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(54) Title: PREPARATION OF SACUBITRIL AND SALT THEREOF AND NOVEL COMPOUNDS USED IN THE PROCESS

(57) Abstract: The invention provides a process for preparing sacubitril. The present invention also provides a novel salt of sacubitril and its crystalline form. The invention further provides crystalline N-(3-carboxy-1- oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salts. Also provided is a a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4- amino-(2R)-methylbutanoic acid ethyl ester.

PREPARATION OF SACUBITRIL AND SALT THEREOF AND NOVEL COMPOUNDS USED IN THE PROCESS

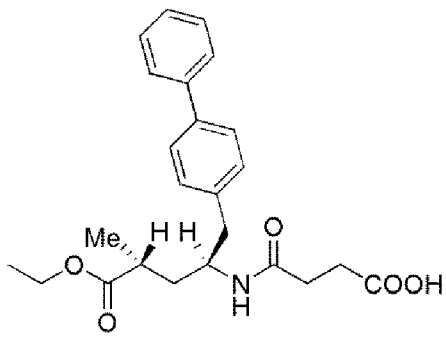
Field

The invention generally relates to methods of preparing a compound, in particular a pharmaceutical compound and more specifically a NEP inhibitor. The invention also relates to pharmaceutical compositions comprising such compounds, processes, starting materials and intermediates for preparing such compounds.

Introduction

Neprilysin (neutral endopeptidase, EC 3.4.24.11) (NEP), is a(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester is an endothelial membrane bound Zn^{2+} metallopeptidase found in many organs and tissues, including the brain, kidneys, lungs, gastrointestinal tract, heart, and the peripheral vasculature. NEP degrades and inactivates a number of endogenous peptides, such as enkephalins, circulating bradykinin, angiotensin peptides, and natriuretic peptides, the latter of which have several effects including, for example, vasodilation and natriuresis/diuresis, as well as inhibition of cardiac hypertrophy and ventricular fibrosis. Thus, NEP plays an important role in blood pressure homeostasis and cardiovascular health.

The present invention is related to the preparation of the NEP inhibitor sacubitril (Formula I). Sacubitril is (2R,4S)-5-biphenyl-4-yl-4-(3-carboxy-propionylamino)-2-methyl-pentanoic acid ethyl ester, also named N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.



(I)

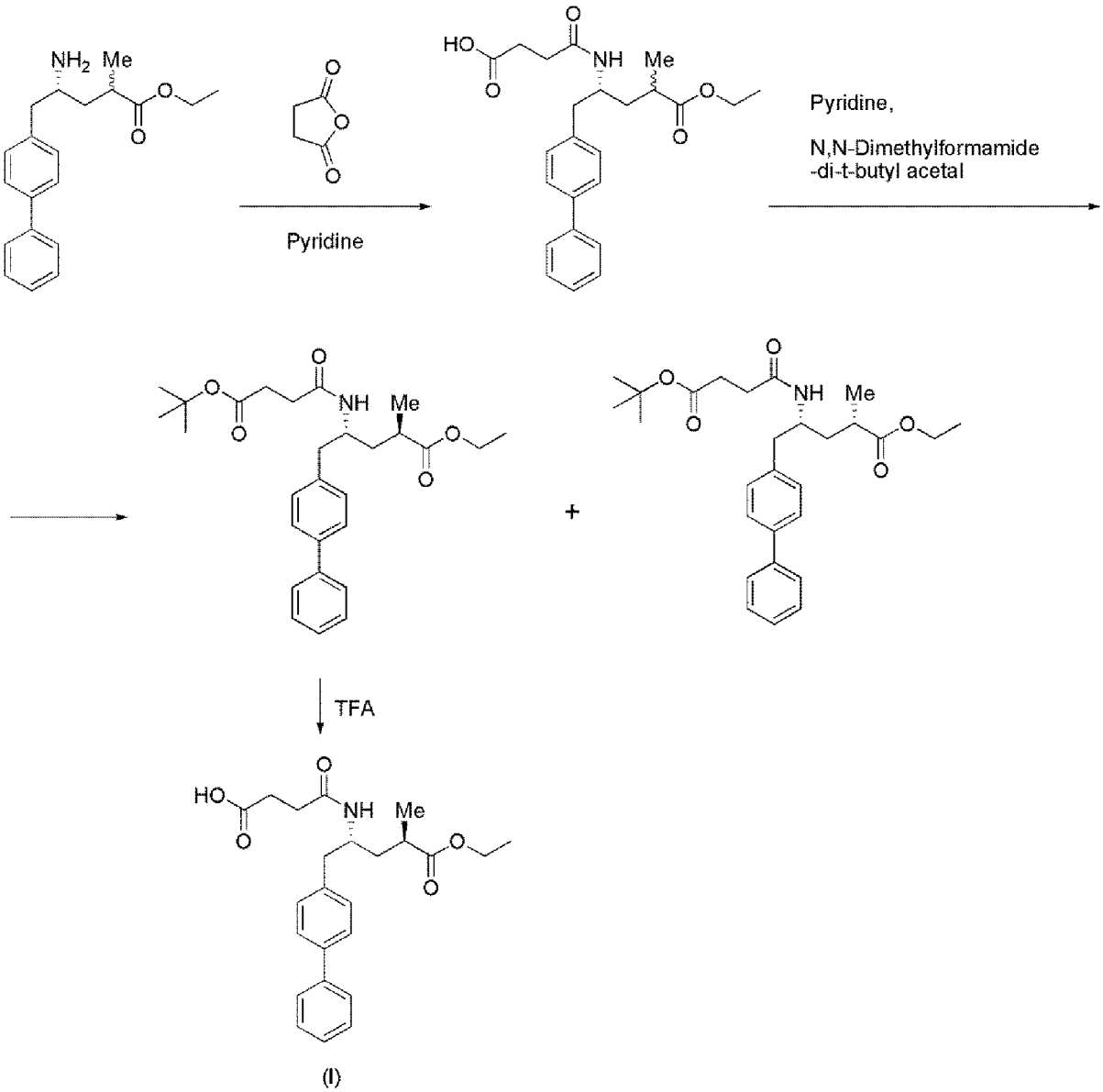
Sacubitril

The use of sacubitril for treating cardiovascular disorders is described in U.S. Patent No. 5,217,996. Sacubitril is useful as a neutral endopeptidase (NEP) inhibitor, e.g. as inhibitors of the ANF-degrading enzyme in mammals, which prolong and potentiate the diuretic, natriuretic and vasodilator properties of ANF in mammals by inhibiting the degradation thereof to less active metabolites. In particular, sacubitril is useful for the treatment of conditions and disorders responsive to the inhibition of neutral endopeptidase EC 3.4.24.11, particularly cardiovascular disorders, such as hypertension, renal insufficiency including edema and salt retention, pulmonary edema and congestive heart failure.

U.S. Patent No. 8,877,938 discloses trisodium sacubtril-valsartan hemipentahydrate in crystalline form, a dual-acting compound where the angiotensin receptor blocker and neutral endopeptidase inhibitor are linked via non-covalent bonding.

U.S. Patent No. 7,468,390 discloses pharmaceutical composition of valsartan or a pharmaceutically acceptable salt thereof with sacubitril or a pharmaceutically acceptable salt thereof.

U.S. patent No. 5,217,996 discloses synthesis of sacubitril isolated as sodium salt. Processes for preparing sacubitril is presented by the following Scheme I:



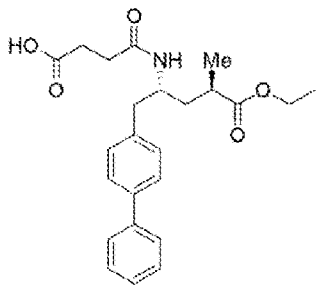
Scheme I

A major drawback of the process disclosed in U.S. Patent No. 5,217,996 is that it involves using a diasteromeric mixture of (4*S*)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester with a ratio of 80:20. The compound, upon treatment with succinic anhydride, gives N-(3-carboxy (*t*)butoxy-1-oxopropyl)-(4*S*)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester. The (*S,R*) and (*S,S*) isomers must then be

separated by column chromatography. Subsequently, separated N-(3carboxy (*t*)butoxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester is treated with trifluroacetic acid (TFA) to obtain sacubitril of compound of formula I. This process cannot be easily scaled up as it involves column chromatography for product separation, which requires specialized equipment that is relatively expensive and time-consuming to operate. Furthermore, chiral separation of unwanted (S,S) isomer is carried out just one step before obtaining final product, which has impact on the overall yield.

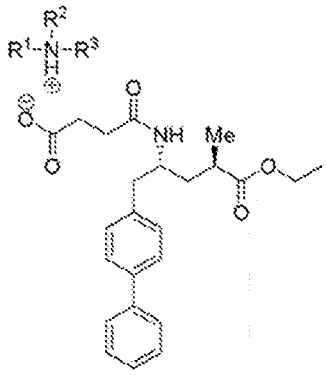
Summary

The present invention relates to a process for preparing sacubitril, more specifically, a process for synthesizing the compound of formula I:



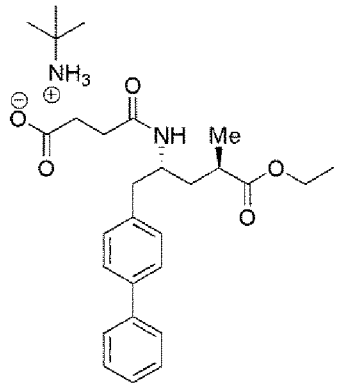
(I)

The present invention also provides novel salts of sacubitril and its crystalline form. The invention thus provides amine salts of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester with the general formula (III):



(III)

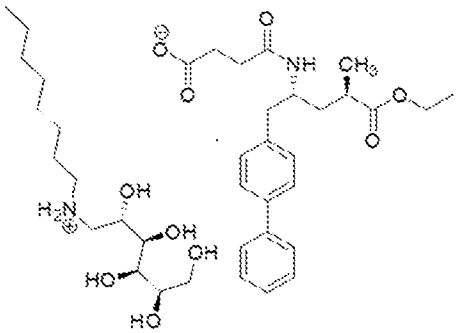
In a particular example, the invention provides crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt compound of formula (III):



(III)

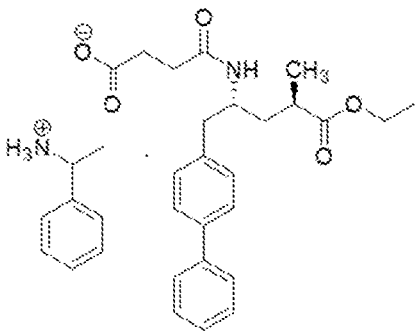
In general, the amine salt can comprise an amine with the general formula $NR^1R^2R^3$, wherein at least one of the groups R^1, R^2, R^3 is not hydrogen or a C_1-C_6 alkyl group. The amine salt of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester can also be an amine salt that is not one of tert-butylamine, isopropylamine, cyclohexylamine, n-propylamine and dicyclohexylamine.

In one embodiment, the amine salt is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt of formula III-b:



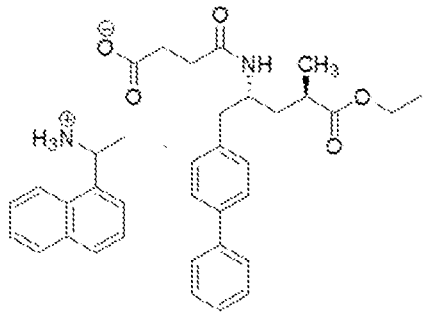
III-b

In another embodiment, the amine salt is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl salt of formula III-b:



III-c

In another embodiment, the amine salt is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphtyl ethyl amine salt of formula III-d:



III-d

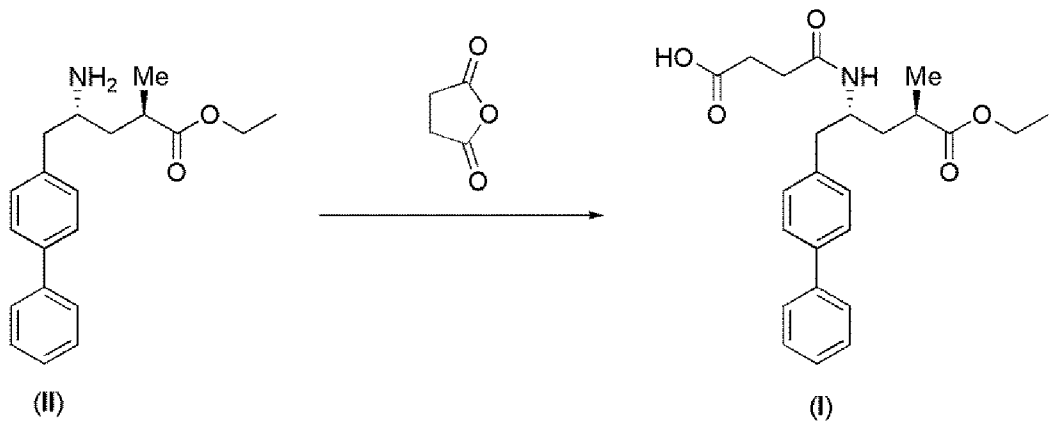
The present invention is in part based on the use of novel (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester to synthesize sacubitril. Using of diastereomerically pure chiral isomer allows a substantially optically pure of sacubitril or salt thereof to be obtained, providing numerous advantages over presently known synthesis routes.

As used herein, "substantially pure" refers to at least about 95% purity, more preferably at least about 96% and most preferably at least about 98% purity or at least about 99% purity.

U.S. Patent No. 8,877,938 uses about 95% pure Sacubitril for the preparation of Trisodium Sacubtril-valsartan hemipentahydrate. In contrast, it is possible to provide substantially pure sacubitril having purity more than 99.5% according to the present invention. As used herein, the term "about" refers to a range of values ± 10% of a specified value. For example, the phrase "about 95" includes ± 10% of 95 and 95 as such.

The present invention also provides process for preparing pure sacubitril which has purity more than 95% including more than 96%, more than 97%, more than 98%, more than 99% and up to 99.5% or more.

In particular, the present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (II).



(II) (I)

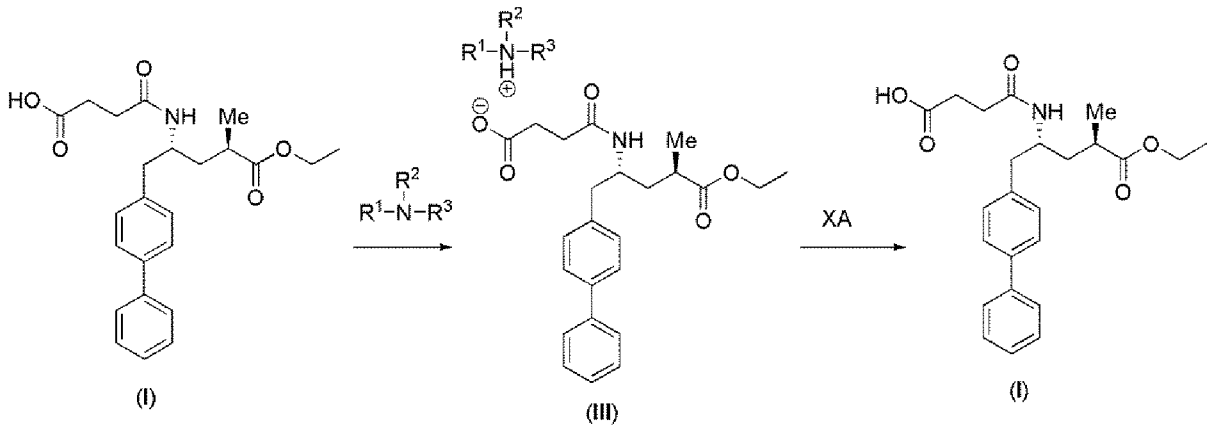
Scheme (II)

The present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I from the reaction mixture.

The present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (III).



Scheme (III)

wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

In particular, the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with amine;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt from the reaction mixture;

c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;

d) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

In some preferred embodiments, one or more of R^1, R^2 and R^3 is not H or a C_1-C_6 alkyl group. Thus the amine salt according to formula (III) can preferably comprise an amine of formula $NR^1R^2R^3$ wherein R^1, R^2 and R^3 are independently hydrogen or alkyl groups, with the provisio that at least one of the groups is not H or a C_1-C_6 alkyl group.

In one embodiment, the amine in Scheme III is n-octyl-D-glucamine. In another embodiment, the amine is phenyl ethyl amine. In another embodiment, the amine is naphtyl ethyl amine.

It can be convenient to perform the reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with an amine in a suitable organic solvent. Preferably the solvent can be a polar solvent, more preferably a non-aqueous polar solvent. In some preferred embodiments, the solvent is a non-protic non-aqueous polar solvent. Preferred polar solvents can include tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide. In a preferred embodiment, the solvent is acetone.

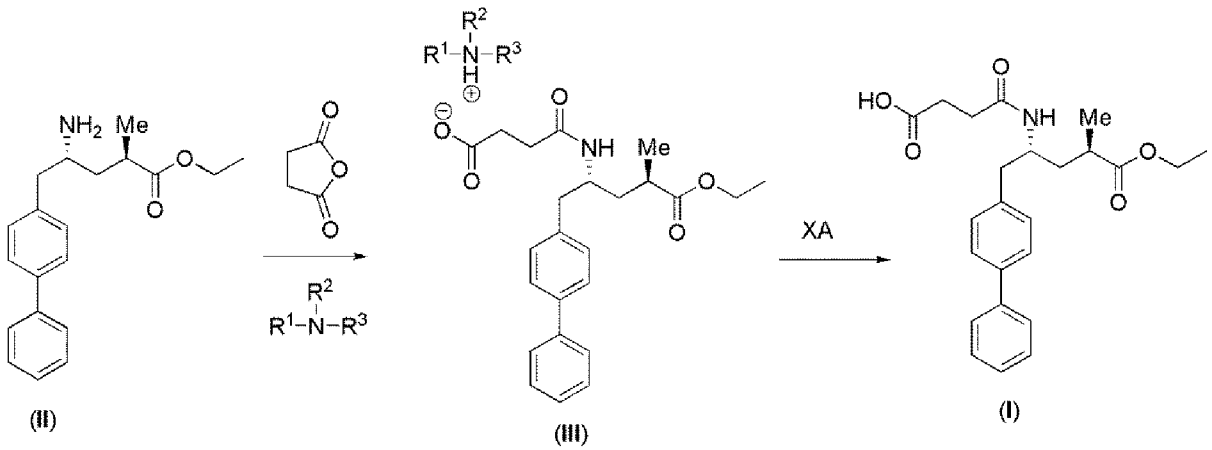
However, the inventors have also discovered that the reaction can be performed in an aqueous solution, which eliminates the need to use organic solvents that can be toxic and costly to remove. For example, the reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with t-butyl amine proceeds to completion in high yield using only water as solvent.

