 0.143 mmol) and VAL (126 mg, 0.287 mmol) was dissolved 10 ml of *t*-BuOH:H₂O (18% v/v) and 700 µL of 1 M NaOMe (0.7 mmol, 2.5 eq.). The solution is lyophilized to yield amorphous Na₃SAC/VAL combination

The above examples are presented to aid in the understanding of the disclosure
25 and enable a person of ordinary skill in the art to make and use the various embodiments, and are not intended and should not be construed to limit in any way the disclosure set forth in the claims which follow hereafter.

What is claimed is:

1. An anhydrous hybrid salt/co-crystal of sacubitril, Na SAC-SAC.
2. The sacubitril co-crystal according to claim 1, comprising about 1:1 of two components, a neutral sacubitril and a sodium salt of sacubitril, .
- 5 3. The sacubitril co-crystal according to claim 1, characterized by having at least 2 or more X-ray powder diffraction peaks selected from about 5.3, 8.8, 10.6, 12.3, 14.8, 15.9, 17.6, 19.4 and $19.9^{\circ} \pm 0.2^{\circ} \theta$.
4. The sacubitril co-crystal according to claim 1, characterized by a thermal event at about 135.5°C , as measured by differential scanning calorimetry.
- 10 5. The sacubitril co-crystal according to claim 1, characterized by a weight loss of 0.4% from about 30°C through about 50°C , as measured by thermal gravimetric analysis.
6. The sacubitril co-crystal of claim 1 which is monoclinic, $P2_1$.
7. The sacubitril co-crystal of claim 1 which has single crystal parameters
 - 15 $a = 5.157 (5) \text{ \AA}$
 - $b = 8.394 (9) \text{ \AA}$
 - $c = 50.092 (6) \text{ \AA}$
 - $\alpha = \gamma = 90^{\circ}$, $\beta = 92.282 (10)^{\circ}$.
8. The sacubitril co-crystal of claim 1 which has a cell volume is about $2166.7 \text{ \AA}^3$.
- 20 9. A method of preparing the sacubitril co-crystal according to claim 1, comprising
 - a) reacting *t*-butylamine salt of sacubitril in ethyl acetate with sodium 2-ethylhexanoate while stirring;
 - b) removing solvent to yield oil; and
 - c) suspending oil in *t*-butyl methyl ether with stirring to yield the sacubitril
 - 25 co-crystal.
10. The method of claim 9 wherein the ratio of *t*-butylamine salt of sacubitril:sodium 2-ethylhexanoate is about 1 mol eq:1 mol eq.
11. The method of claim 9 wherein the ratio of *t*-butylamine salt of sacubitril_{mol}:ethyl acetate_{vol(L)} is about 1:50.
- 30 12. The method of claim 9 wherein the stirring in step a) occurs at about room temperature for about 4 d.

13. The method of claim 9 wherein the solvent removal is undertaken at reduced pressure.
14. The method of claim 9 wherein the ratio of *t*-butylamine salt of sacubitril_{mol}: *t*-butyl methyl ether_{vol(L)} is about 1:100.
- 5 15. The method of claim 9 wherein the stirring in step c) occurs at RT overnight.
16. A method of preparing the sacubitril co-crystal according to claim 1, comprising:
- a) dissolving calcium salt of sacubitril in mixture of aqueous HCl and ethyl acetate with stirring;
 - b) separating the ethyl acetate layer from the aqueous layer;
 - 10 c) drying the ethyl acetate with MgSO₄;
 - d) concentrating the dried ethyl acetate to yield sacubitril as an oil;
 - e) dissolving sacubitril is dissolved in ethyl acetate; and
 - f) treating the sacubitril in ethyl acetate as follows:
- sacubitril conversion 1
- 15 i) treating sacubitril in ethyl acetate with NaOH with stirring at RT overnight;
 - ii) cooling the mixture of step i) to about 5 °C for about 3 days until a suspension appears;
 - iii) filtering the suspension to collect the filtrate; and
 - 20 iv) drying the filtrate under air for about 1 h before drying under vacuum for about 1 h to yield Na SAC-SAC;
- sacubitril conversion 2
- i) treating sacubitril dissolved in ethyl acetate is treated with NaOMe in methanol with stirring at RT overnight to form a suspension;
 - 25 ii) filtering the suspension to collect the filtrate;
 - iii) washing the filtrate with ethyl acetate; and
 - iv) drying the washed filtrate under air for about 2 hours before drying under vacuum for about 1 h to yield Na SAC-SAC; or
- sacubitril conversion 3
- 30 i) treating sacubitril in ethyl acetate with NaOMe in methanol;
 - ii) adding seeds of Na SAC-SAC to mixture of step i);

- iii) stirring the mixture of step ii) at about 20 °C for about 20 h to yield a precipitate;
 - iv) cooling the precipitate mixture of step iii) to 10 °C for 36 h;
 - v) filtering the precipitate;
 - 5 vi) drying the precipitate under air for about 1 h before drying under vacuum for about 1 h to yield Na SAC-SAC.
17. The method of claim 16 wherein the calcium salt of sacubitril is Form I hemi calcium salt of sacubitril.
18. The method of claim 16 wherein in step a) the HCl is provided as about 0.1 M
10 HCl and ratio of $\text{HCl}_{\text{vol}}:\text{ethyl acetate}_{\text{vol}}$ is about 1:1.
19. The method of claim 16 wherein the ratio of calcium salt of $\text{sacubitril}_{\text{weight(mg)}}:\text{ethyl acetate}_{\text{vol(mL)}}$ is about 33:1.
20. The method of claim 16 further comprises extracting the separated aqueous layer of step b) with additional ethyl acetate; and separating the ethyl acetate layer used
15 for extracting and combining all ethyl acetate layers before the drying of step c).
21. The method of claim 20 wherein the ratio of volumes of ethyl acetate used in steps a) and ethyl acetate used in optional second extraction are 1:1.
22. The method of claim 16 wherein the ratio of $\text{sacubitril}_{\text{mol}}:\text{ethyl acetate}_{\text{volume(L)}}$ in step e) is about 1:5.6.
- 20 23. The method of claim 16 wherein the ratio of NaOH:sacubitril is about 1 mol eq:2 mol eq.
24. The method of claim 23 wherein the NaOH is provided as about 5.0 M NaOH.
25. The method of claim 16 wherein the ratio of NaOMe:sacubitril is about 1 mol eq:2 mol eq.
- 25 26. The method of claim 25 wherein the NaOMe is provided as about 2.1 M NaOMe in MeOH.
27. A method of preparing the sacubitril co-crystal according to claim 1, comprising
- a) dissolving calcium salt of sacubitril in mixture of HCl (aq.) and ethyl acetate with stirring at RT for 1 h;
 - 30 b) separating the ethyl acetate layer from the aqueous layer;
 - c) washing the ethyl acetate with water before separating the ethyl acetate;