Yet another advantage of the invention is the possibility to perform the reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester with an amine in the absence of any additional solvent, which is particularly feasible for amines that are in a liquid state at or near room temperature. This means that the reaction involves mixing the ethyl ester with a neat amine, as for example manifested by the reaction of t-butyl amine with N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.

The possibility of running the reaction in the absence of an organic solvent, or even without the use of any solvent at all, leads to reduced cost of the process, increased productivity on industrial scale and environmental advantage, since there is no need to remove and discard toxic organic solvents.

Conversion of the amine salt from step (b) to pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester can be conveniently performed by reacting the addition salt with an acid, such as hydrochloric acid or other suitable organic or inorganic acids.

The present invention also provides a process of preparing compound of formula (I) illustrated by the following scheme (IV).



Scheme (IV)

wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

In some preferred embodiments, one or more of R^1, R^2 and R^3 is a group that is not H or a C_1-C_6 alkyl group. Thus the amine salt according to formula (III) can preferably comprise an amine that independently contains hydrogen or alkyl groups, with the provisio that at least one of the groups is not H or a C_1-C_6 alkyl group.

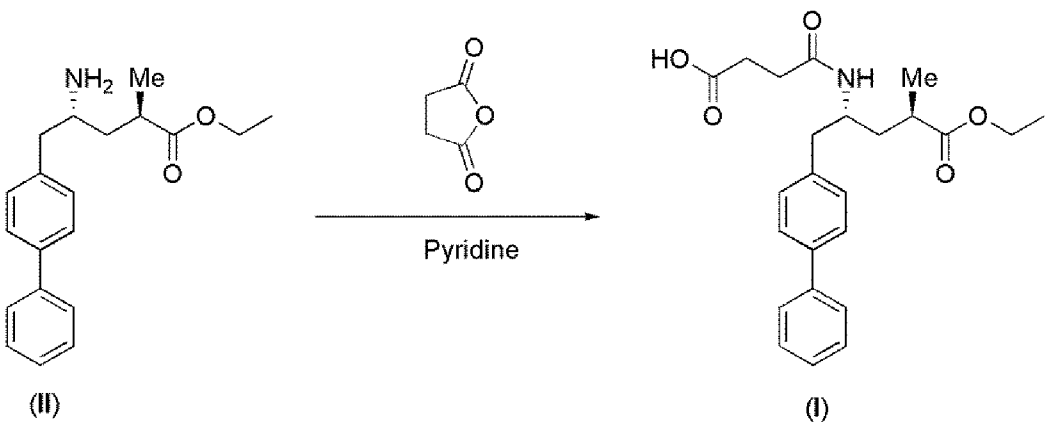
In one embodiment, the amine in Scheme IV is n-octyl-D-glucamine. In another embodiment, the amine is phenyl ethyl amine. In another embodiment, the amine is naphtyl ethyl amine.

The present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of amine;
b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt of formula III from the reaction mixture;
c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
d) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

The amine is preferably an amine with formula $NR^1R^2R^3$, wherein R^1, R^2 and R^3can be selected from H or an alkyl group. Preferably, one or more of R^1, R^2 and R^3 is not a C_1-C_6 alkyl group. Even more preferably, the amine is selected from n-octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.

The present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (V).



(II) (I)

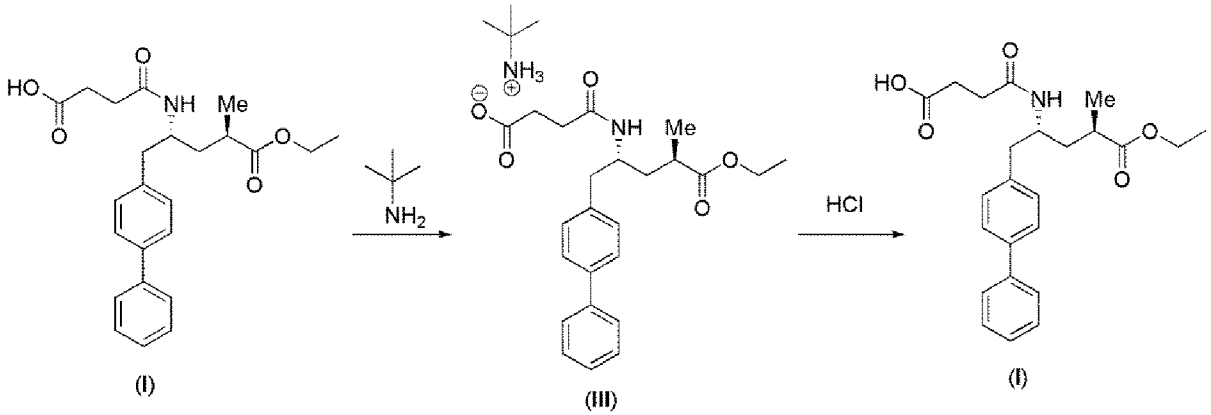
Scheme (V)

In particular, the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of pyridine;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I from the reaction mixture.

The present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (VI).



Scheme (VI)

In particular the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine;
b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt from the reaction mixture;
c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt with acid;
d) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

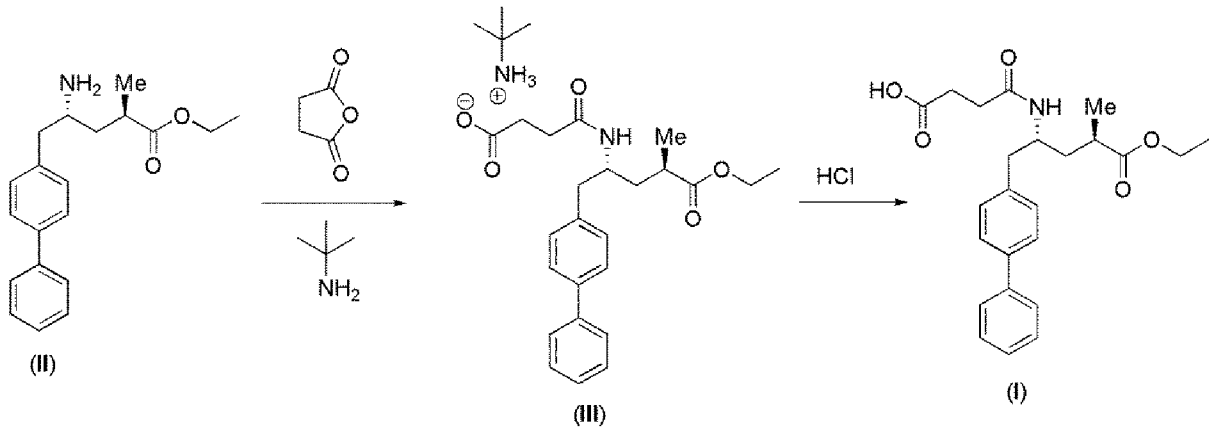
The reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine can be performed in a suitable organic solvent.

It can however be convenient to perform the reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine in the absence of a solvent. Thus, in one embodiment according to the invention, step a) in the above scheme comprises reacting N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine, without the addition or inclusion of a solvent. The product amine salt of formula (III) can be isolated directly from the reaction mixture.

Alternatively, the reaction of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine can also be performed in an aqueous solution.

The product amine salt can be washed using a suitable organic solvent, such as acetone or other polar solvent.

The present invention further provides a process of preparing compound of formula (I) illustrated by the following scheme (VII).



Scheme (VII)

In particular, the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of with *t*-butyl amine to form N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester with *t*-butyl amine salt;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt from the reaction mixture;

c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt with acid;

d) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

Included in the invention is also the novel use of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof to produce sacubitril.

The invention further provides novel salts of sacubitril. In particular, the invention provides novel N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salts, specifically novel N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt. The invention also provides N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-Glucamine salt, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt

and N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.

The invention further provides crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt. Preferably, the compound is characterized by

a. at least one, such as a least 2, at least 3, at least 4, at least5, at least 6, at least , at least 7, at least 8, at least 9, or all of X-ray diffraction peaks with 2-theta values 4.11, 8.06, 9.88, 15.70, 16.16, 17.63, 17.78, 19.76, 20.23, and 23.10; and/or
b. a differential scanning calorimetric thermogram with a endothermic peak at about 133.7°C or 133.7+/- 3°C.

It should be appreciated and is well known to the skilled person that the powder x-ray diffraction pattern can have 2-theta values that show a slight deviation from the above recited values. Thus, in one embodiment, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt of the invention is characterized by at least one, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or all of X-ray diffraction peaks with 2-theta values 4.11+/- 0.1°, 8.06+/- 0.1°, 9.88+/- 0.1°, 15.70+/- 0.1°, 16.16+/- 0.1°, 17.63+/- 0.1°, 17.78+/- 0.1°, 19.76+/- 0.1°, 20.23+/- 0.1° and 23.10 +/- 0.1°, and a differential scanning calorimetric thermogram with an endothermic peak at about 133.7+/- 3°C. More preferably, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt is characterized by powder X-ray diffraction peaks with 2-theta values 4.11+/- 0.1°, 8.06+/- 0.1°, 9.88+/- 0.1°, 15.70+/- 0.1°, 16.16+/- 0.1°, 17.63+/- 0.1°, 17.78+/- 0.1°, 19.76+/- 0.1°, 20.23+/- 0.1° and 23.10 +/- 0.1° and a differential scanning calorimetric thermogram with an endothermic peak at about 133.7+/- 3°C.

The invention also provides crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-Glucamine salt that is characterized by at least one, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or all of X-ray diffraction peaks with 2-theta values 4.40+/- 0.1°, 8.68+/- 0.1°, 10.37+/- 0.1°, 10.68+/- 0.1°, 12.81+/- 0.1°, 13.36+/- 0.1°, 14.48+/- 0.1°, 16.81+/- 0.1°, 16.99+/- 0.1°, 18.12+/-0.1°, 18.87+/-0.1°, 19.00+/-0.1°, 19.37+/-0.1°, 19.85+/-0.1°, 20.81+/-0.1°, 21.32+/-0.1°, 21.50+/-0.1° and 22.51+/-0.1°. Also provided is crystalline crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-Glucamine salt that is characterized by X-ray diffraction spectrum as shown in FIG. 4. The compound can also, or additionally, be characterized by a differential scanning calorimetric thermogram with an endothermic peak at about 126.7+/- 3°C, and an IR spectrum as shown in FIG. 5.

Further provided is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl phenyl ethyl amine salt that is characterized by at least one, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or all of X-ray diffraction peaks with 2-theta values 7.53+/- 0.1°, 8.36+/- 0.1°, 8.55+/- 0.1°, 10.93+/- 0.1°, 15.13+/- 0.1°, 15.96+/- 0.1°, 16.80+/- 0.1°, 17.36+/- 0.1°, 17.68+/- 0.1°, 18.82+/- 0.1°, 19.40+/-0.1°, 20.58+/-0.1°, 22.01+/-0.1°, 23.11+/-0.1°, 24.30+/-0.1°, 24.90+/-0.1°, 25.88+/-0.1°, 26.45+/- 0.1°, 28.08+/-0.1°, 28.66+/-0.1°, 28.96+/-0.1° and 29.34+/-0.1°. Also provided is crystalline crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl

amine salt that is characterized by X-ray diffraction spectrum as shown in as shown in FIG. 7. The compound can also, or additionally, be characterized by a differential scanning calorimetric thermogram with an endothermic peak at about 128.7+/- 3°C, and an IR spectrum as shown in FIG. 8.

Further provided is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl naphthyl ethyl amine salt that is characterized by at least one, such as at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or all of X-ray diffraction peaks with 2-theta values 3.76+/- 0.1°, 6.84+/- 0.1°, 7.17+/- 0.1°, 8.39+/- 0.1°, 9.20+/- 0.1°, 11.07+/- 0.1°, 13.70+/- 0.1°, 14.29+/- 0.1°, 15.11+/- 0.1°, 16.10+/- 0.1°, 16.79+/-0.1°, 17.75+/-0.1°, 18.01+/-0.1°, 18.45+/-0.1°, 18.90+/-0.1°, 19.92+/-0.1°, 20.29+/-0.1°, 20.44+/- 0.1°, 21.31+/-0.1°, 21.67+/-0.1°, 22.31+/-0.1°, 22.54+/-0.1°, 25.14+/-0.1°, 25.39+/-0.1°, 26.23+/-0.1°, 27.00+/- 0.1°, 27.93+/-0.1° and 30.03+/-0.1°. Also provided is crystalline crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt that is characterized by X-ray diffraction spectrum as shown in as shown in FIG. 10. The compound can also, or additionally, be characterized by a differential scanning calorimetric thermogram with an endothermic peak at about 138.1+/- 3°C, and an IR spectrum as shown in FIG. 11.

The present invention also provides a pharmaceutical composition comprising N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester salt thereof prepared by any of the processes described herein. In one embodiment, the composition comprises N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt. In another embodiment, the composition comprises N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt. In another embodiment, the composition comprises N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt. In another embodiment, the composition comprises N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.

The present invention further provides a process of preparing trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate comprising:

i) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with valsartan;

ii) treating the reaction mixture with an aqueous base, such as an aqueous sodium hydroxide solution, and

iii) isolating trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate from the resulting reaction mass.

The N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt can be any amine salt as disclosed herein. For example, the amine salt can be a t-butyl salt, an n-octyl-d-glucamine salt, a phenyl ethyl amine salt, or a naphtyl ethyl amine salt of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.

Included in the present invention is also a process of preparaing trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate comprising

- treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester *t*-butyl amine salt with valsartan in presence of aqueous sodium hydroxide solution, and

- isolating trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate from reaction mass.

The advantage of the above process is that the preparation of sacubitril from sacubitril amine salt can be avoided, since the addition salt can directly be used for making the complex with valsartan. Furthermore, the amine salts are crystalline solid materials while sacubitril is oily. Hence, the handling of the addition salt is easy, making it convenient for a direct reaction with valsartan to generate sacubitril-valsartan hemipentahydrate complex.

The above features along with additional details of the invention, are described further in the examples below, which are intended to further illustrate the invention but are not intended to limit its scope in any way.

Brief Description of the Drawings

The skilled person will understand that the drawings, described below, are for illustration purposes only. The drawings are not intended to limit the scope of the present teachings in any way.

FIG. 1 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt by X-ray diffraction (XRD), as obtained by the process of the invention.

FIG. 2 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt, as obtained by the process of the invention.

FIG. 3 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt, as obtained by the process of the invention.

FIG. 4 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt by X-ray diffraction (XRD), as obtained by the process of the invention.

FIG. 5 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt, as obtained by the process of the invention.

FIG. 6 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt, as obtained by the process of the invention.

FIG. 7 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt by X-ray diffraction (XRD), as obtained by the process of the invention.

FIG. 8 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt, as obtained by the process of the invention.

FIG. 9 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt, as obtained by the process of the invention.

FIG. 10 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt by X-ray diffraction (XRD), as obtained by the process of the invention.

FIG. 11 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt, as obtained by the process of the invention.

FIG. 12 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt, as obtained by the process of the invention.

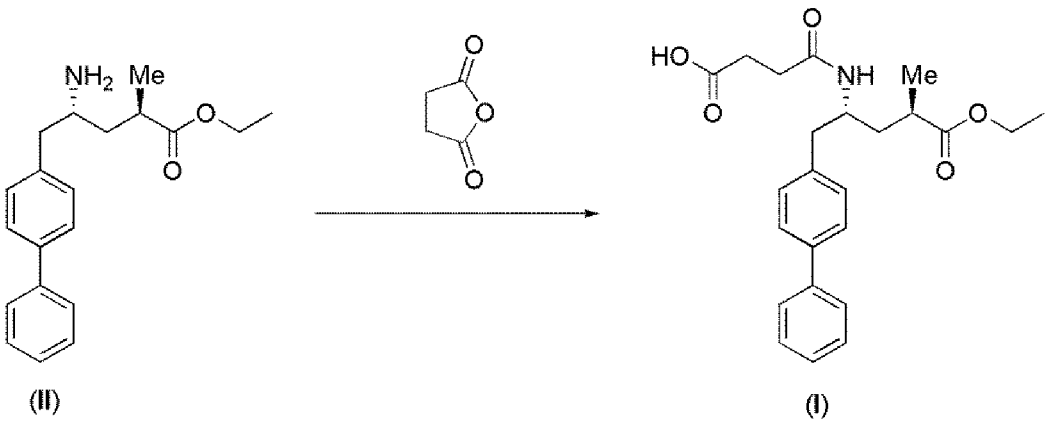
Description of Various Embodiments

In the following, exemplary embodiments of the invention will be described, referring to the figures. These examples are provided to provide further understanding of the invention, without limiting its scope.

In the following description, a series of steps are described. The skilled person will appreciate that unless required by the context, the order of steps is not critical for the resulting configuration and its effect. Further, it will be apparent to the skilled person that irrespective of the order of steps, the presence or absence of time delay between steps, can be present between some or all of the described steps.

As used herein, including in the claims, singular forms of terms are to be construed as also including the plural form and vice versa, unless the context indicates otherwise. Thus, it should be noted that as used herein, the singular forms “a,” “an,” and “the” include plural references unless the context clearly dictates otherwise.

The present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (II).



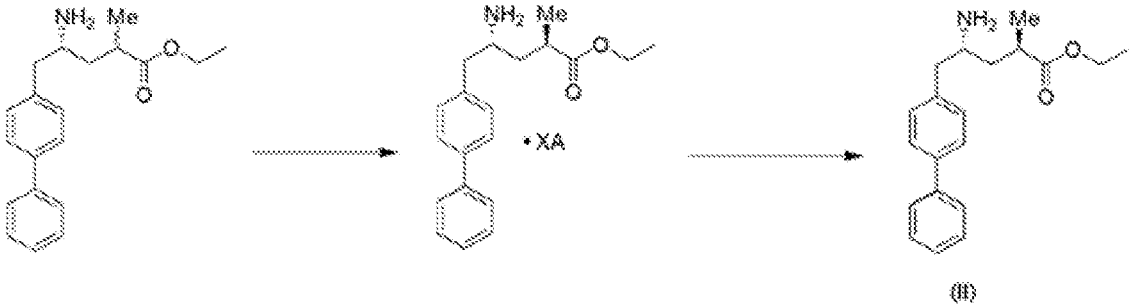
(II) (I)

Scheme (II)

The first step of the synthesis is to treat (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof with succinic anhydride.