- d) drying the ethyl acetate with MgSO_4 ;
 - e) concentrating the dried ethyl acetate to yield sacubitril as an oil; and
 - f) dissolving sacubitril in ethyl acetate;
 - g) adding NaOMe in methanol to the sacubitril ethyl acetate mixture;
 - 5 h) seeding the mixture with Na SAC-SAC with stirring overnight at RT to yield a precipitate;
 - i) cooling the mixture to about 5 °C for about 3 days;
 - j) filtering the precipitate; and
 - k) drying the precipitate under air for about 30 min to yield Na SAC-SAC.
- 10 28. The method of claim 27 wherein the calcium salt of sacubitril is Form I hemi calcium salt of sacubitril.
29. The method of claim 27 wherein in step a) the HCl is provided as about 0.1 M HCl and ratio of $\text{HCl}_{\text{vol}}:\text{ethyl acetate}_{\text{vol}}$ is about 1.8:1.
30. The method of claim 27 wherein the ratio of calcium salt of
- 15 $\text{sacubitril}_{\text{weight(mg)}}:\text{ethyl acetate}_{\text{vol(mL)}}$ is about 59:1.
31. The method of claim 27 that optionally further comprises extracting the separated aqueous layer of step b) with additional ethyl acetate; and separating the ethyl acetate layer used for extracting and combining all ethyl acetate layers before the washing of step c).
- 20 32. The method of claim 27 wherein in the ratio of volumes of ethyl acetate used in steps a) and ethyl acetate used in optional second extraction is 1:1.8.
33. The method of claim 27 wherein the ratio of water for washing to ethyl acetate (vol:vol) in step c) is about 1:12.
34. The method of claim 27 wherein the ratio of $\text{SAC}_{\text{mol}}:\text{ethyl acetate}_{\text{volume(L)}}$ in step f)
- 25 is about 1:6.5.
35. The method of claim 27 wherein the ratio of NaOMe:sacubitril is about 1 mol eq:2 mol eq.
36. The method of claim 35 wherein in step g) the NaOMe is provided as about 2.1 M NaOMe.
- 30 37. A method of preparing the sacubitril co-crystal according to claim 1, comprising

- a) dissolving calcium salt of sacubitril in mixture of 0.1 M HCl (aq.) and dichloromethane with stirring at RT for 1.5 h;
 - b) separating the dichloromethane layer from the aqueous layer;
 - c) washing the combined dichloromethane with water (50 mL) before separating the dichloromethane;
 - d) concentrating the dichloromethane to yield sacubitril as an oil;
 - e) dissolving sacubitril is dissolved in ethyl acetate;
 - f) adding NaOMe to the sacubitril in ethyl acetate mixture;
 - g) seeding the mixture with Na SAC-sacubitril with stirring at RT for about 2 h to yield a suspension;
 - h) cooling the suspension with stirring at about 5 °C for about overnight;
 - i) filtering the precipitate; and
 - j) drying the precipitate under suction for about 1.5 h to yield Na SAC-SAC.
38. The method of claim 37 wherein the calcium salt of sacubitril is Form I hemi calcium salt of sacubitril.
39. The method of claim 37 wherein in step a) the HCl is provided as about 0.1 M HCl and ratio of $\text{HCl}_{\text{vol}}:\text{dichloromethane}_{\text{vol}}$ is about 1.1.
40. The method of claim 37 wherein the ratio of calcium salt of sacubitril $_{\text{weight(mg)}}:\text{dichloromethane}_{\text{vol(mL)}}$ is about 33.3:1.
41. The method of claim 37 that optionally further comprises extracting the separated aqueous layer of step b) with additional dichloromethane; and separating the dichloromethane layer used for extracting and combining all dichloromethane layers before the washing of step c).
42. The method of claim 41 wherein in the ratio of volumes of dichloromethane used in steps a) and dichloromethane used in optional second extraction is 1:1.
43. The method of claim 37 wherein the ratio of water used for washing to dichloromethane (vol:vol) in step c) is about 1:6.
44. The method of claim 37 wherein the ratio of sacubitril $_{\text{mol}}:\text{ethyl acetate}_{\text{volume(L)}}$ in step e) is about 1:6.5.
45. The method of claim 37 wherein the ratio of NaOMe:sacubitril is about 1 mol eq:2 mol eq.