Compound of formula II

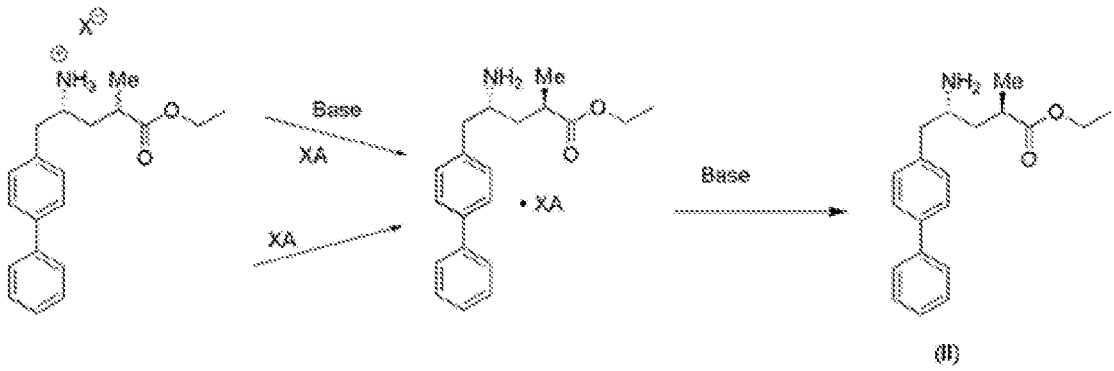
According to the present invention, (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof can be obtained by preparing (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester from (4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester illustrated by the following scheme.



wherein XA is a chiral acid, preferably a chiral organic acid.

The chiral acid can typically be selected from the group consisting of mandelic acid (2-hydroxy-2-phenylacetic acid), tartaric acid (2,3-dihydroxybutanedioic acid), di-p-toluyl tartaric acid (2,3-bis[(4-methylbenzoyl)oxy]butanedioic acid), dibenzoyl tartaric acid (2,3-dibenzoyloxybutanedioic acid), camphor sulfonic acid ((7,7-dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)methanesulfonic acid) and the like.

The compound of formula II can also be produced by the synthetic routes illustrated in the following scheme.



wherein X^- is the anion of the organic or inorganic acid, and XA is any chiral acid, preferably a chiral organic acid.

The salt of (4S)-(p-phenylphenylmethyl)-4-amino-2-methylbutanoic acid ethyl ester may be first treated with base depending on the conjugated acid of the acid addition salt. If it is a strong conjugate acid, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, oxalic acid, maleic acid, malonic acid and the like, the acid addition salt is treated with base before treatment with the chiral organic acid. On the other hand, in case of acid addition salt of weak conjugate acid, such as mandelic acid, acetic acid, succinic acid, propionic acid, crotonic acid, lactic acid, formic acid, glutaric acid, adipic acid, benzoic acid and the like, the acid addition salt does not need to be treated with base before treatment with the chiral organic acid.

Preferably, the salt of compound II is (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester D-(-)-tartrate.

Crystalline (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester D-(-)-tartrate may be characterized by at least one of

a) powder X-ray diffraction peaks with 2-theta 5.59, 8.63, 11.13, 14.82, 16.22, 16.82, 18.45, 19.86, 20.73 and 21.29, and/or

b) a differential scanning calorimetric thermogram with a endothermic peak at about 177°C.

Treatment of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof with succinic anhydride may be carried out in base, more preferably in an organic base. The base neutralizes the salt as well as maintains the basic condition of the reaction which enhances reaction rate.

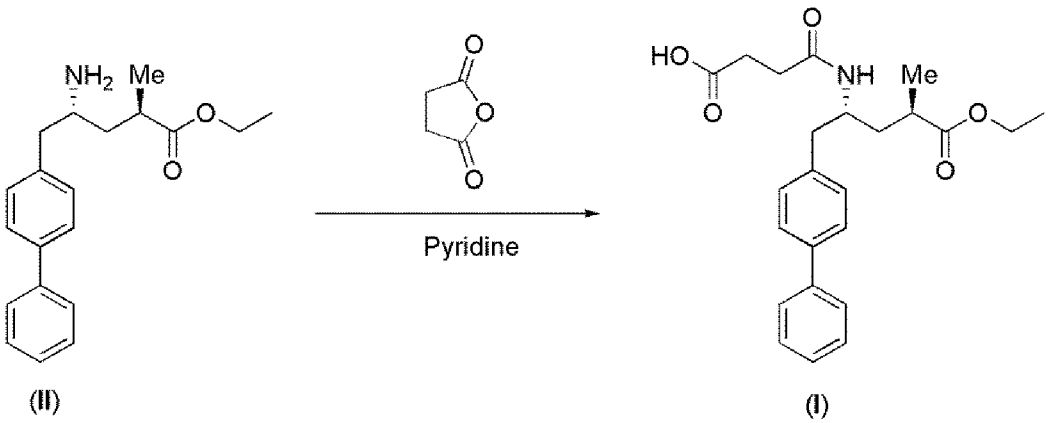
Examples of organic bases that may be used include but are not limited to triethylamine, tributylamine, diisopropylethylamine, diethylamine, tert-butyl amine, N-methylmorpholine, 4-(N,N-dimethylamino)pyridine and pyridine. Preferably, the base is pyridine, TEA, t-butyl amine, sodium carbonate, sodium bicarbonate or sodium acetate.

Most preferably, treatment of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof with succinic anhydride is carried out in the presence of pyridine.

If the compound of formula II is present in the form of salt, the salt is preferably selected from the list of tartaric acid, dibenzoyl tartaric acid, or di-para-toluoyl tartaric acid, mandelic acid and camphor sulfonic acid. Preferably, (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester is present in the form of tartrate salt.

In the follow step, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt is isolated from the reaction mixture. Standard work-up procedures s known in the art can be employed. These typically include removal of solvents, preferably by evaporation, separating the reaction mixture into organic and aqueous layers by liquid-liquid extraction, and purification by filtration and recrystallization. For example, the solvent in the mixture may be first removed, preferably by evaporation under reduced pressure. Then, the solvent can be distilled from reaction mixture, for example under vacuum or partial vacuum.

Thus, the present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (V).



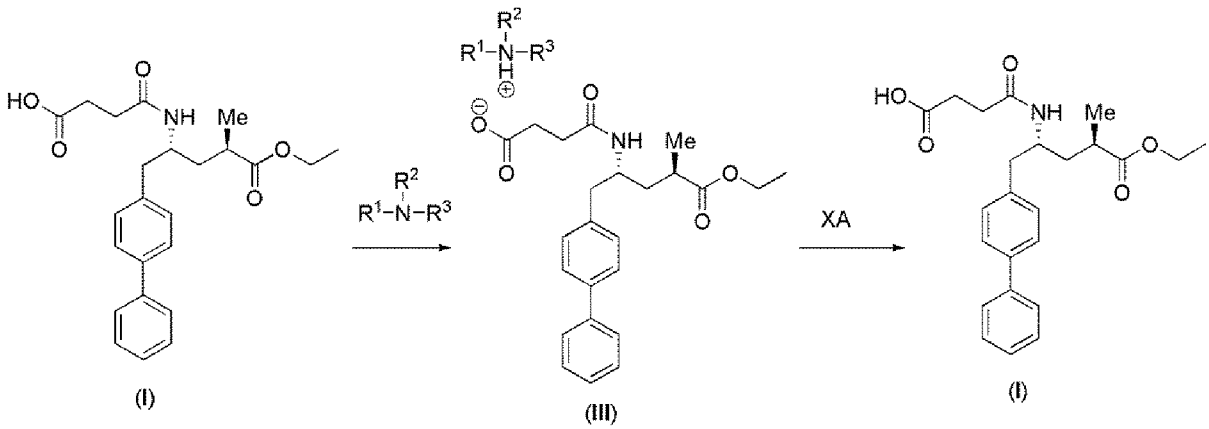
Scheme (V)

Preferably, step a) in scheme (II) is carried out in the presence of pyridine. Thus, the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of pyridine;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I from the reaction mixture.

The present invention provides a process of preparing substantially pure compound of formula (I) illustrated by the following scheme (III).



Scheme (III)

wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

It has been surprisingly found that the purity of sacubitril of compound of formula (I) was about 90%, which after formation of t-butyl amine salt of compound of formula (III) increases to about 98.5% and when it converted back to sacubitril of formula (I) purity increased to about 99.5%.

Thus, the present invention also provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with amine;

b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt from the reaction mixture;

c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;

d) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

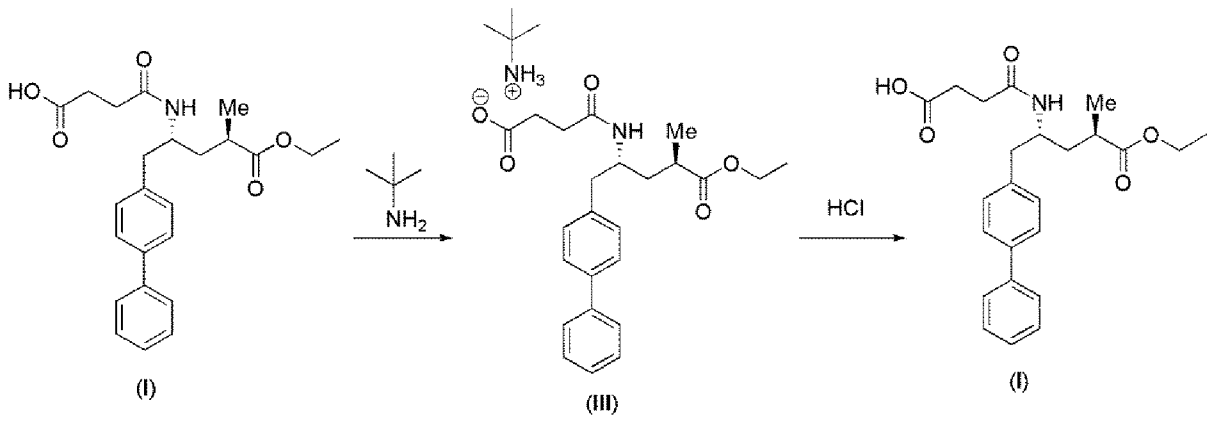
For example, in step a) N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof is treated with amine. Preferably, the amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.

In step b) the amine salt can be isolated from the reaction mixture using standard work-up procedures s known in the art or described in the present application.

In step c), isolated N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt is treated with acid, including inorganic acid or organic acids, to neutralize the amine salt, resulting in substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.

Representative examples acid with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, or with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid and the like. Preferbly, the acid is hydrochloric acid.

Preferably, the amine used in step a) of scheme (III) is *t*-butyl amine. Thus, the present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (VI).



Scheme (VI)

The present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

e) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with *t*-butyl amine;

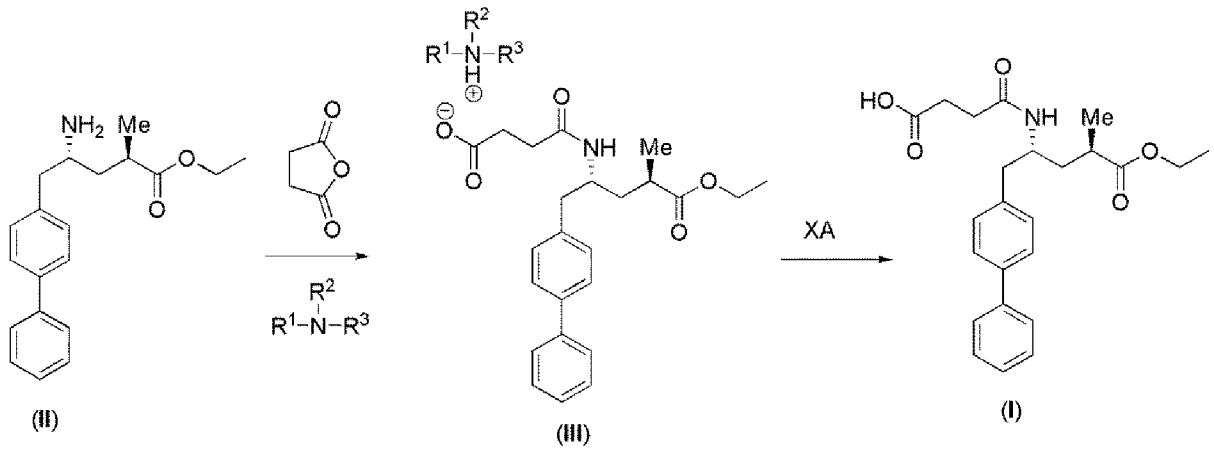
f) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt from the reaction mixture;

g) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt with acid;

h) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester obtained by the process described in the present application may have a purity ≥ 99%, such as ≥99.1%, ≥99.2%, ≥99.3%, ≥99.4% and ≥99.5%.

The present invention provides a process of preparing compound of formula (I) illustrated by the following scheme (IV).



Scheme (IV)

wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

The first step a) of the synthesis is to treat (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof with succinic anhydride in the presence of amine. It is within the skilled person in the art to determine which amine can be used. In general, any amine which is able to neutralize the salt can be used. Preferably, the amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, t-butyl amine.

When (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester treated is in the form of salt, the salt may be selected from the list of tartaric acid, dibenzoyl tartaric acid, or di-para-toluoyl tartaric acid,

mandelic acid and camphor sulfonic acid. Preferably, (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate is used.

The present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of amine;
b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt of formula III from the reaction mixture;
c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
d) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

In step b), N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt of formula III is isolated from the reaction mixture. Standard work-up procedures s known in the art can be employed.

In the following step c), isolated N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt is treated with acid, including inorganic acid or organic acids, to neutralize the amine, leading to formation of free N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

Representative examples acid with inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, nitric acid, and phosphoric acid, or with organic acids such as formic acid, acetic acid, propionic acid, oxalic acid, malonic acid, succinic acid, fumaric acid, maleic acid, lactic acid, malic acid and the like.

Preferably, the amine used in step a) of scheme (IV) is t-butyl amine salt. Thus, the present invention provides a method of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I, comprising:

a) treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of with *t*-butyl amine to form N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester with *t*-butyl amine salt;
b) isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt from the reaction mixture;
c) treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt with acid;
d) isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.

The inventors have discovered that N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester obtained by the process described in the present application may have a purity ≥ 99%, such as ≥99.1%, ≥99.2%, ≥99.3%, ≥99.4% and ≥99.5%.

Amine salts of sacubitril

The invention further provides novel crystalline forms of sacubitril salts.

Specifically, the invention provides N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt and crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt can be characterized by

a. at least one of X-ray diffraction peaks with 2-theta values 4.11, 8.06, 9.88, 15.70, 16.16, 17.63, 17.78, 19.76, 20.23, and 23.10; or
b. a differential scanning calorimetric thermogram with a endothermic peak at about 133.7+/- 3°C.

Preferably, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt is characterized by at least one of X-ray diffraction peaks with 2-theta values 4.11, 8.06, 9.88, 15.70, 16.16, 17.63, 17.78, 19.76, 20.23 and 23.10 and a differential scanning calorimetric thermogram with an endothermic peak at about 133.7+/- 3°C.

FIG. 1 and Table 1 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt by X-ray diffraction (XRD), as obtained by the invention.

Table 1

Pos. [°2Th.]	Height[cts]	FWHW[°2Th.]	d-spacing [Å]	Rel. Int. [%]
4.1078	410.42	0.0964	21.51072	6.74
8.0644	6090.33	0.0827	10.96369	100.00
8.7982	22.60	0.1653	10.05094	0.37
9.8756	1132.71	0.1033	8.95662	18.60
12.3426	215.42	0.1929	7.17139	3.54
12.6862	253.39	0.1653	6.97795	4.16
13.0629	488.94	0.1102	6.77755	8.03
13.9659	112.50	0.1378	6.34130	1.85
15.1536	534.27	0.1653	5.84685	8.77
15.7054	917.86	0.0620	5.64266	15.07
16.1609	1766.25	0.1102	5.48464	29.00
16.3355	819.84	0.0689	5.42641	13.46
16.5690	625.34	0.1696	5.35044	10.27
16.8372	342.84	0.1378	5.26582	5.63
17.6350	3201.64	0.0758	5.02934	52.57
17.7819	3417.88	0.1240	4.98814	56.12
19.0064	597.75	0.0964	4.66944	9.81
19.4116	958.71	0.1378	4.57288	15.74
19.6255	1180.38	0.0895	4.52351	19.38
19.7636	1502.09	1.5007	4.49221	24.66
20.2346	3372.32	0.1033	4.38870	55.37

21.4348	592.60	0.1929	4.14560	9.73
21.6570	796.92	0.1240	4.10357	13.09
22.0551	519.89	0.1102	4.03039	8.54
23.1051	1089.48	0.0689	3.84955	17.89
23.7847	231.85	0.2480	3.74107	3.81
24.5794	873.26	0.0964	3.62189	14.34
25.6517	338.44	0.1102	3.47286	5.56
26.0697	457.99	0.1102	3.41813	7.52
26.3150	460.21	0.1102	3.38682	7.56
27.3954	489.90	0.1102	3.25566	8.04
28.6540	314.32	0.3031	3.11545	5.16
29.1971	150.45	0.2204	3.05873	2.47
31.7402	182.28	0.2204	2.81923	2.99

FIG. 2 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt, as obtained by the process of the invention. Thus, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt may have an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 2.

The term "substantially similar" as used herein means an analytical spectrum, such as XRD pattern, 1H-NMR spectrum, FT-IR spectrum, Raman spectrum, TGA thermogram, etc., which resembles the reference spectrum to a great degree in both the peak locations and their intensity.

FIG. 3 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt, as obtained by the process of the invention. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt may have a differential scanning calorimetric thermogram substantially similar to a differential scanning calorimetric thermogram as depicted in Fig. 3.

The invention further provides N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt and crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt can be characterized by an X-ray diffraction pattern substantially as shown in Table 2 and FIG. 4 herein. The compound can also be characterized by

a. at least one of X-ray diffraction peaks with 2-theta values 4.40+/- 0.1°, 8.68+/- 0.1°, 10.37+/- 0.1°, 10.68+/- 0.1°, 12.81+/- 0.1°, 13.36+/- 0.1°, 14.48+/- 0.1°, 16.81+/- 0.1°, 16.99+/- 0.1°, 18.12+/-0.1°, 18.87+/-0.1°, 19.00+/-0.1°, 19.37+/-0.1°, 19.85+/-0.1°, 20.81+/-0.1°, 21.32+/-0.1°, 21.50+/-0.1° and 22.51+/-0.1°; and/or
b. a differential scanning calorimetric thermogram with a endothermic peak at about 126.7+/- 3°C.

Preferably, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt is characterized by at least one of X-ray diffraction peaks with 2-theta values 4.40, 8.68, 10.37, 10.68, 12.81, 13.36, 14.48, 16.81, 16.99, 18.12, 18.87, 19.00, 19.37, 19.85, 20.81, 21.32, 21.50 and 22.51; and a differential scanning calorimetric thermogram with an endothermic peak at about 126.7+/- 3°C.

FIG. 4 and Table 2 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt by X-ray diffraction (XRD), as obtained by the invention.

Table 2

Pos. [°2 theta]	d-spacing [A]	height [cts]	Area	Rel Int [%]
4.3972	20.09542	16884.11	1491.38	100.00
8.6843	10.18248	589.93	52.11	3.49
8.8003	10.04854	293.21	15.94	1.74
9.5376	9.27330	234.84	51.06	1.39
9.6361	9.17874	330.59	29.20	1.96
10.3749	8.52672	1394.18	75.78	8.26
10.6841	8.28062	1303.17	141.67	7.72
12.1787	7.26758	110.65	18.04	0.66
12.8159	6.90763	1844.63	125.34	10.93
13.3630	6.62600	737.45	70.15	4.37
14.2357	6.22172	421.95	45.87	2.50
14.4838	6.11570	709.44	77.13	4.20
15.4130	5.74904	450.93	30.64	2.67
15.6873	5.64912	103.80	8.30	0.61
16.2552	5.45300	490.27	59.96	2.90
16.8148	5.27279	578.50	70.75	3.43
16.9944	5.21746	542.26	58.95	3.21
17.6574	5.02301	308.59	50.32	1.83
18.1298	4.89319	1059.63	64.80	6.28
18.8737	4.70198	1716.69	174.97	10.17
19.0053	4.66971	740.31	1.97	4.38
19.3687	4.58290	824.48	84.03	4.88
19.8511	4.47261	1025.47	111.48	6.07
20.8065	4.26935	2247.96	274.93	13.31
21.3213	4.16741	2611.23	722.93	15.47
21.5032	4.13257	2996.12	325.72	17.75
22.0667	4.02830	547.54	89.05	3.24
22.5151	3.94908	1149.53	117.16	6.81
23.1052	3.84953	315.61	34.31	1.87
23.5143	3.78348	301.63	40.99	1.79
24.4876	3.63526	386.80	63.08	2.29
25.4190	3.50413	532.61	115.81	3.15
26.2413	3.39617	963.53	98.20	5.71
27.5593	3.23667	362.73	39.43	2.15
28.7217	3.10827	208.21	56.59	1.23
29.8803	2.99033	362.61	59.13	2.15
30.0883	2.97013	375.91	40.87	2.23
30.4801	2.93284	218.80	47.57	1.30

31.1487	2.87139	426.85	81.21	2.53
31.6734	2.82502	317.58	38.84	1.88
33.9008	2.64433	301.67	73.79	1.79

FIG.5 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt, as obtained by the process of the invention. Thus, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octhyl-D-glucamine salt can have an IR spectrum substantially similar to an IR spectrum as depicted in FIG.5.

FIG.6 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt, as obtained by the process of the invention. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-glucamine salt can have a differential scanning calorimetric thermogram substantially similar to a differential scanning calorimetric thermogram as depicted in FIG.6.

The invention further provides N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt and crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt can be characterized by an X-ray diffraction pattern substantially as shown in Table 3 and FIG. 7. The compound can also be characterized by

a. at least one of X-ray diffraction peaks with 2-theta values 7.53, 8.36, 8.55, 10.93, 15.13, 15.96, 16.80, 17.36, 17.68, 18.82, 19.40, 20.58, 22.01, 23.11, 24.30, 24.90, 25.88, 26.45, 28.08, 28.66, 28.96 and 29.34°; or
b. a differential scanning calorimetric thermogram with a endothermic peak at about 128.7+/- 3°C.

Preferably, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt is characterized by at least one of X-ray diffraction peaks with 2-theta values 7.53, 8.36, 8.55, 10.93, 15.13, 15.96, 16.80, 17.36, 17.68, 18.82, 19.40, 20.58, 22.01, 23.11, 24.30, 24.90, 25.88, 26.45, 28.08, 28.66, 28.96 and 29.34° and a differential scanning calorimetric thermogram with an endothermic peak at about 128.7+/- 3°C.

FIG. 7 and Table 3 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt by X-ray diffraction (XRD), as obtained by the invention.

Table 3

Pos. [°2 theta]	d-spacing [A]	height [cts]	Area	Rel Int [%]
3.8287	23.07804	152.30	14.49	5.02
7.5329	11.73601	770.45	57.58	25.42
8.3626	10.57349	3030.98	226.54	100.00
8.5509	10.34105	470.48	38.36	15.52
10.6473	8.30917	130.52	10.44	4.31

10.9312	8.09402	308.42	29.34	10.18
11.5324	7.67335	104.18	22.65	3.44
13.6109	6.50586	158.16	17.19	5.22
13.9791	6.33533	119.22	25.92	3.93
15.1252	5.85777	1268.19	112.02	41.84
15.9593	5.55344	675.94	73.48	22.30
16.8022	5.27670	637.02	56.27	21.02
17.3649	5.10698	1601.76	119.72	52.85
17.6772	5.01744	781.35	95.56	25.78
18.8174	4.71592	836.88	136.47	27.61
19.4004	4.57549	974.06	72.80	32.14
20.5835	4.31509	2992.80	264.36	98.74
22.0133	4.03795	972.80	99.15	32.10
23.1074	3.84918	2134.06	290.00	70.41
24.2992	3.66302	1172.99	111.58	38.70
24.9010	3.57584	378.50	82.30	12.49
25.8822	3.44246	219.10	71.46	7.23
26.4536	3.36939	221.01	72.08	7.29
27.1339	3.28644	172.30	37.46	5.68
28.0837	3.17741	341.31	37.11	11.26
28.6552	3.11533	369.33	60.23	12.19
28.9580	3.08343	392.05	53.28	12.93
29.3381	3.04435	246.34	40.17	8.13
31.5401	2.83665	178.14	67.78	5.88
33.2018	2.69838	103.29	33.69	3.41
30.4801	2.93284	218.80	47.57	1.30
31.1487	2.87139	426.85	81.21	2.53
31.6734	2.82502	317.58	38.84	1.88
33.9008	2.64433	301.67	73.79	1.79

FIG.8 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt, as obtained by the process of the invention. Thus, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt may have an IR spectrum substantially similar to an IR spectrum as depicted in FIG. 8.

FIG. 9 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt, as obtained by the process of the invention. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt may have a differential scanning calorimetric thermogram substantially similar to a differential scanning calorimetric thermogram as depicted in FIG. 9.

Further provided is N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphtyl ethyl amine salt and crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphtyl ethyl amine salt. Crystalline N-(3-carboxy-1-oxopropyl)-

(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt as obtained by the invention can be characterized by X-ray diffraction pattern substantially as shown in Table 4 and FIG. 10. The compound can also be characterized by

a. at least one of X-ray diffraction peaks with 2-theta values 3.76, 6.84, 7.17+, 8.39, 9.20, 11.07, 13.70, 14.29, 15.11, 16.10, 16.79, 17.75, 18.01, 18.45, 18.90, 19.92, 20.29, 20.44, 21.31, 21.67, 22.31, 22.54, 25.14, 25.39, 26.23, 27.00, 27.93 and 30.03°; and/or

b. a differential scanning calorimetric thermogram with a endothermic peak at about 138.1+/- 3°C.

Preferably, the N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt is characterized by at least one of X-ray diffraction peaks with 2-theta values 3.76, 6.84, 7.17+, 8.39, 9.20, 11.07, 13.70, 14.29, 15.11, 16.10, 16.79, 17.75, 18.01, 18.45, 18.90, 19.92, 20.29, 20.44, 21.31, 21.67, 22.31, 22.54, 25.14, 25.39, 26.23, 27.00, 27.93 and 30.03 and a differential scanning calorimetric thermogram with an endothermic peak at about 138.1+/- 3°C.

FIG. 10 and Table 4 shows structural analysis of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt by X-ray diffraction (XRD), as obtained in the example of the invention.

Table 4

Pos. [°2Th.]	Height[cts]	FWHW[°2Th.]	d-spacing [Å]	Rel. Int. [%]
3.7626	23.48341	1501.28	122.41	38.45
6.8366	12.92978	1533.22	177.10	39.27
7.1731	12.32393	2324.22	236.88	59.52
7.5212	11.75422	94.47	12.84	2.42
8.3899	10.53905	747.44	50.79	19.14
9.1989	9.61392	1928.32	222.74	49.39
11.0728	7.99077	317.65	34.53	8.14
11.2911	7.83678	133.81	14.55	3.43
12.0852	7.32356	96.62	21.01	2.47
13.6977	6.46485	1883.36	268.73	48.23
14.2892	6.19856	2922.32	297.84	74.84
15.1170	5.86092	315.46	42.87	8.08
15.3440	5.77473	139.72	11.18	3.58
16.1038	5.50395	487.46	72.87	12.48
16.4134	5.40080	107.92	46.93	2.76
16.7902	5.28045	403.53	65.80	10.33
17.7482	4.99753	1237.85	185.04	31.70
18.0147	4.92419	1309.29	249.09	33.53
18.4539	4.80799	1191.69	161.94	30.52
18.9033	4.69467	3904.66	557.15	100.00
19.9168	4.45800	475.46	142.14	12.18
20.2861	4.37767	961.74	130.69	24.63
20.4427	4.34450	911.68	99.11	23.35
21.3088	4.16983	869.35	153.58	22.26
21.6718	4.10080	1141.31	170.61	29.23
22.3143	3.98416	2228.55	242.28	57.07
22.5371	3.94528	2158.32	263.97	55.28
24.2247	3.67412	174.55	37.95	4.47
25.1395	3.54246	770.18	115.13	19.72
25.3867	3.50851	503.46	68.42	12.89

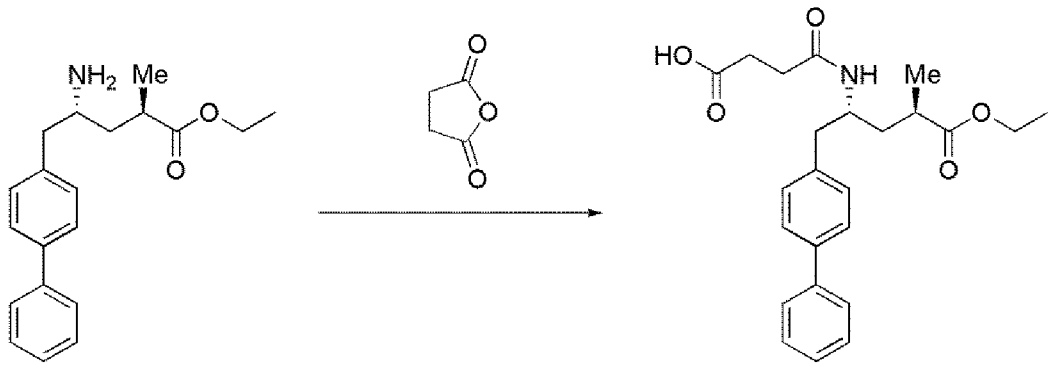
26.2348	3.39699	591.42	160.74	15.15
27.0010	3.30231	357.37	77.70	9.15
27.9371	3.19375	384.14	83.52	9.84
30.0271	2.97604	401.90	87.39	10.29
32.3275	2.76933	213.25	69.55	5.46
33.1696	2.70093	144.32	47.07	3.70
34.3333	2.61200	143.69	54.68	3.68
36.5056	2.46141	131.34	28.56	3.36
38.6560	2.32929	221.34	54.14	5.67

FIG. 11 shows an Infrared Spectrum (IR) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt, as obtained by the process of the invention. Thus, N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt may have an IR spectrum substantially similar to an IR spectrum as depicted in FIG. 11.

FIG. 12 shows results of Differential Scanning Calorimetry (DSC) of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt, as obtained by the process of the invention. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt may have a differential scanning calorimetric thermogram substantially similar to a differential scanning calorimetric thermogram as depicted in FIG. 12.

Particular embodiments of the present invention include:

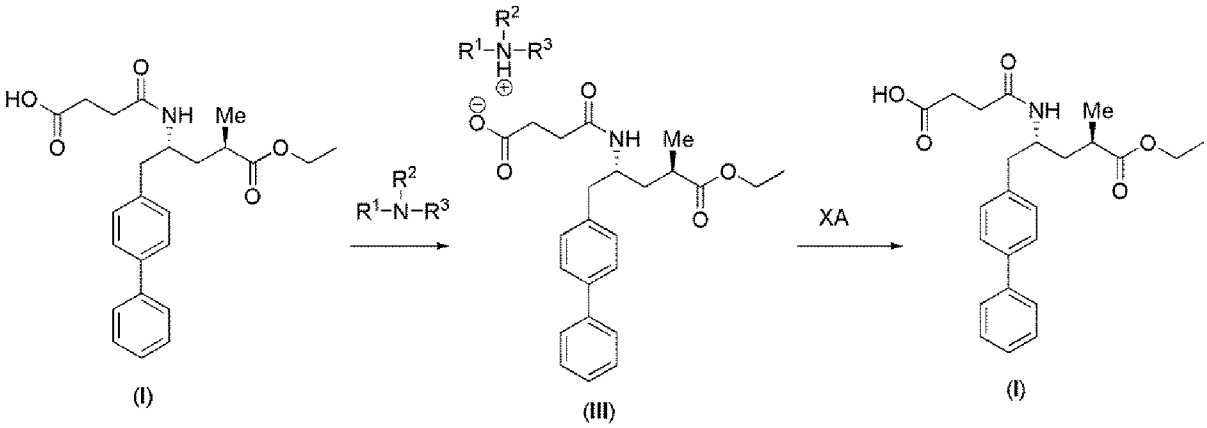
1. A process of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester comprising the steps of:
    a) Treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride;
    b) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I from the reaction mixture;



(II) (I)

2. The process of clause 1 step a), wherein compound of formula II is present in the form of salt then salt is selected from the list of tartaric acid, dibenzoyl tartaric acid, di-para-toluoyl tartaric acid, mandelic acid and camphor sulfonic acid.
3. The process of clause 1 step a) or clause 2, wherein salt is tartrate salt.
4. The process of clause 1, wherein reaction is carried out in presence of base.

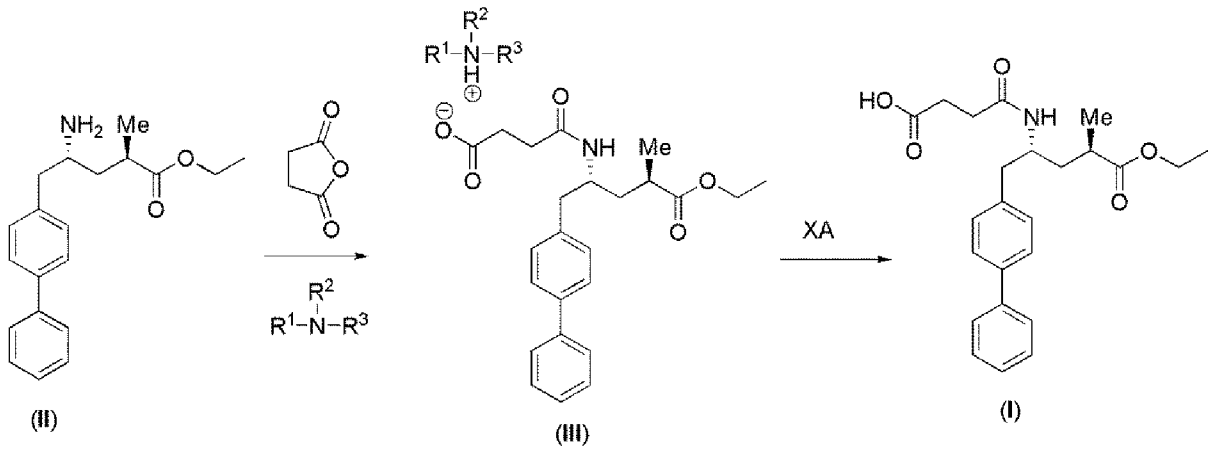
5. The process of clause 1 or 4, wherein base is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
6. The process of any of the preceding clauses, wherein the base is pyridine.
7. A process of preparing substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula (I) comprising the steps of:
    a) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with amine;
    b) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt from the reaction mixture;
    c) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
    d) Isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.



wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

8. The process of clause 7, wherein the compound of formula I isolated in step d) has purity more than 95% including more than 96%, more than 97%, more than 98%, more than 99% and up to 99.5% or more.
9. The process of clause 7, wherein amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
10. The process of clause 8 and 9, wherein amine is *t*-butyl amine.
11. The process of clause 7 or clause 8, wherein the base is an amine $NR^1R^2R^3$ with the provisio that at least one of the substituents R^1, R^2 or R^3 is not H or a C_1-C_6 alkyl.
12. The proceass of clause 11, wherein the base is selected from the group consisting of n-Octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.
13. The process of any one of the clauses 7 to 12, wherein step a) is performed using water as a solvent.
14. The process of any one of the clauses 7 to 12, wherein step a) is performed without addition of a solvent.
15. The process of any one of the clauses 7 to 14, wherein acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, oxalic acid, maleic acid, malonic acid, acetic acid, succinic acid, proponic acid, lactic acid, and formic acid.
16. The process of clause 15, wherein acid is hydrochloric acid.

17. A process of preparing substancially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula (I) comprising the steps of:
    a) Treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of amine;
    b) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt of formula III from the reaction mixture;
    c) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
    d) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula



wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

18. The process of clause 17 step a), wherein compound of formula II is present in the form of salt then salt is selected from the list of tartaric acid, dibenzoyl tartaric acid, or di-para-toluoyl tartaric acid, mandelic acid and camphor sulfonic acid.
19. The process of clause 17 or 18, wherein amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
20. The process of any one of the clauses 17 to 19, wherein amine is *t*-butyl amine.
21. The process of clause 17 or 18, wherein the base is an amine with formula $NR^1R^2R^3$ with the provisio that at least one of the substituents R^1, R^2 or R^3 is not H or a C_1-C_6 alkyl.
22. The process of clause 17, 18 or 20, wherein the base is selected from the group consisting of n-Octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.
23. The process of any one of the clauses 17 to 22, wherein step a) is performed using water as a solvent.
24. The process of any one of the clauses 17 to 22, wherein step a) is performed without addition of a solvent.
25. The process of any one of the clauses 17 to 24, wherein acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, oxalic acid, maleic acid, malonic acid, acetic acid, succinic acid, proponic acid, lactic acid, and formic acid.
26. The process of any one of the previous clauses 7 to 25, wherein substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I has a purity above 95%, preferably above 96%, more preferably above 97%, even more preferably above 98%, most preferably abo e 99%.