46. The method of claim 45 wherein in step e) the NaOMe is provided as about 2.1 M NaOMe in methanol.
47. A method of preparing amorphous sodium salt of sacubitril, comprising
- 5 a) dissolving in methanol the sacubitril co-crystal according to claim 1 and NaOMe in MeOH; and
- b) removing the solvent under reduced pressure to yield amorphous sodium salt of sacubitril.
48. The method of claim 47 wherein the ratio of the sacubitril co-crystal:NaOMe is about 1:1.2.
- 10 49. The method of claim 47 wherein the NaOMe is provided as about 1 M NaOMe and ratio of the sacubitril co-crystal_{weight(g)}:MeOH_{vol(L)} is about 5:1.
50. A method of preparing amorphous Na₃SAC/VAL, comprising
- a) dissolving in methanol the sacubitril co-crystal according to claim 1, valsartan and NaOMe;
- 15 b) removing the solvent under pressure to give a oil;
- c) dissolving the oil in water;
- d) treating the solution of step b) with NaOMe (about 5 drops of 1 M); and
- e) lyophilizing the mixture of step c) to yield amorphous Na₃SAC/VAL combination.
- 20 51. The method of claim 50 wherein the ratio of sacubitril co-crystal:valsartan:NaOMe is about 1:2.3:2.5.
52. The method of claim 50 wherein the NaOMe is provided as about 1 M NaOMe and ratio of sacubitril co-crystal_{weight(g)}:MeOH_{vol(L)} is about 24:1.
53. A method of preparing amorphous Na₃SAC/VAL, comprising
- 25 a) dissolving sacubitril co-crystal of claim 1, valsartan and NaOMe in *t*-butanol:H₂O; and
- b) lyophilizing the mixture of step a) to yield amorphous Na₃SAC/VAL combination.
54. The method of claim 53 wherein the ratio of sacubitril co-crystal of claim 1, valsartan:NaOMe is about 1:2:2.5.
- 30 55. The method of claim 53 wherein the *t*-BuOH:H₂O is 18% v/v

56. The method of claim 53 wherein the NaOMe is provided as about 1 M NaOMe and ratio of sacubitril co-crystal_{weight(g)}: *t*-butanol:H₂O_{vol(L)} is about 12:1

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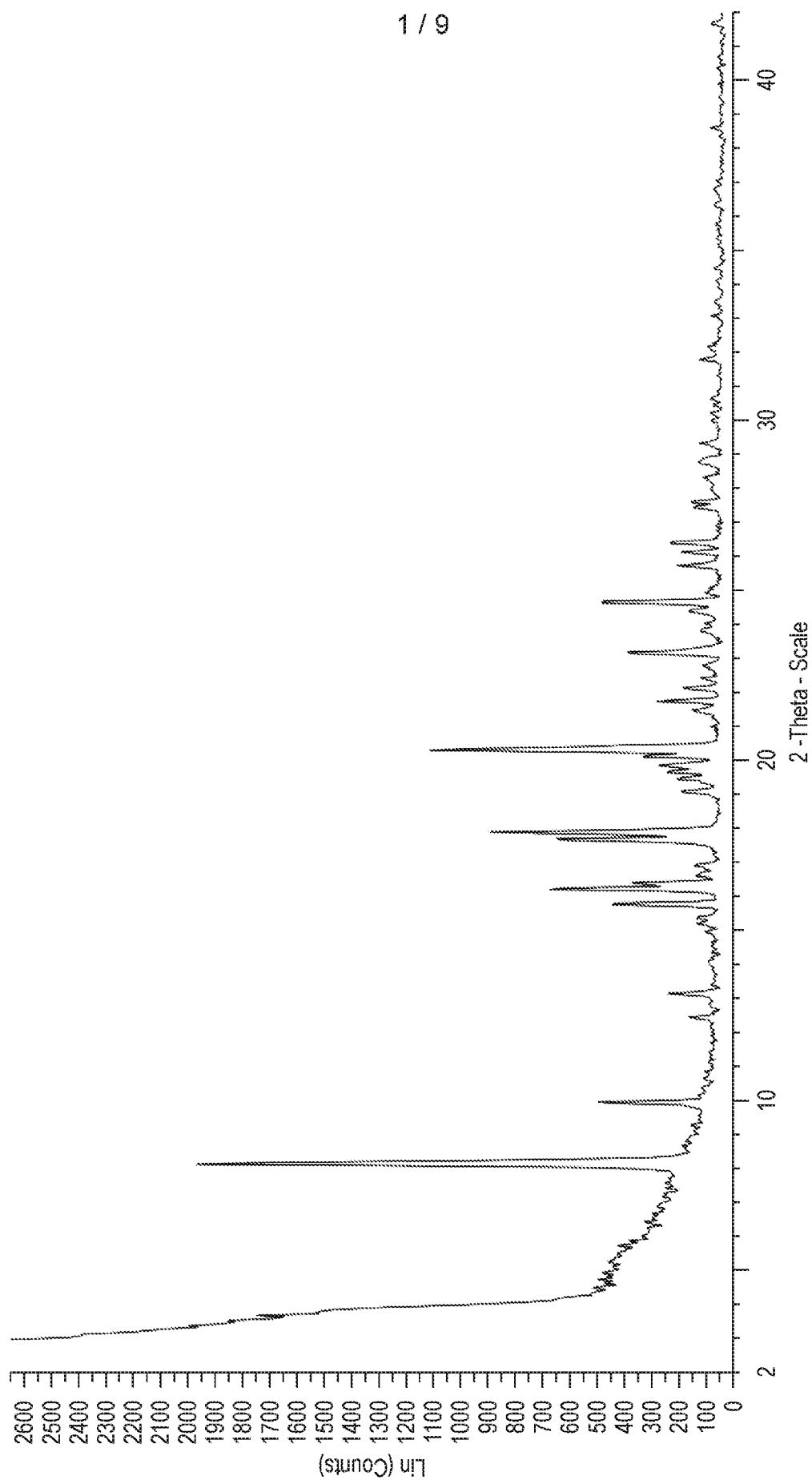