27. The process of any one of the previous clauses 7 to 25, wherein substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I has a purity above 99.5%.
28. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt.
29. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt.
30. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt characterized by at least one of the following:
    a) Powder X-ray diffraction peaks with 2-theta values of 4.11, 8.06, 9.88, 15.70, 16.16, 17.63, 17.78, 19.76, 20.23 and 23.10 +/- 0.1°;
    b) A differential scanning calorimetric thermogram with a endothermic peak at about 133.7°C +/- 3°C.

31. The crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt of clause 29 or clause 30, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 2.
32. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt.
33. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine of formula III-b.
34. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt characterized by at least one of the following:
    a. 4.40, 8.68, 10.37, 10.68, 12.81, 13.36, 14.48, 16.81, 16.99, 18.12, 18.87, 19.00, 19.37, 19.85, 20.81, 21.32, 21.50 and 22.51 +/-0.1°; and
    b. a differential scanning calorimetric thermogram with an endothermic peak at about 126.7+/-3°C.
35. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt of clause 33 or 34, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 5.
36. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine of formula III-c.
37. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt.
38. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt characterized by at least one of the following:
    a. 7.53, 8.36, 8.55, 10.93, 15.13, 15.96, 16.80, 17.36, 17.68, 18.82, 19.40, 20.58, 22.01, 23.11, 24.30, 24.90, 25.88, 26.45, 28.08, 28.66, 28.96 and 29.34 +/- 0.1° and
    b. a differential scanning calorimetric thermogram with an endothermic peak at about 128.7+/-3°C.

39. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt of clause 37 or 38, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 8.
40. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt of formula III-d.
41. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.
42. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt characterized by at least one of the following:
    a. 3.76, 6.84, 7.17+, 8.39, 9.20, 11.07, 13.70, 14.29, 15.11, 16.10, 16.79, 17.75, 18.01, 18.45, 18.90, 19.92, 20.29, 20.44, 21.31, 21.67, 22.31, 22.54, 25.14, 25.39, 26.23, 27.00, 27.93 and 30.03 +/- 0.1°; and/or
    b. a differential scanning calorimetric thermogram with a endothermic peak at about 138.1+/- 3°C.
43. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt of clause 41 or 42, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 11.
44. A pharmaceutical composition comprising a compound according to any of clauses 28 to 43.
45. Use of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof to prepare sacubitril or salt thereof.
46. Use of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate salt to to prepare sacubitril or salt thereof.
47. A pharmaceutical composition comprising N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester salt thereof prepared by a process according to any one of clauses 1 to 27.
48. A process of preparang trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate comprising,
    - treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with valsartan in presence of aqueous sodium hydroxide solution, and
    - isolating trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate from reaction mass;
    wherein the amine is an amine with formula $NR^1R^2R^3$, with the provisio that at least one of the substituents R^1, R^2, R^3 is not H or a C_1-C_6 alkyl group.
49. The process of clause 48, wherein the amine is selected from the group consisting of n-octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.

Examples

The present invention will now be exemplified by the following non-limiting examples.

Example 1: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester from (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid

To a suspension of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid (30g) in dichloromethane (450ml), pyridine (210ml) was added and reaction mixture was stirred for 10-15 minutes. Succinic anhydride (14.46g) was added to a reaction mixture under stirring and reaction mixture was stirred for about 8-10 hours. Solvent was distilled out from the reaction mixture and ethyl acetate (150ml) was added in to it. Reaction mixture was stirred for few minutes. Organic layer was separated and washed with dilute hydrochloric acid solution (1N, 100ml X 4times) followed by washing with brine solution (100 ml X 2 times). Organic layer was separated and dried over sodium sulfate. After removal of solvent by distillation oily product 35g (88.28%) having 90% HPLC purity was obtained.

Example 2 : Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester from (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate salt.

To a suspension of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate (30g) in dichloromethane (450ml), pyridine (210ml) was added and reaction mixture was stirred for 10-15 minutes. Succinic anhydride (9.76g) was added to a reaction mixture under stirring and reaction mixture was stirred for about 8-10 hours. Solvent was distilled out from the reaction mixture and ethyl acetate (150ml) was added in to it. Reaction mixture was stirred for few minutes. Organic layer was separated and washed with dilute hydrochloric acid solution (1N, 100ml X 4times) followed by washing with brine solution (100 ml X 2 times). Organic layer was separated and dried over sodium sulfate. After removal of solvent by distillation oily product 25g (93.5%) having 90% HPLC purity was obtained.

Example 3: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt

To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (25g) in acetone (250ml) was added *t*-butyl amine (4.44g) under stirring at 10-15°C. Reaction mixture was stirred for2-3 hours at 25-30°C. Solid product was filtered and washed with acetone (100ml). After drying 23g (78%) product was obtained. The HPLC purity of the product is 98.9%.

The final product is characterized a powder X-ray diffraction (XRD) pattern as shown in Figure 1. The XRD pattern shows the following main peaks as 2-theta values as indicated in the following table:

Table 5

Sr. No.	2-theta values
1	4.11
2	8.06
3	9.88
4	15.70
5	16.16
6	17.63
7	17.78
8	19.76
9	20.23
10	23.10

Example 4: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester

N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt (25g) was dissolved in dichloromethane (250ml) and solution was stirred for 10-15 minutes. To this solution water (150ml) was added and then slowly added hydrochloric acid (20%, 50ml). Reaction mixture was stirred for 15-20minutes. Organic layer was separated and aqueous layer extracted with dichloromethane (2 X 100ml). Combined organic layer washed with water (2 X 100ml). Organic layer was dried over sodium sulfate. After removing solvent under vacuum 20.5g (96.57%) oily product was obtained. The HPLC purity of the product is 99.5%.

Example 5: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester from (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid

To a suspension of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid (30g) in dichloromethane (450ml), *t*-butyl amine (210ml) was added and reaction mixture was stirred for 10-15 minutes. Succinic anhydride (14.46g) was added to a reaction mixture under stirring and reaction mixture was stirred for about 8-10 hours. Solvent was distilled out from the reaction mixture and ethyl acetate (150ml) was added in to it. Reaction mixture was stirred for few minutes. Organic layer was separated and washed with dilute hydrochloric acid solution (1N, 100ml X 4times) followed by washing with brine solution (100 ml X 2 times). Organic layer was separated and dried over sodium sulfate. After removal of solvent by distillation oily product 31.7g (80%) having 90% HPLC purity was obtained.

Example 6: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester from (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate salt.

To a suspension of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate (30g) in dichloromethane (450ml), *t*-butyl amine (210ml) was added and reaction mixture was stirred for 10-15 minutes. Succinic anhydride (9.76g) was added to a reaction mixture under stirring and reaction mixture was stirred for about 8-10 hours. Solvent was distilled out from the reaction mixture and ethyl acetate (150ml) was added in to it. Reaction mixture was stirred for few minutes. Organic layer was separated and washed with dilute hydrochloric

acid solution (1N, 100ml X 4times) followed by washing with brine solution (100 ml X 2 times). Organic layer was separated and dried over sodium sulfate. After removal of solvent by distillation oily product 24.3g (90.8%) having 90% HPLC purity was obtained.

Example 7: Preparation of trisodium sacubitril- valsartan hemipentahydrate.

To a solution of sacubitril t-butyl amine salt (2g) in acetone (30ml) was added valsartan (1.8g) and reaction mixture was stirred for ten minutes to get clear solution. To this reaction mass sodium hydroxide solution (0.5g in 2ml water) was added slowly by maintaining reaction temperature in between 10-20°C and stireed reaction mixture for for one hour. Solvent was removed under vacuum and to get a residue. The residue was terturated in acetone(30ml). Product was filtered and washed with acetone (30ml). After drying 3.3g (71%) solid crystalline product was obtained.

Example 8: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt without the use of solvent.

To a round bottom flask containing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (2.5g) was added *t*-butyl amine (0.44g). Formation of solid product was observed within few minutes after addition. Reaction mixture was kept on hold for 24 hours. 2.7g (92%) product was isolated. The HPLC purity of the product is more than 99%.

Example 9: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt in the absence of organic solvent.

To a round bottom flask containing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (2.5g) was added *t*-butyl amine (0.44g) and water (25ml). Reaction mixture was stirred for 2-3 hours. Water was removed by distillation. After drying 2.5g (85%) product was isolated. The HPLC purity of the product is more than 99%.

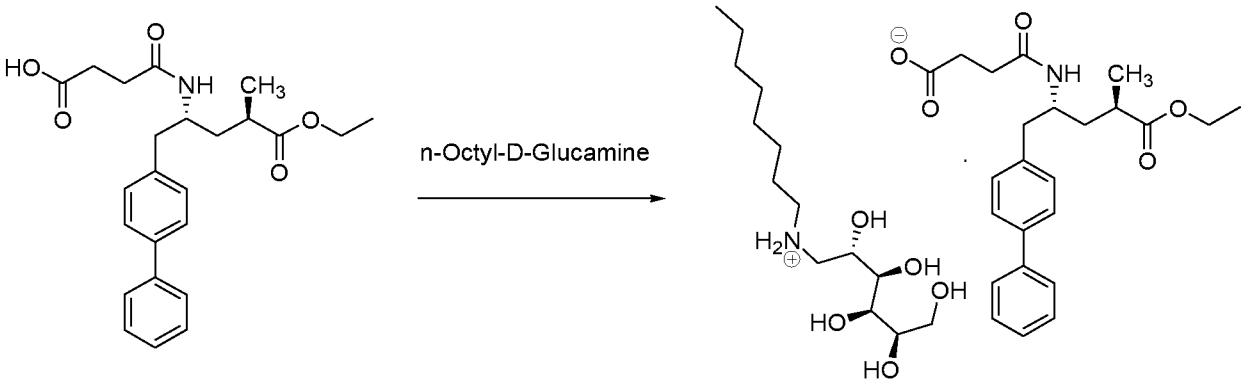
Example 10: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt using t-butyl amine as solvent and base.

To a round bottom flask containing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (2.5g) was added *t*-butyl amine (7.5ml). Reaction mixture was stirred for 2-3 hours. Product was filtered. After drying 2.4g (81.6%) product was isolated. The HPLC purity of the product is more than 99%.

Example 11: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt.

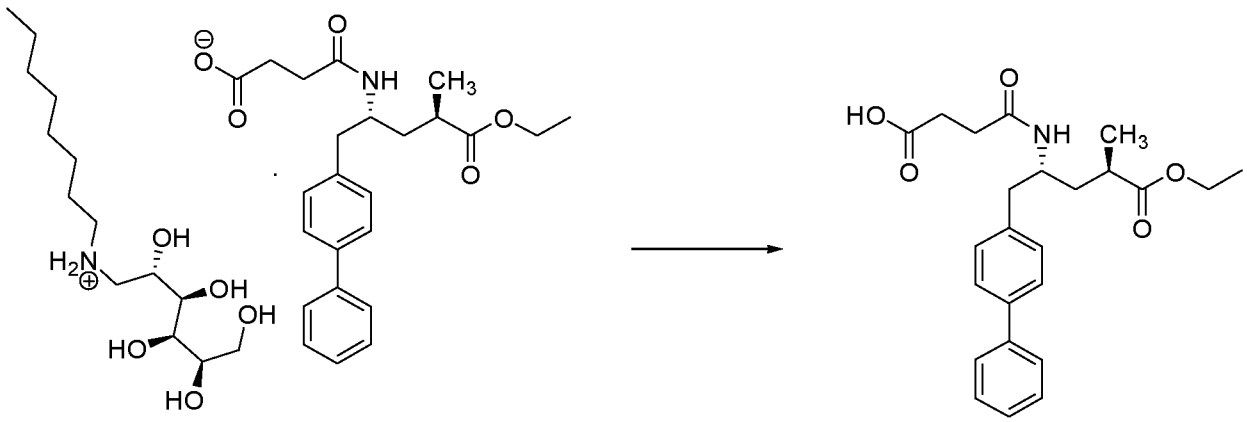
To a round bottom flask containing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (2.5g) was added *t*-butyl amine (7.5ml). Reaction mixture was stirred for 2-3 hours. Product was filtered and washed with acetone (5ml). After drying 2.2g (75%) product was isolated. The HPLC purity of the product is more than 99%.

Example 12: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-Glucamine salt.



To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (25g) in acetone (250ml) was added n-Octyl-D-Glucamine (17.83g) under stirring at 10-15°C. Reaction mixture was stirred for 5-10 minutes at 25-30°C and then heated to reflux. At reflux temperature added water (5ml) in the reaction mixture. The reaction mixture was cooled to 10-20°C and stirred at this temperature for 2-3 hours. Solid product was filtered and washed with acetone (50ml). After drying 35g (82%) product was obtained. The HPLC purity of the product is 99%.

Example 13: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.



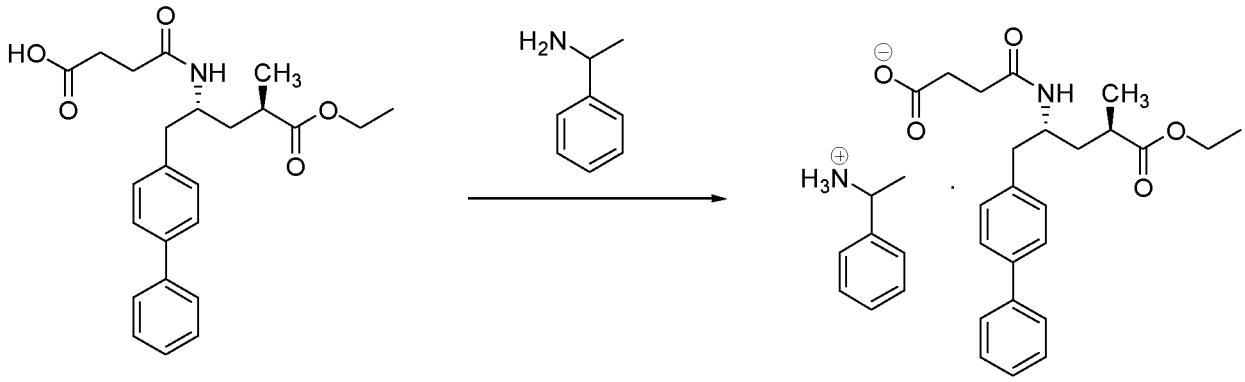
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-Octyl-D-Glucamine salt (25g) was dissolved in dichloromethane (250ml) and solution was stirred for 10-15 minutes. To this solution water (150ml) was added and then slowly added hydrochloric acid (20%, 50ml). Reaction mixture

was stirred for 15-20minutes. Organic layer was separated and aqueous layer extracted with dichloromethane (2 X 100ml). Combined organic layer washed with water (2 X 100ml). Organic layer was dried over sodium sulfate. After removing solvent under vacuum 13g (89%) oily product was obtained. The HPLC purity of the product is 99.5%.

Example 14: Preparation of trisodium sacubitril- valsartan hemipentahydrate.

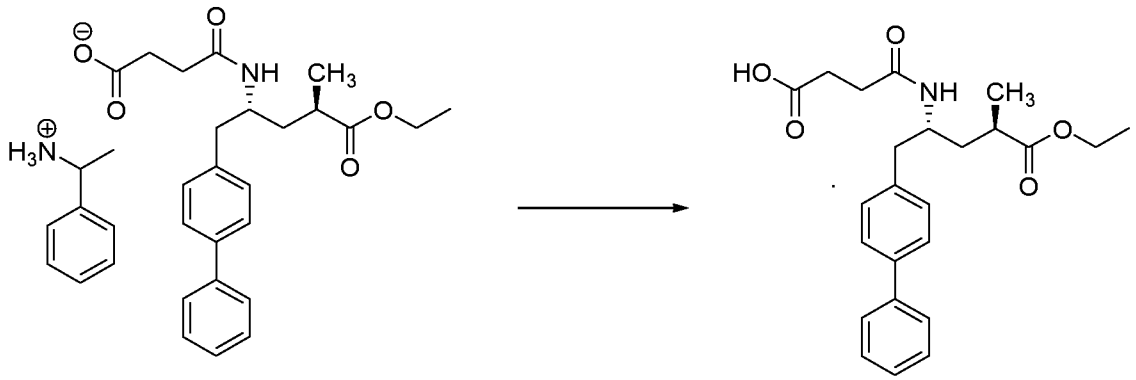
To a suspension of sacubitril n-Octyl-D-Glucamine salt (2g) in acetone (30ml) and water (10ml) was added valsartan (1.23g) and reaction mixture was stirred for ten minutes. To this reaction mass sodium hydroxide solution (0.34g in 2ml water) was added slowly by maintaining reaction temperature in between 10-20°C and stirred reaction mixture for one hour. Insoluble n-Octyl-D-Glucamine was removed by filteration. Solvent was removed under vacuum and to get a residue. The residue was triturated in acetone (30ml). Product was filtered and washed with acetone (30ml). After drying 2g (75%) solid crystalline product was obtained.

Example 15: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt.



To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (25g) in acetone (250ml) was added phenyl ethyl amine (7.36g) under stirring at 10-15°C. Reaction mixture was stirred for 5-10 minutes at 25-30°C and then heated to reflux. At reflux temperature added water (5ml) in the reaction mixture. The reaction mixture was cooled to 10-20°C and stirred at this temperature for 2-3 hours. Solid product was filtered and washed with acetone (50ml). After drying 26g (80%) product was obtained. The HPLC purity of the product is 99%.

Example 16: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.

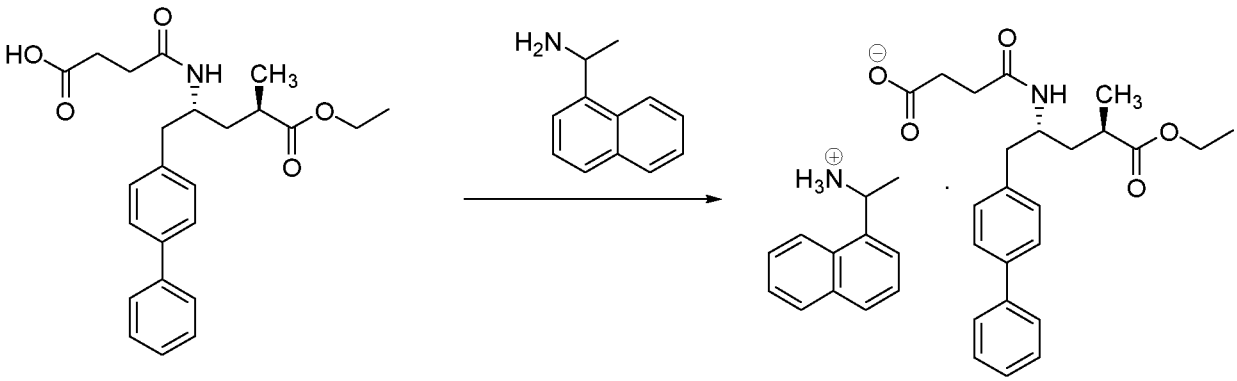


N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt (25g) was dissolved in dichloromethane (250ml) and solution was stirred for 10-15 minutes. To this solution water (150ml) was added and then slowly added hydrochloric acid (20%, 50ml). Reaction mixture was stirred for 15-20minutes. Organic layer was separated and aqueous layer extracted with dichloromethane (2 X 100ml). Combined organic layer washed with water (2 X 100ml). Organic layer was dried over sodium sulfate. After removing solvent under vacuum 17g (90%) oily product was obtained. The HPLC purity of the product is 99.5%.