FIG. 1

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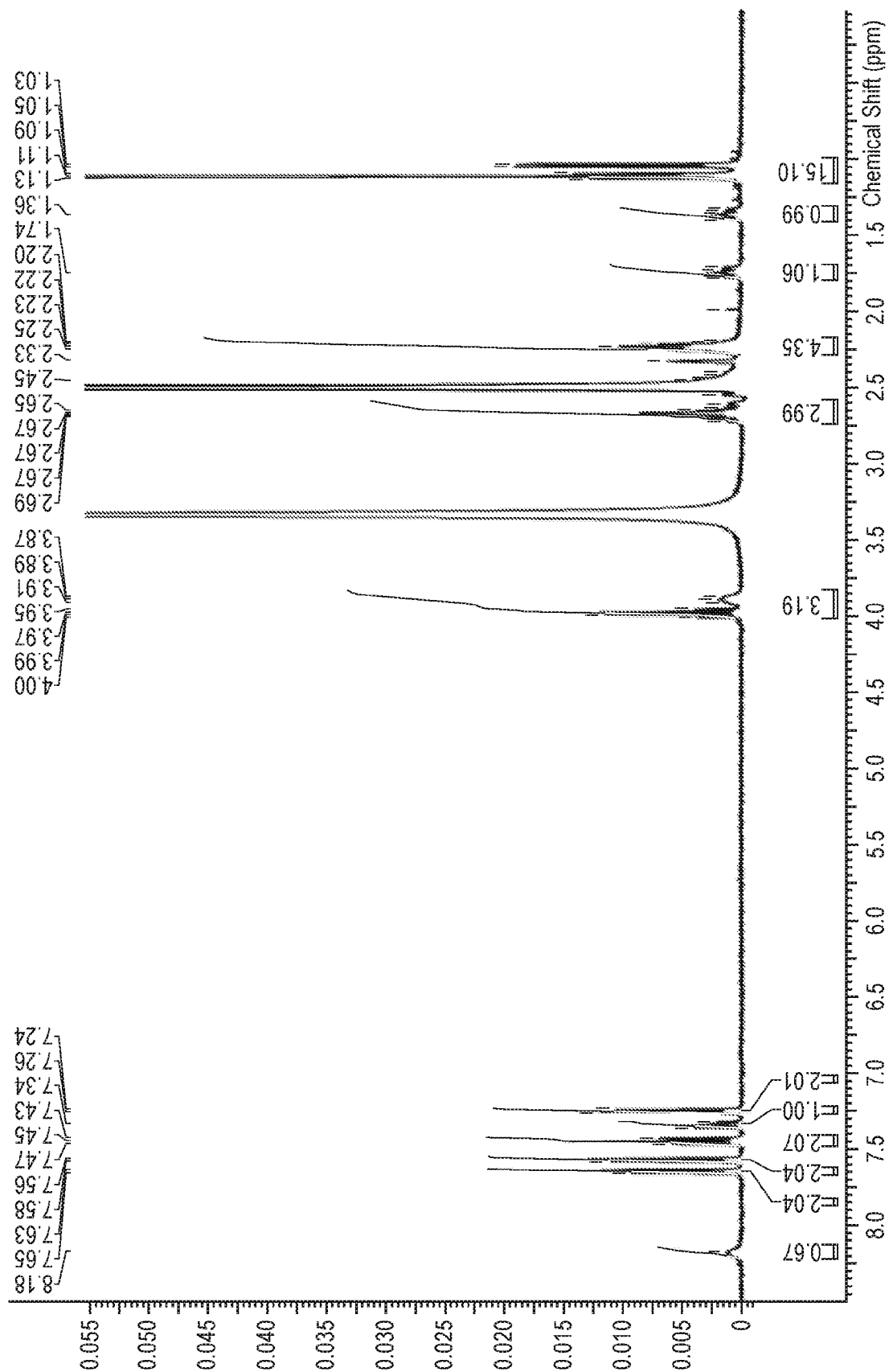


FIG. 2

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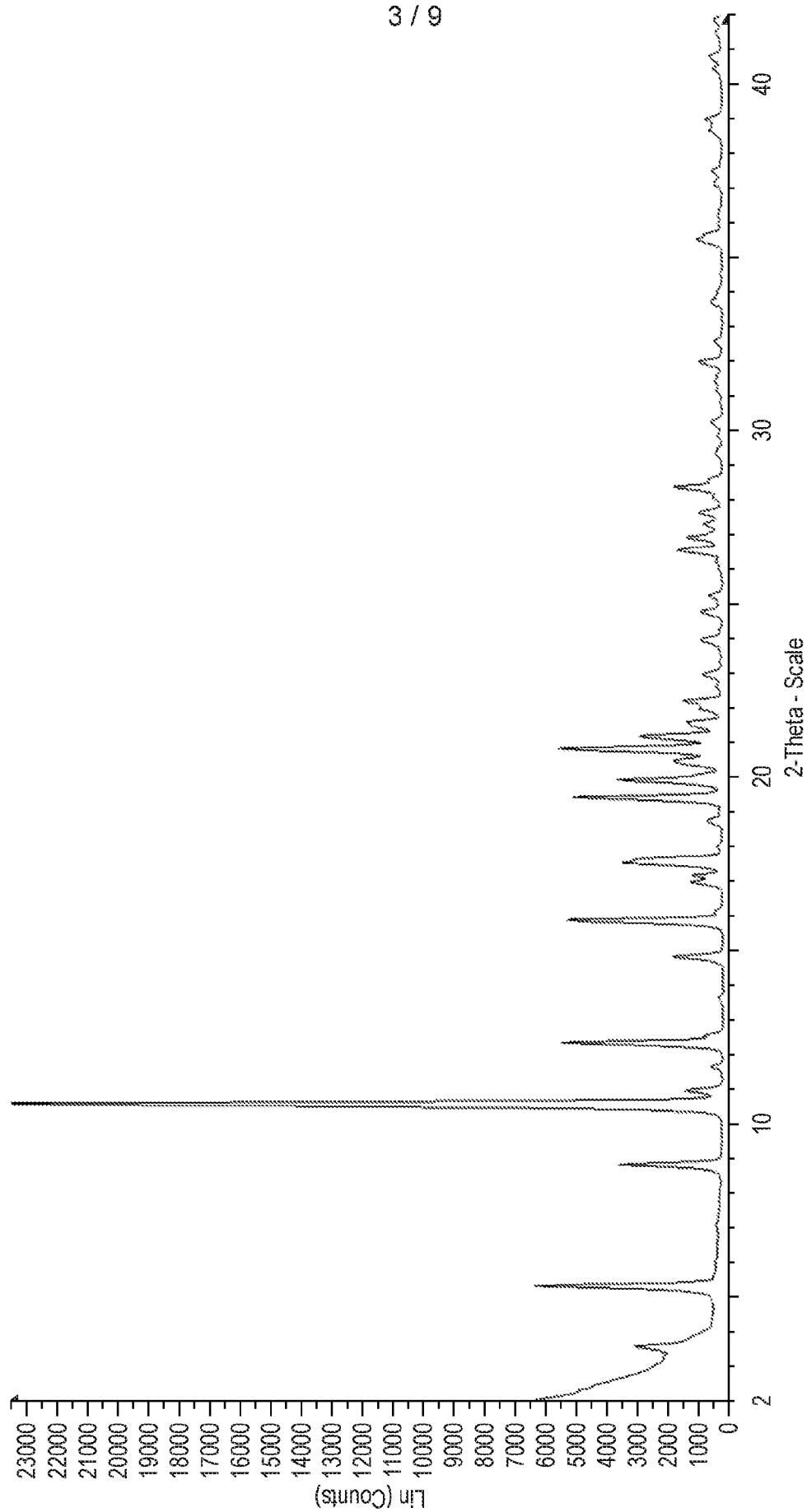