Example 17: Preparation of trisodium sacubitril- valsartan hemipentahydrate.

To a solution of sacubitril phenyl ethyl amine salt (2g) in acetone (30ml) was added valsartan (1.64g) and reaction mixture was stirred for ten minutes. To this reaction mass sodium hydroxide solution (0.44g in 2ml water) was added slowly by maintaining reaction temperature in between 10-20°C and stirred reaction mixture for one hour. Solvent was removed under vacuum. The obtained residue was triturated in acetone (30ml). Product was filtered and washed with acetone (30ml). After drying 2.5g (72%) solid crystalline product was obtained.

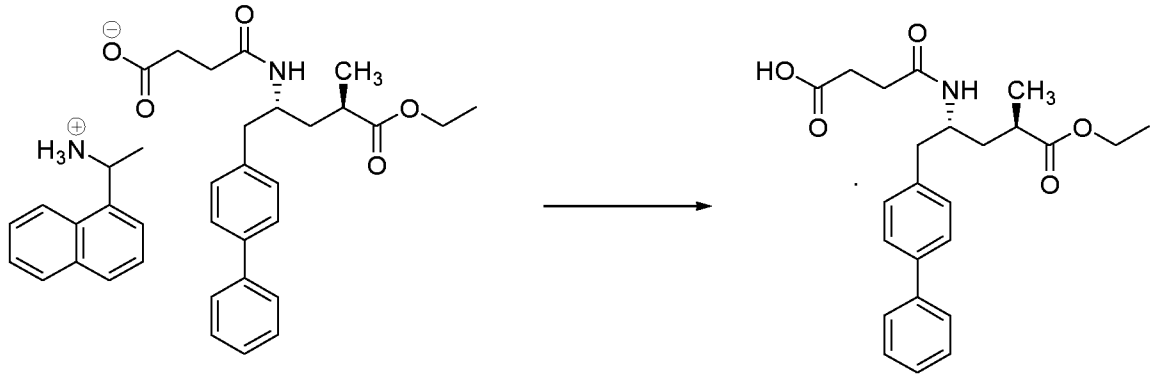
Example 18: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.



To a solution of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester (20g) in acetone (200ml) was added naphthyl ethyl amine (8.3g) under stirring at 10-15°C. Reaction mixture was stirred for 5-10 minutes at 25-30°C and then heated to reflux. The reaction mixture was cooled to 10-

20°C and stirred at this temperature for 2-3 hours. Solid product was filtered and washed with acetone (40ml). After drying 20g (70.6%) product was obtained. The HPLC purity of the product is more than 99%.

Example 19: Preparation of N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester.



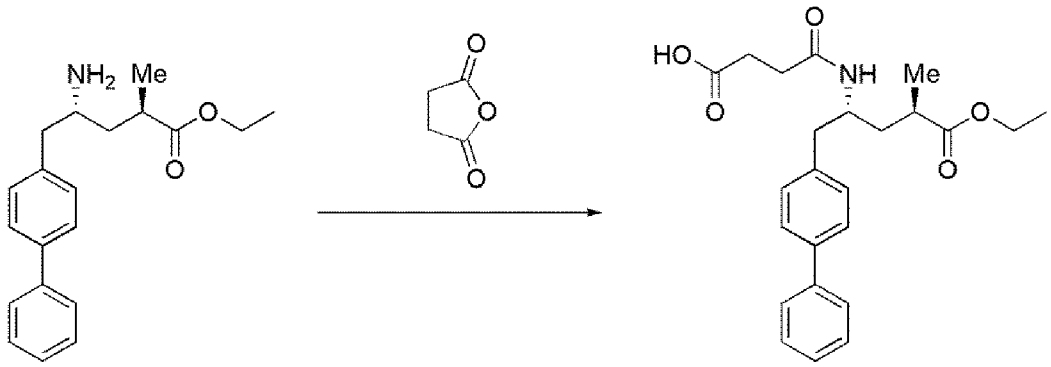
N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt (20g) was dissolved in dichloromethane (200ml) and solution was stirred for 10-15 minutes. To this solution water (100ml) was added and then slowly added hydrochloric acid (20%, 40ml). Reaction mixture was stirred for 15-20minutes. Organic layer was separated and aqueous layer extracted with dichloromethane (2 X 75ml). Combined organic layer washed with water (2 X 75ml). Organic layer was dried over sodium sulfate. After removing solvent under vacuum 13.3g (94%) oily product was obtained. The HPLC purity of the product is 99.5%.

Example 20: Preparation of trisodium sacubitril- valsartan hemipentahydrate.

To a solution of sacubitril naphthyl ethyl amine salt (10g) in acetone (150ml) was added valsartan (7.47g) and reaction mixture was stirred for ten minutes. To this reaction mass sodium hydroxide solution (2.2g in 10ml water) was added slowly by maintaining reaction temperature in between 10-20°C and stirred reaction mixture for one hour. Solvent was removed under vacuum. The obtained residue was triturated in acetone (30ml). Product was filtered and washed with acetone (150ml). After drying 13.2g (80%) solid crystalline product was obtained.

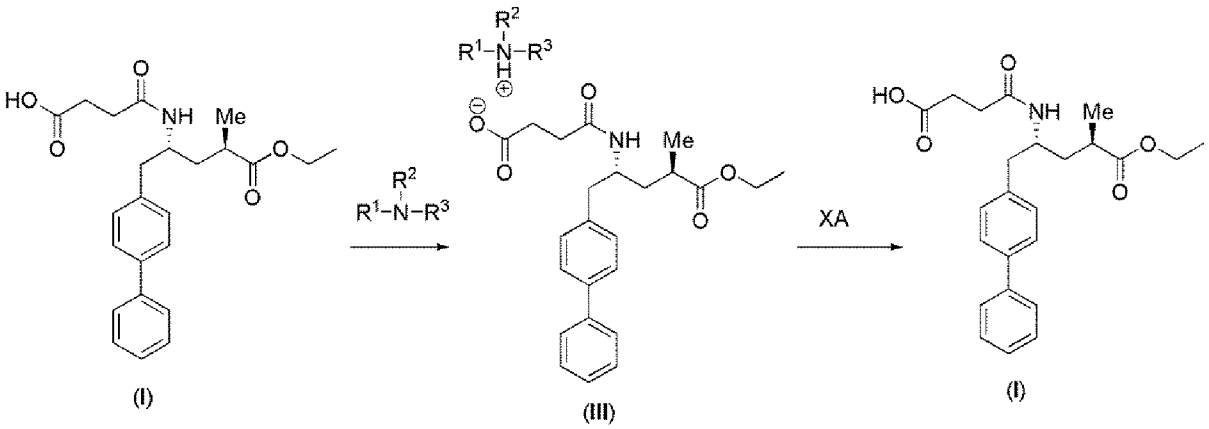
Claims

1. A process of preparing N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester comprising the steps of:
    c) Treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride;
    d) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I from the reaction mixture;



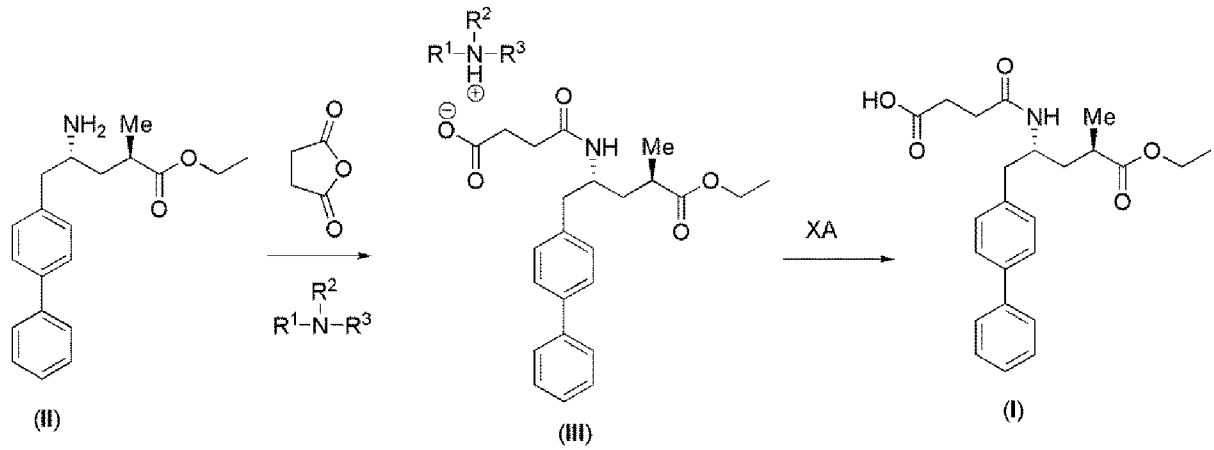
(II) (I)

2. The process of claim 1 step a), wherein compound of formula II is present in the form of salt then salt is selected from the list of tartaric acid, dibenzoyl tartaric acid, di-para-toluoyl tartaric acid, mandelic acid and camphor sulfonic acid.
3. The process of claim 1 step a) or claim 2, wherein salt is tartrate salt.
4. The process of claim 1, wherein reaction is carried out in presence of base.
5. The process of claim 1 or 4, wherein base is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
6. The process of any of the preceding claims, wherein the base is pyridine.
7. A process of preparing substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula (I) comprising the steps of:
    e) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I or salt thereof with amine;
    f) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt from the reaction mixture;
    g) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
    h) Isolating substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I.



wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

8. The process of claim 7, wherein the compound of formula I isolated in step d) has purity more than 95% including more than 96%, more than 97%, more than 98%, more than 99% and up to 99.5% or more.
9. The process of claim 7, wherein amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
10. The process of claim 8 and 9, wherein amine is *t*-butyl amine.
11. The process of claim 7 or claim 8, wherein the base is an amine $NR^1R^2R^3$ with the provisio that at least one of the substituents R^1, R^2 or R^3 is not H or a C_1-C_6 alkyl.
12. The proceass of claim 11, wherein the base is selected from the group consisting of n-Octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.
13. The process of any one of the claims 7 to 12, wherein step a) is performed using water as a solvent.
14. The process of any one of the claims 7 to 12, wherein step a) is performed without addition of a solvent.
15. The process of any one of the claims 7 to 14, wherein acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, oxalic acid, maleic acid, malonic acid, acetic acid, succinic acid, proponic acid, lactic acid, and formic acid.
16. The process of claim 15, wherein acid is hydrochloric acid.
17. A process of preparing substancially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula (I) comprising the steps of:
    e) Treating (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of compound of formula II or salt thereof with succinic anhydride in presence of amine;
    f) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt of formula III from the reaction mixture;
    g) Treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with acid;
    h) Isolating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula



wherein R^1, R^2 and R^3 are independently hydrogen or alkyl group; and XA is acid.

18. The process of claim 17 step a), wherein compound of formula II is present in the form of salt then salt is selected from the list of tartaric acid, dibenzoyl tartaric acid, or di-para-toluoyl tartaric acid, mandelic acid and camphor sulfonic acid.
19. The process of claim 17 or 18, wherein amine is selected from triethylamine, dimethylamine, pyridine, piperidine, ammonia, diisopropylethylamine, *t*-butyl amine.
20. The process of any one of the claims 17 to 19, wherein amine is *t*-butyl amine.
21. The process of claim 17 or 18, wherein the base is an amine $NR^1R^2R^3$ with the provisio that at least one of the substituents R^1, R^2 or R^3 is not H or a C_1-C_6 alkyl.
22. The process of claim 17, 18 or 20, wherein the base is selected from the group consisting of n-Octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.
23. The process of any one of the claims 17 to 22, wherein step a) is performed using water as a solvent.
24. The process of any one of the claims 17 to 22, wherein step a) is performed without addition of a solvent.
25. The process of any one of the claims 17 to 24, wherein acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, oxalic acid, maleic acid, malonic acid, acetic acid, succinic acid, proponic acid, lactic acid, and formic acid.
26. The process of any one of the previous claims 7 to 25, wherein substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I has a purity above 95%, preferably above 96%, more preferably above 97%, even more preferably above 98%, most preferably abo e 99%.
27. The process of any one of the previous claims 7 to 25, wherein substantially pure N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester of formula I has a purity above 99.5%.
28. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt.
29. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt.
30. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt characterized by at least one of the following:

c) Powder X-ray diffraction peaks with 2-theta values of 4.11, 8.06, 9.88, 15.70, 16.16, 17.63, 17.78, 19.76, 20.23 and 23.10 +/- 0.1°;

d) A differential scanning calorimetric thermogram with a endothermic peak at about 133.7°C +/- 3°C.

31. The crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester t-butyl amine salt of claim 29 or claim 30, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 2.

32. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt.

33. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt.

34. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt characterized by at least one of the following:

a. 4.40, 8.68, 10.37, 10.68, 12.81, 13.36, 14.48, 16.81, 16.99, 18.12, 18.87, 19.00, 19.37, 19.85, 20.81, 21.32, 21.50 and 22.51 +/-0.1°; and

b. a differential scanning calorimetric thermogram with an endothermic peak at about 126.7+/- 3°C.

35. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester n-octyl-D-glucamine salt of claim 33 or 34, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 5.

36. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt.

37. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt.

38. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt characterized by at least one of the following:

a. 7.53, 8.36, 8.55, 10.93, 15.13, 15.96, 16.80, 17.36, 17.68, 18.82, 19.40, 20.58, 22.01, 23.11, 24.30, 24.90, 25.88, 26.45, 28.08, 28.66, 28.96 and 29.34 +/- 0.1° and

b. a differential scanning calorimetric thermogram with an endothermic peak at about 128.7+/- 3°C.

39. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester phenyl ethyl amine salt of claim 37 or 38, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 8.

40. N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.

41. Crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt.

42. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt characterized by at least one of the following:

a. 3.76, 6.84, 7.17+, 8.39, 9.20, 11.07, 13.70, 14.29, 15.11, 16.10, 16.79, 17.75, 18.01, 18.45, 18.90, 19.92, 20.29, 20.44, 21.31, 21.67, 22.31, 22.54, 25.14, 25.39, 26.23, 27.00, 27.93 and 30.03 +/- 0.1°; and/or

b. a differential scanning calorimetric thermogram with a endothermic peak at about 138.1+/- 3°C.

43. A crystalline N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester naphthyl ethyl amine salt of claim 41 or 42, further characterized by having an IR spectrum substantially similar to an IR spectrum as depicted in Fig. 11.

44. A pharmaceutical composition comprising a compound according to any of claims 28 to 43.

45. Use of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester or salt thereof to prepare sacubitril or salt thereof.

46. Use of (4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid D-(-)-tartrate salt to to prepare sacubitril or salt thereof.

47. A pharmaceutical composition comprising N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester salt thereof prepared by a process according to any one of claims 1 to 27.

48. A process of preparang trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate comprising,

- treating N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester amine salt with valsartan in presence of aqueous sodium hydroxide solution, and
- isolating trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate from reaction mass;

wherein the amine is selected from the group consisting of n-octyl-D-glucamine, phenyl ethyl amine and naphthyl ethyl amine.

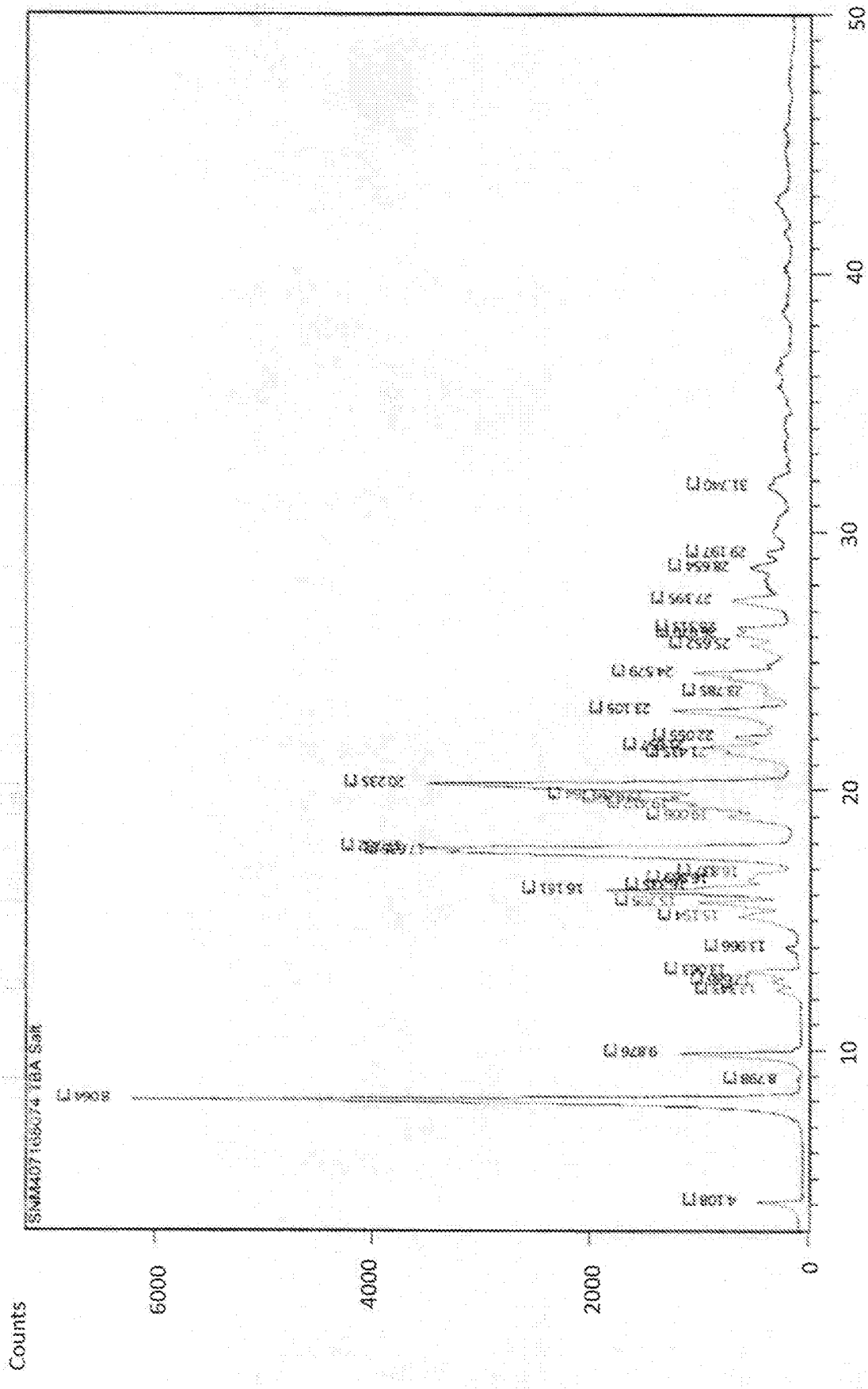

Counts
6000
4000
2000
0
10
20
30
40
50
Position [2°Theta] (Copper (Cu))