FIG. 3

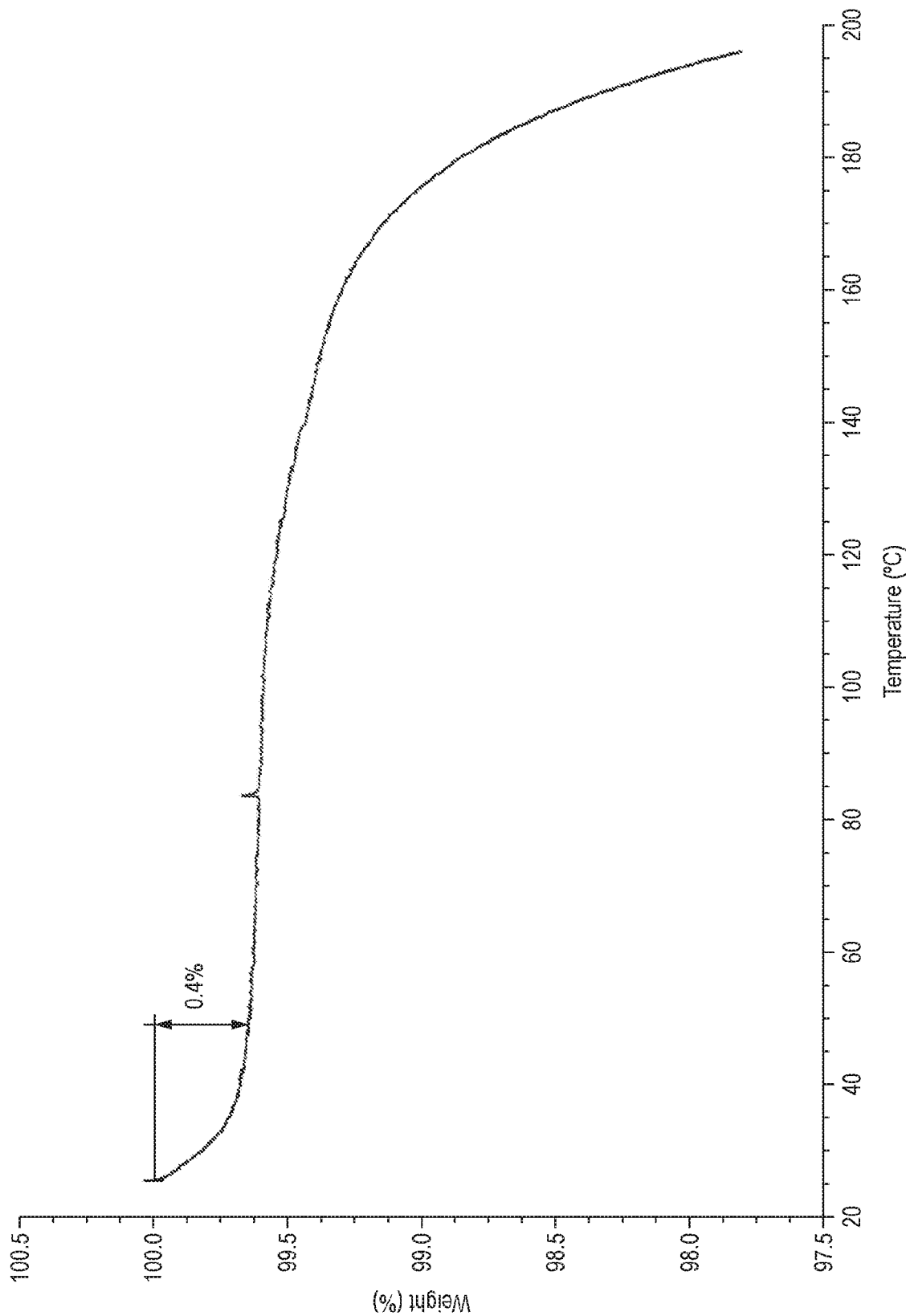


FIG. 4

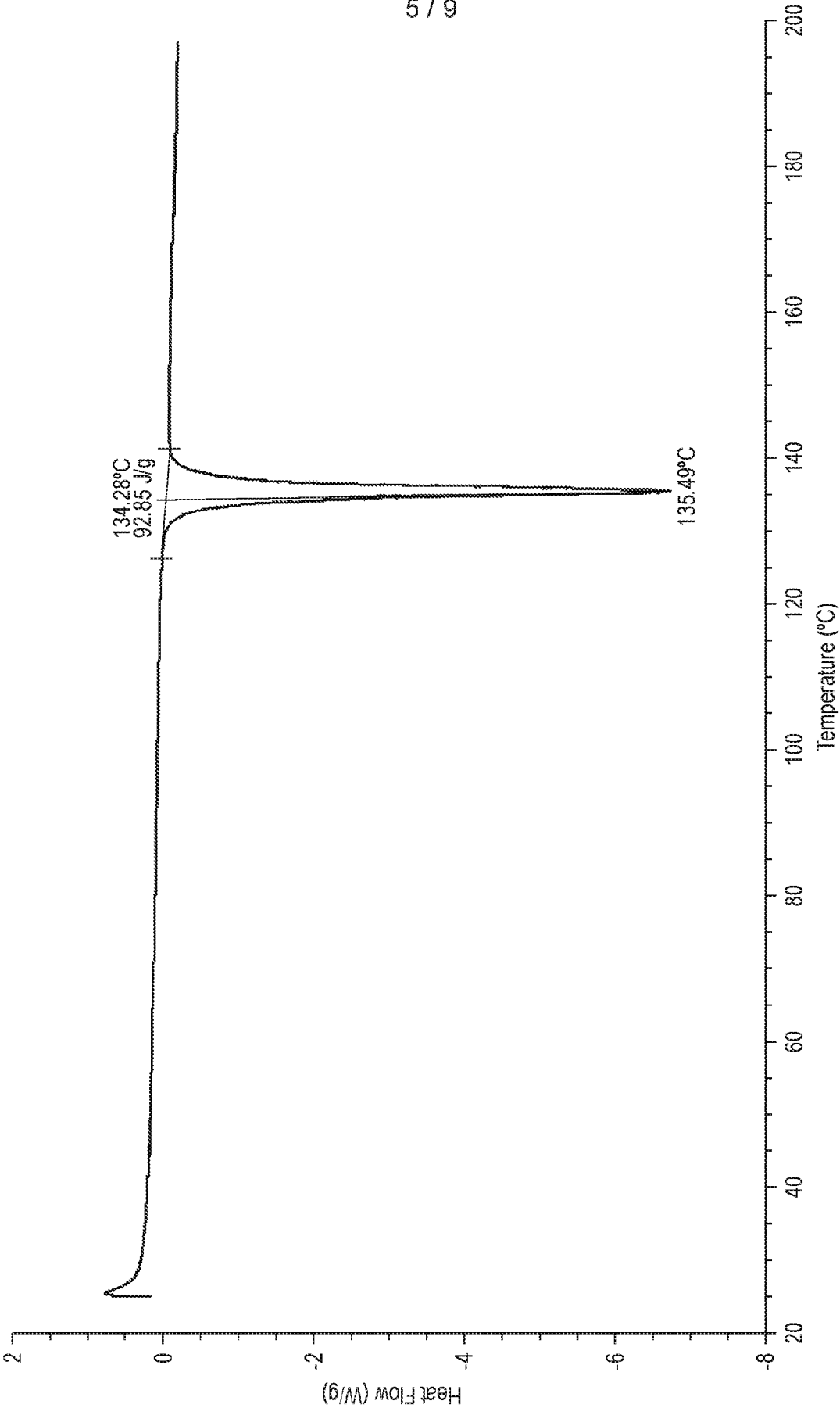
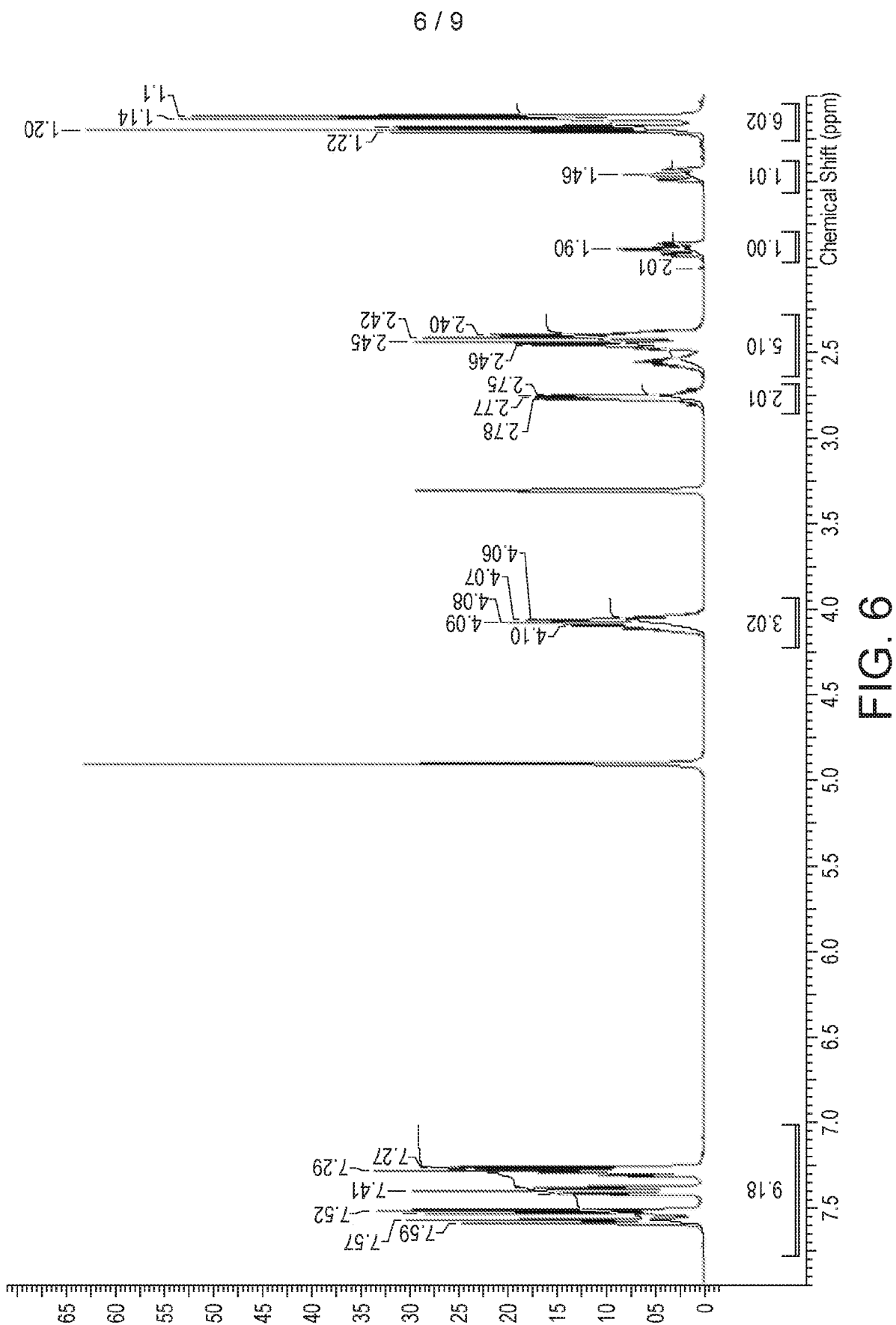
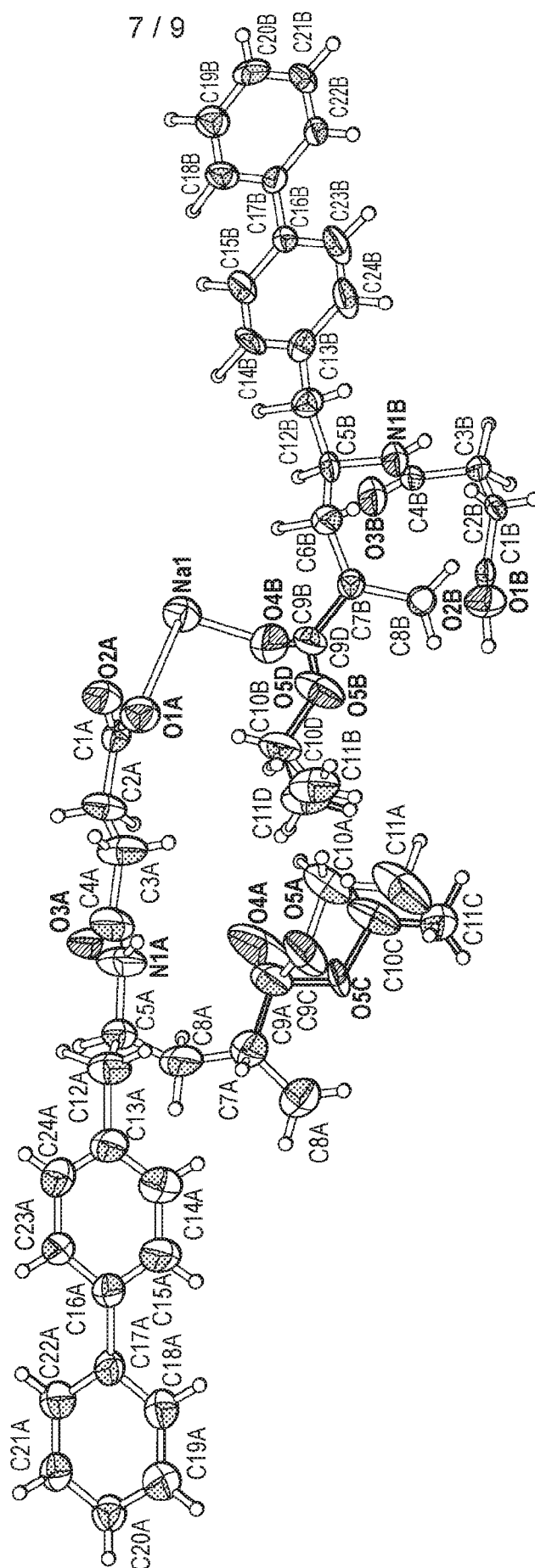