FIG. 1

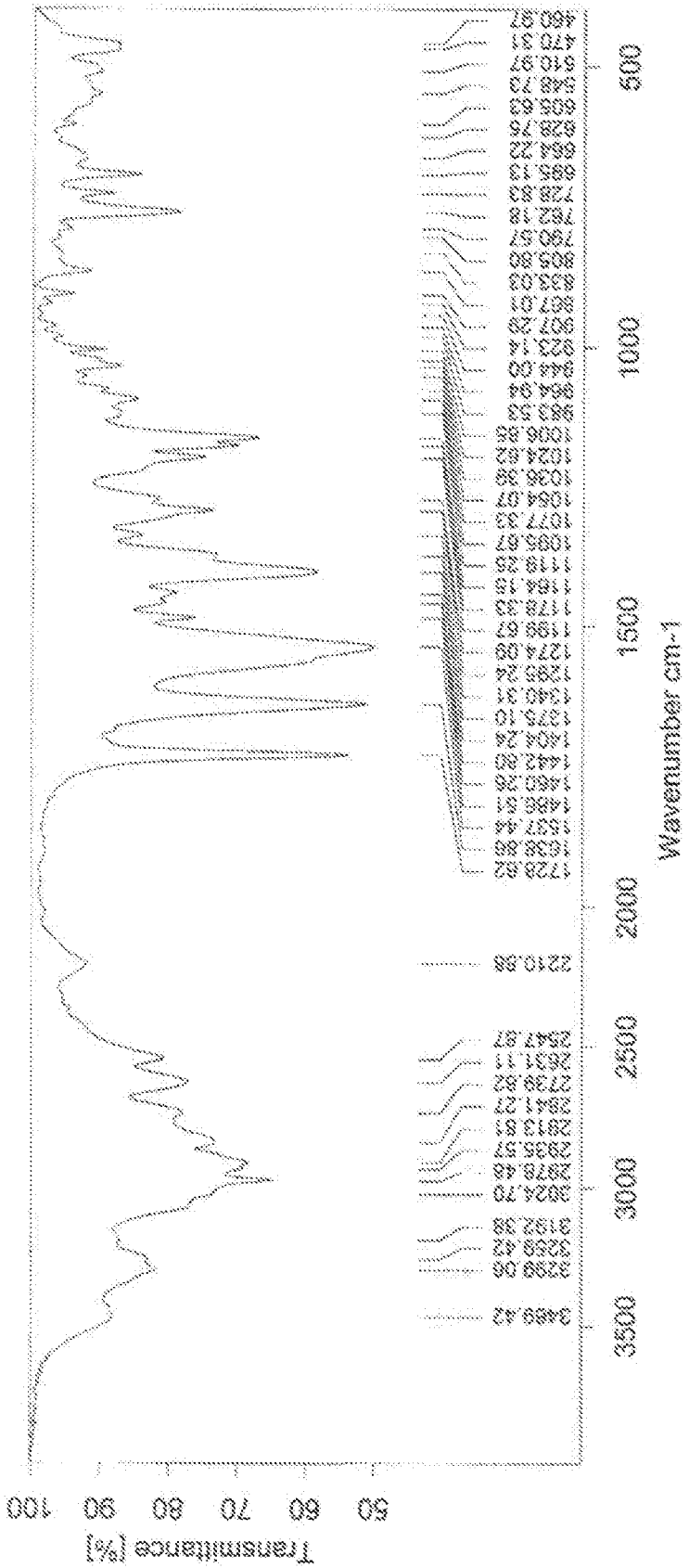

Transmittance [%]
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70
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50
Wavenumber cm-1
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3000
2500
2000
1500
1000
500
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3299.06
3259.42
3192.38
3024.70
2978.46
2936.57
2913.81
2841.27
2739.82
2631.11
2547.87
2210.86
1728.62
1638.86
1537.44
1486.51
1460.26
1442.80
1404.24
1375.10
1340.31
1295.24
1274.08
1198.67
1178.33
1164.18
1118.26
1095.67
1077.33
1064.07
1036.39
1024.62
1006.86
963.53
944.04
844.09
823.14
807.29
807.01
833.03
805.80
780.57
762.18
728.83
695.13
664.22
628.76
606.63
548.73
510.97
470.31
460.97

FIG. 2

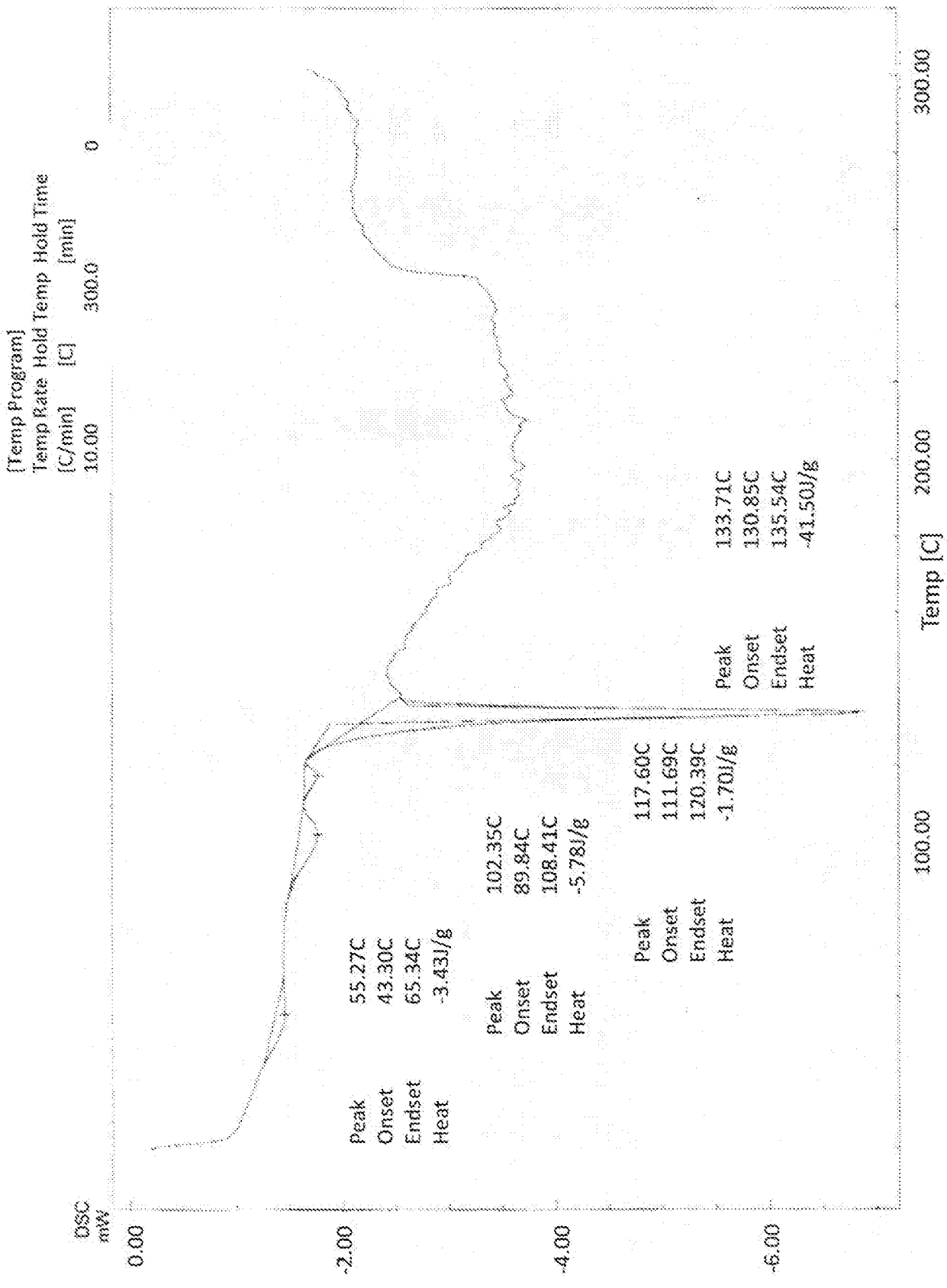

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(C/min) [C] [min]
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Onset 43.30C
Endset 65.34C
Heat -3.43J/g
Peak 102.35C
Onset 89.84C
Endset 108.41C
Heat -5.78J/g
Peak 117.60C
Onset 111.69C
Endset 120.39C
Heat -1.70J/g
Peak 133.71C
Onset 130.85C
Endset 135.54C
Heat -41.50J/g
DSC mW
0.00
-2.00
-4.00
-6.00
100.00
200.00
300.00
Temp [C]

FIG. 3

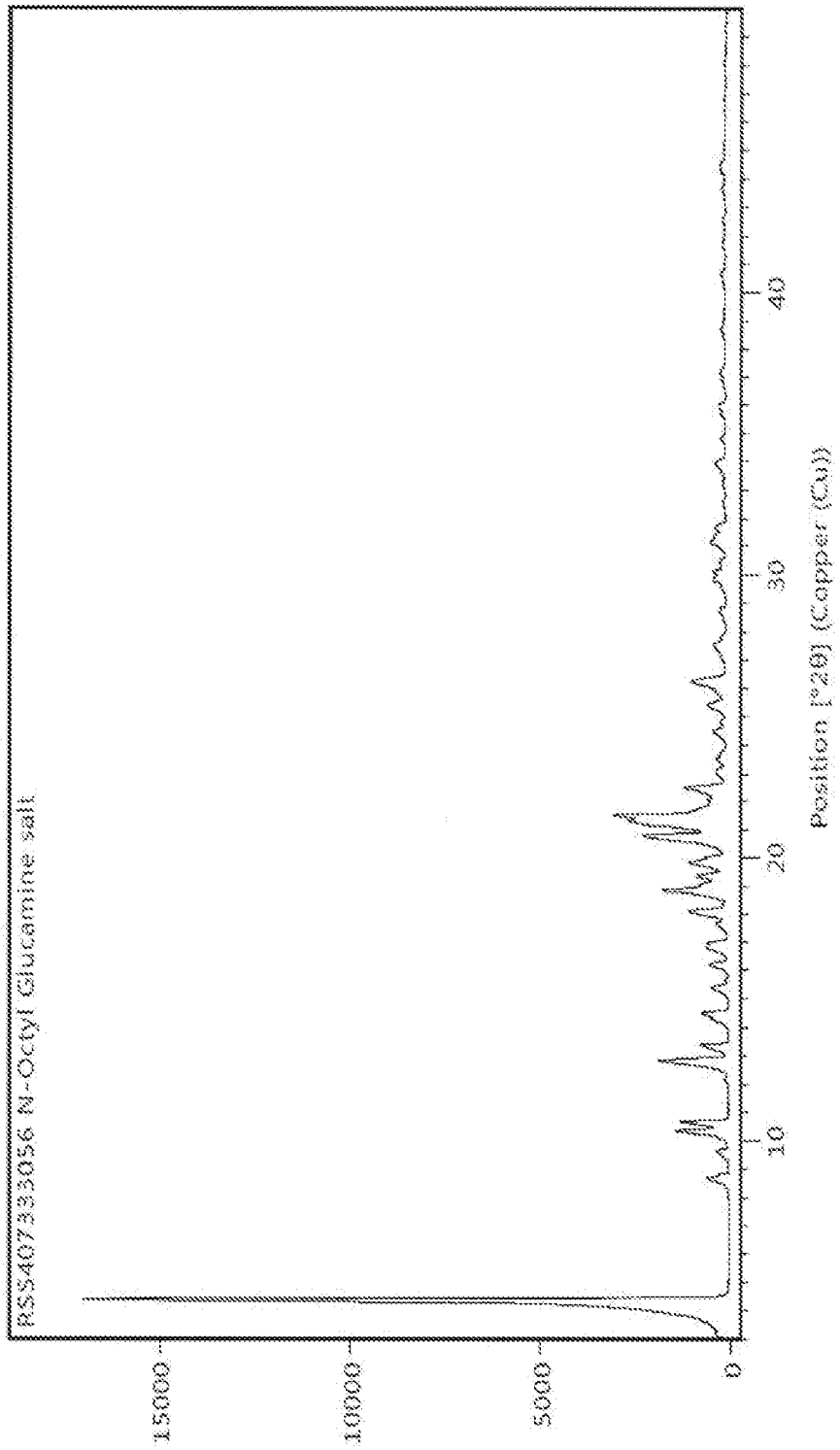

RSS407333056 N-Octyl Glucamine salt
15000
10000
5000
0
10
20
30
40
Position [°2θ] (Copper (Cu))

FIG. 4

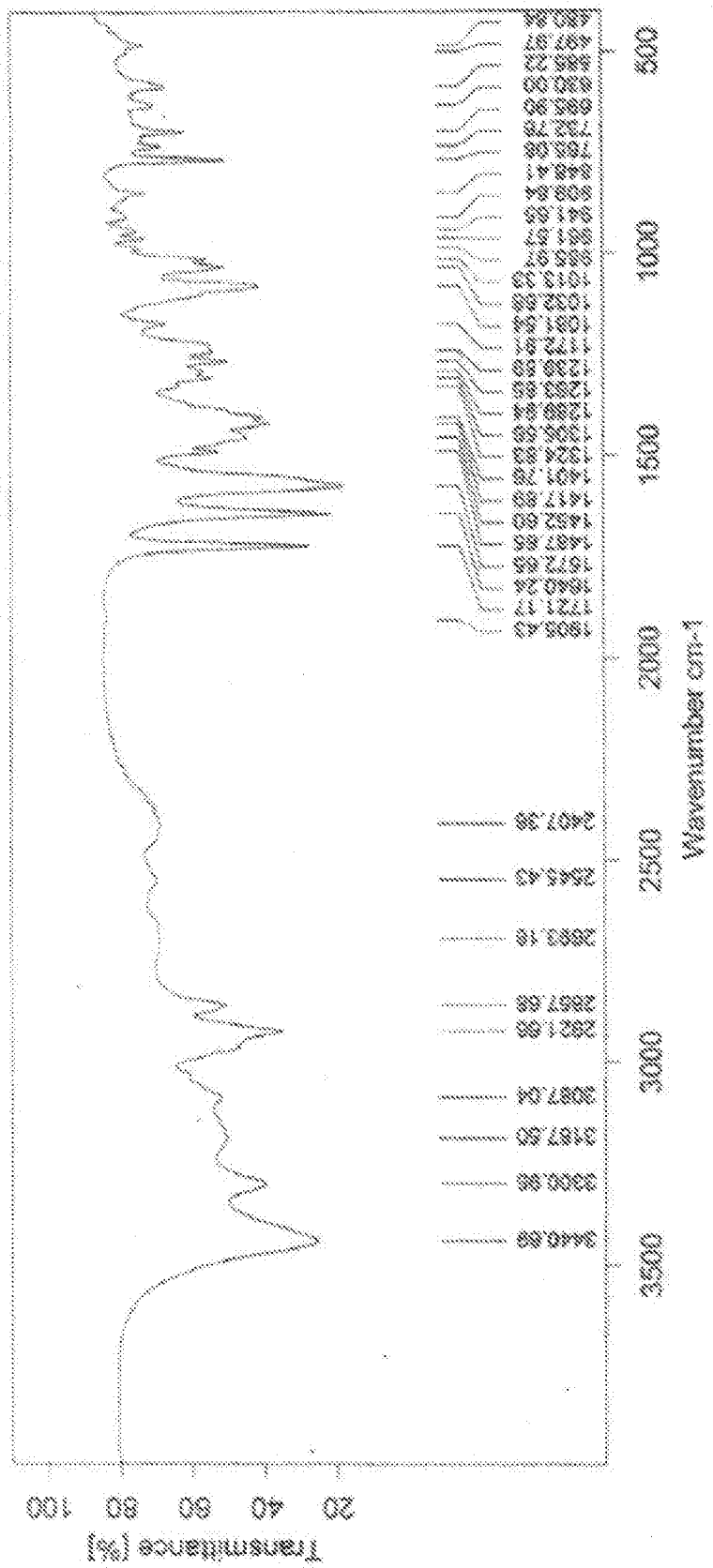

Transmittance [%]
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40
60
80
100
Wavenumber cm-1
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3000
2500
2000
1600
1000
500
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3300.89
3167.50
3007.04
2921.89
2867.68
2362.16
2345.40
2401.38
1909.40
1721.17
1640.24
1572.65
1452.80
1407.66
1401.78
1417.89
1324.63
1306.59
1258.44
1238.58
1172.81
1091.84
1032.08
1013.03
965.97
891.07
841.63
798.41
730.78
695.90
630.00
486.22
457.97
420.84