FIG. 5





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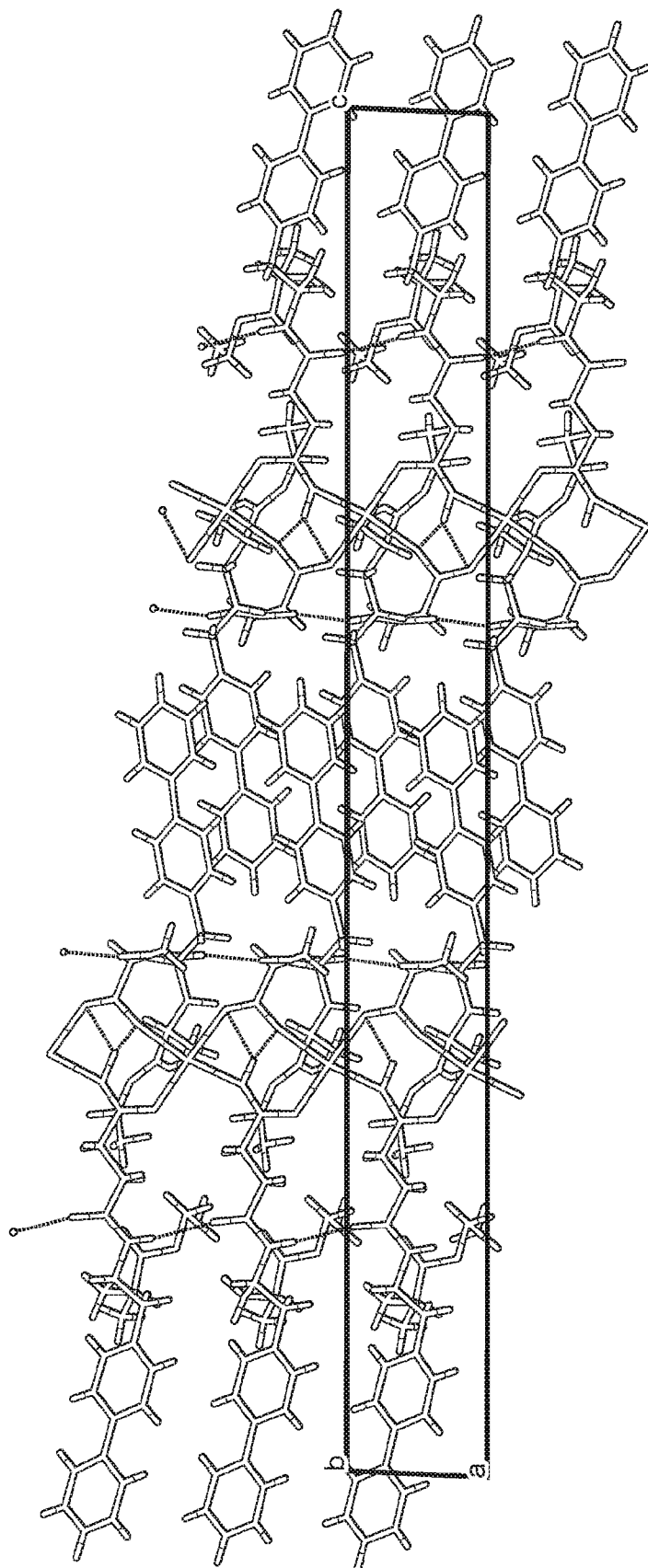


FIG. 8

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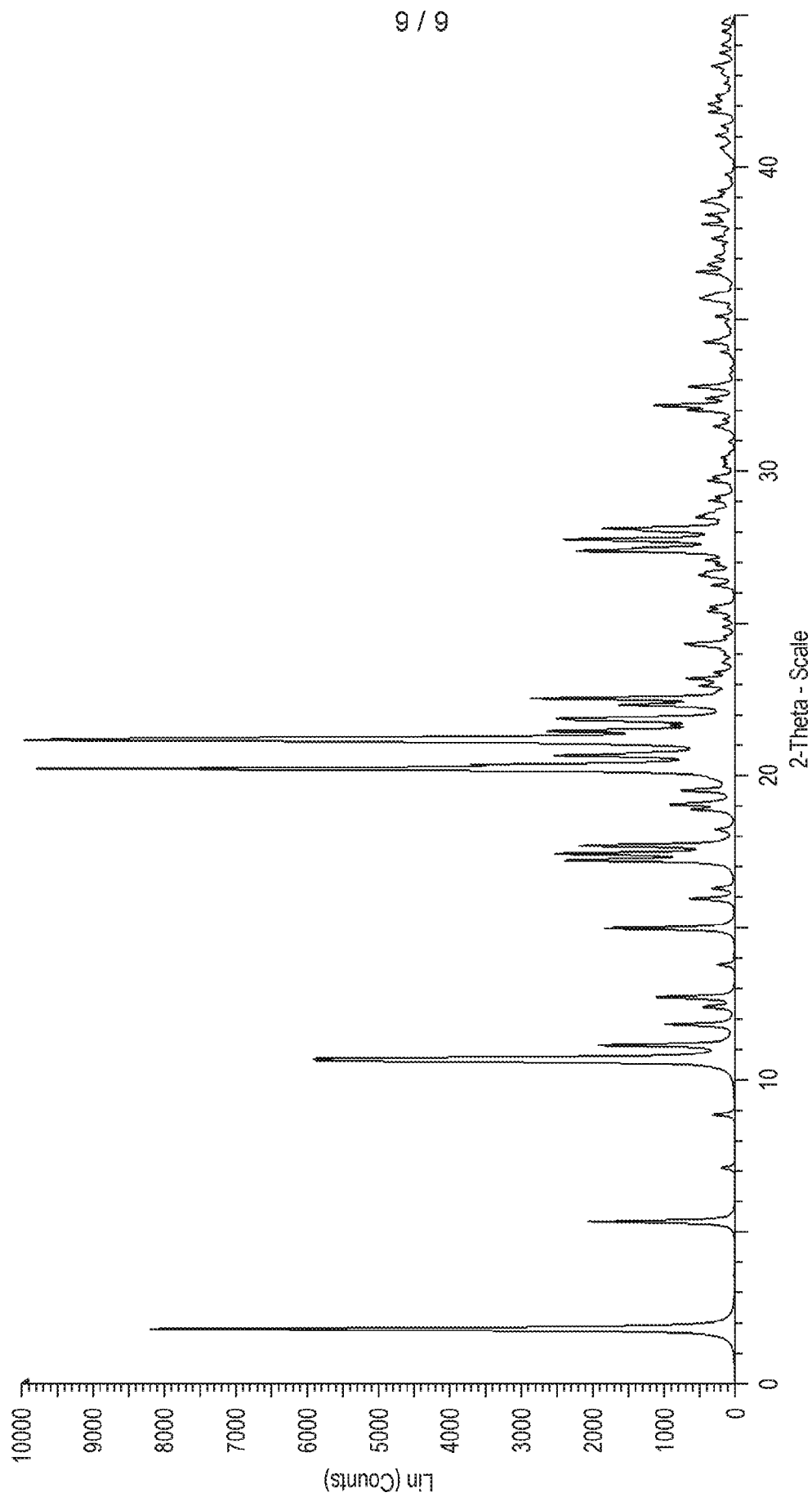


FIG. 9

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2019/051696

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C233/47 C07D257/04
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07D

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

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

EPO-Internal, CHEM ABS Data, WPI Data

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Further documents are listed in the continuation of Box C.



See patent family annex.

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Date of the actual completion of the international search

5 August 2019

Date of mailing of the international search report

16/09/2019

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/GB2019/051696

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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