FIG. 5

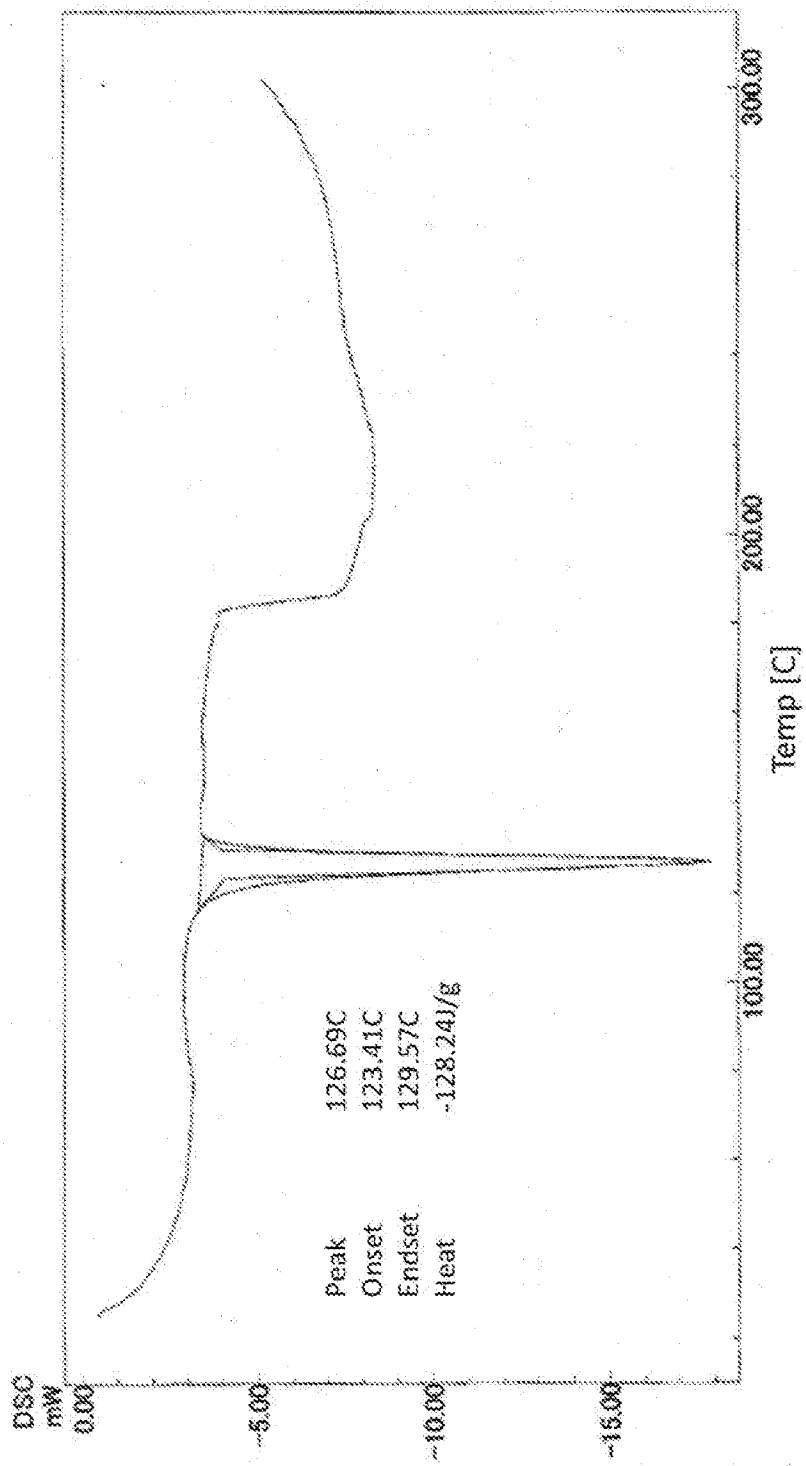

DSC
mW
0.00
-5.00
-10.00
-15.00
100.00
200.00
300.00
Temp [C]
Peak 126.69C
Onset 123.41C
Endset 129.57C
Heat -128.24J/g

FIG. 6

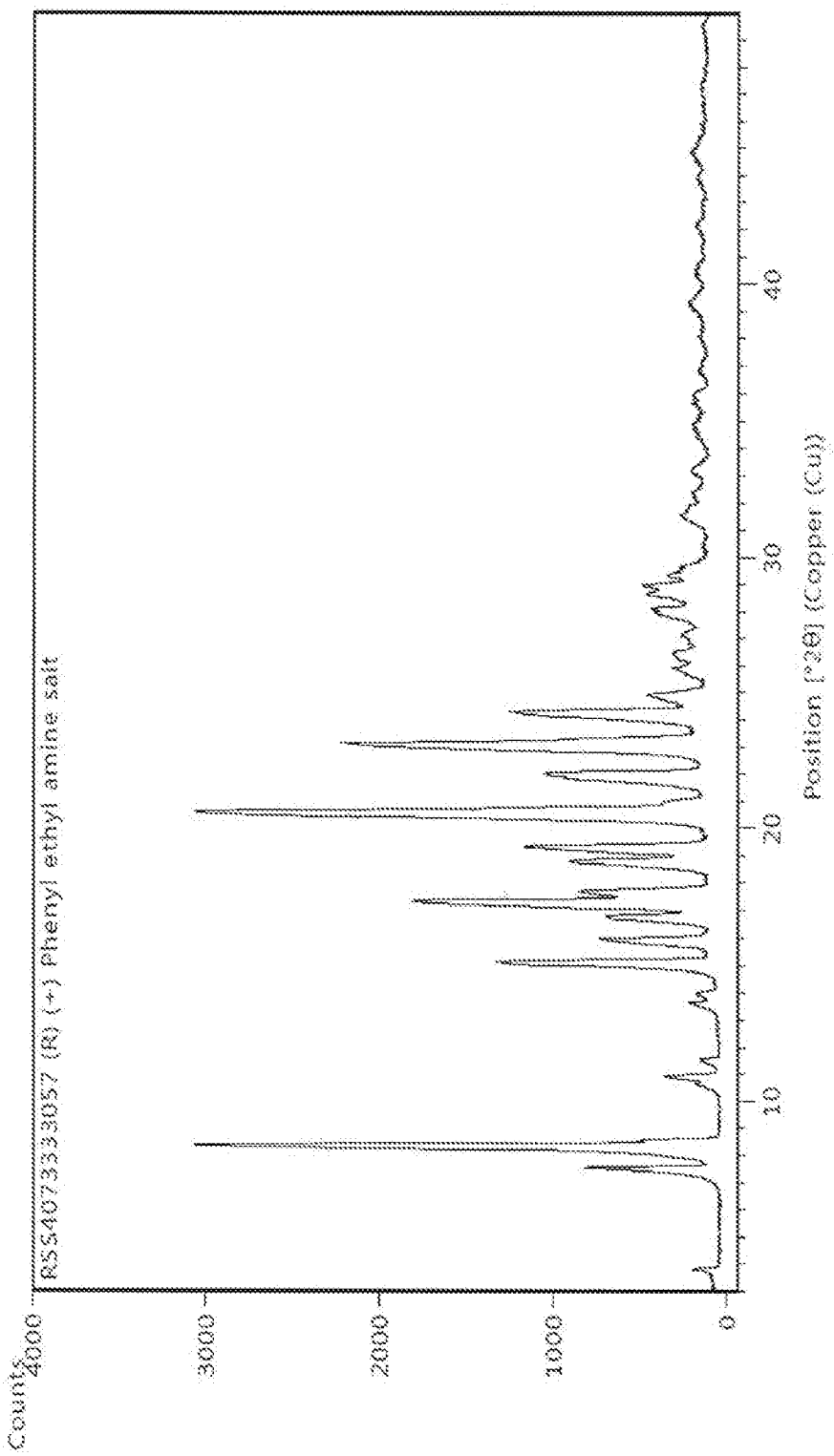

RSS407333057 (R) (+) Phenyl ethyl amine salt
Counts
4000
3000
2000
1000
0
10
20
30
40
Position [°2θ] (Copper (Cu))

FIG. 7

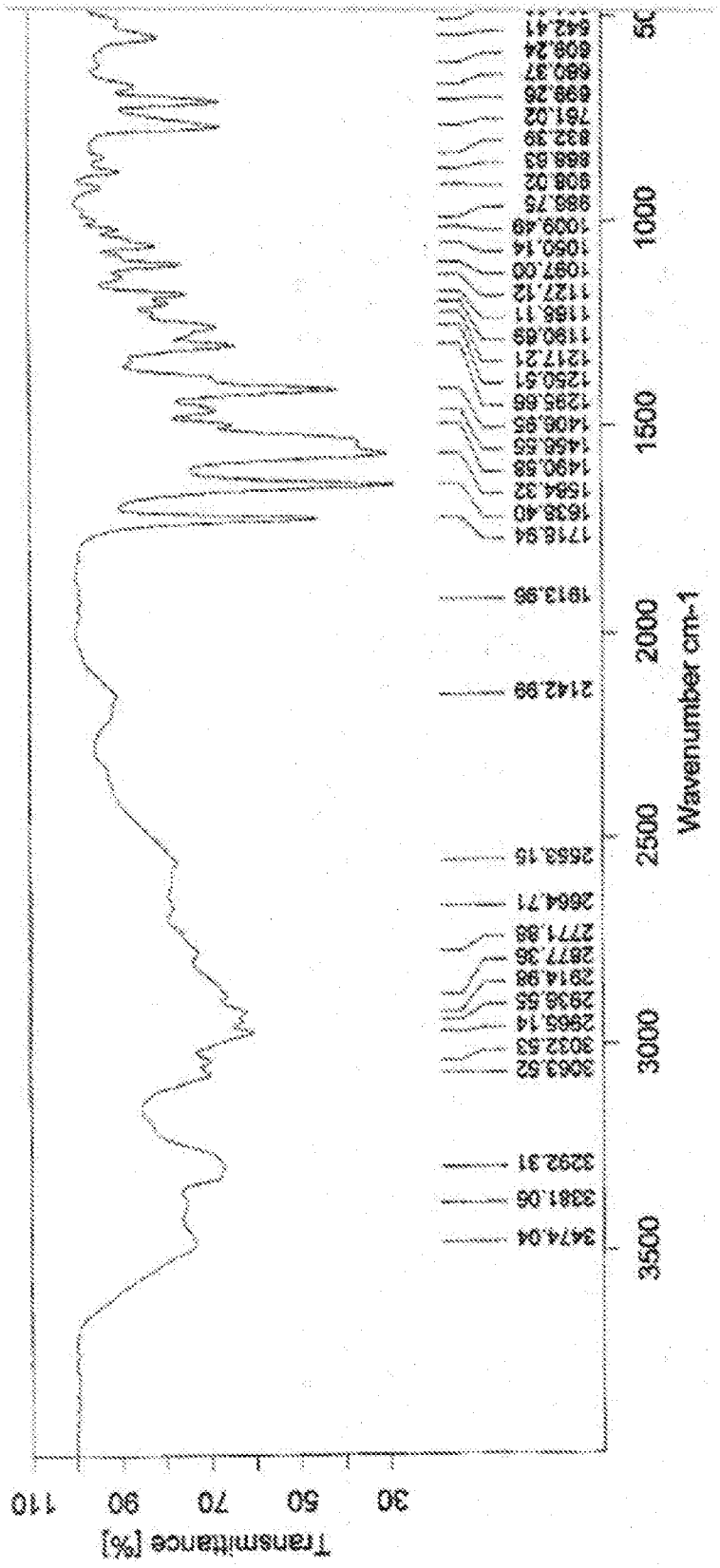

Transmittance [%]
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60
30
Wavenumber cm-1
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3000
2500
2000
1500
1000
500
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3381.06
3292.31
3063.52
3032.63
2965.14
2936.55
2914.98
2877.36
2771.88
2664.71
2553.15
2142.98
1913.86
1716.94
1638.40
1594.32
1490.58
1456.65
1406.95
1385.66
1260.61
1217.21
1190.69
1156.11
1127.12
1097.00
1050.14
1009.49
986.75
928.02
888.53
832.58
781.52
698.28
660.37
608.24
542.41

FIG. 8

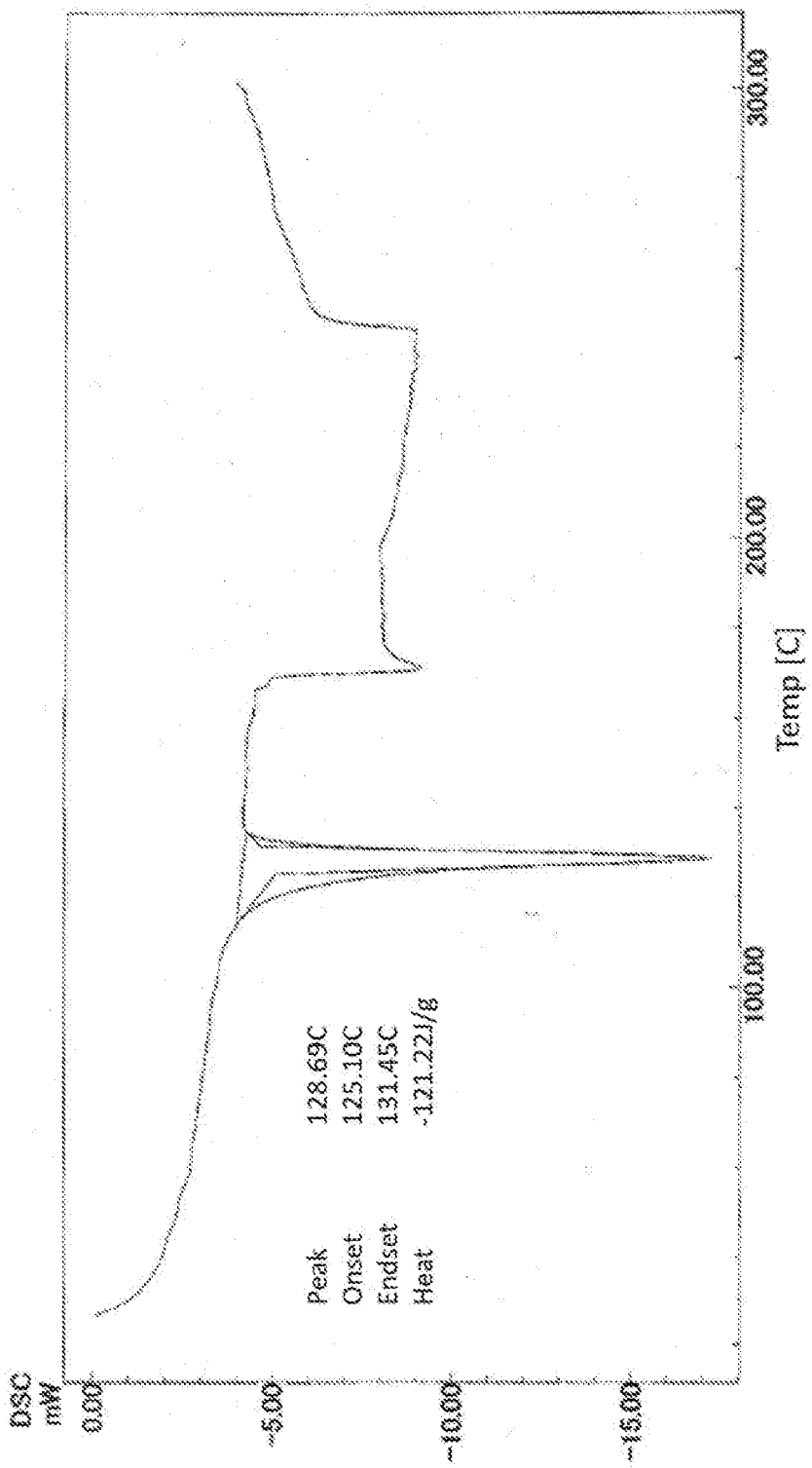

DSC
mW
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-5.00
-10.00
-15.00
100.00
200.00
300.00
Temp [C]
Peak 128.69C
Onset 125.10C
Endset 131.45C
Heat -121.22J/g

FIG. 9

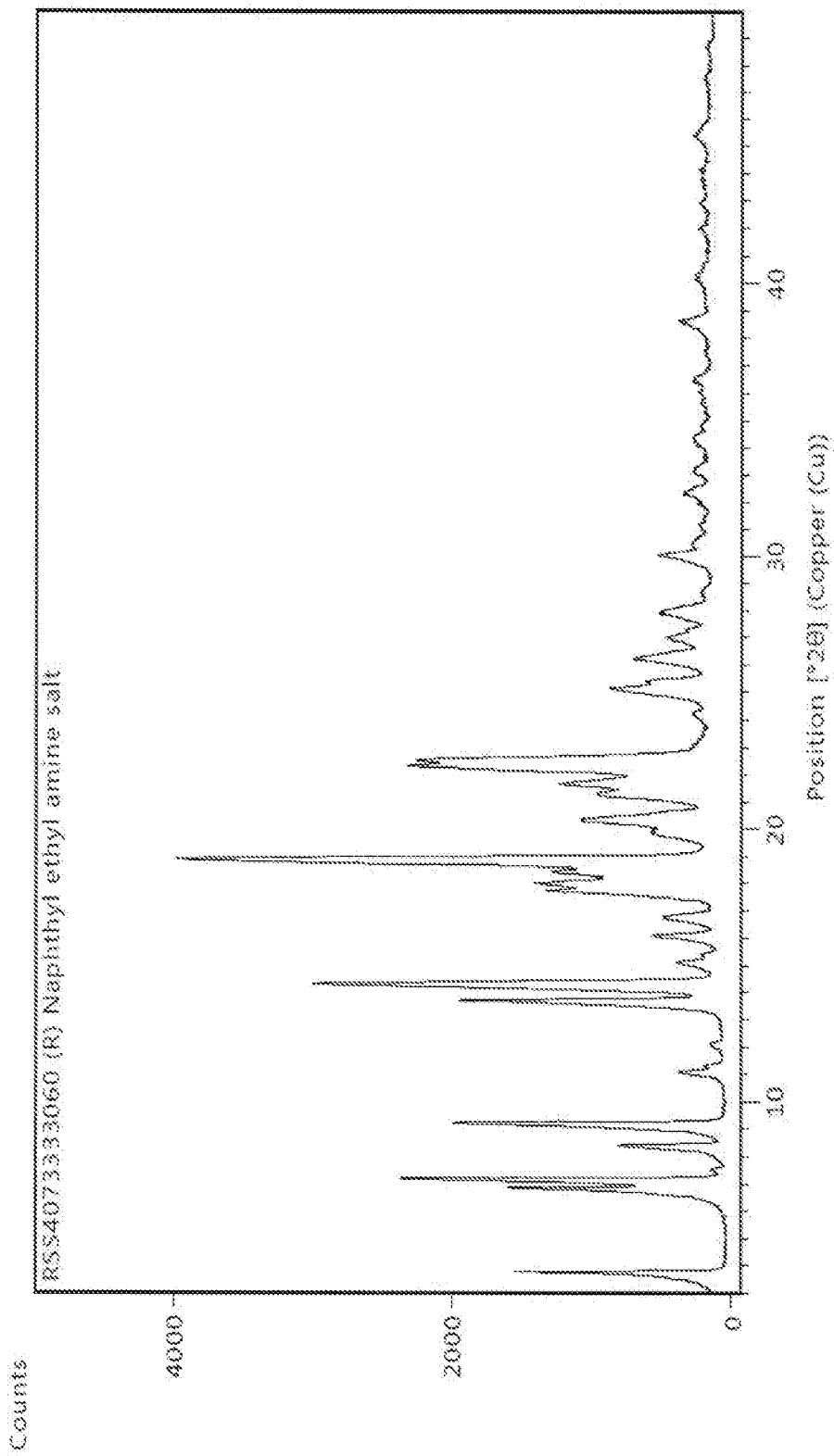

RSS407333060 (R) Naphthyl ethyl amine salt
Counts
4000
2000
0
10
20
30
40
Position [°2θ] (Copper (Cu))

FIG. 10

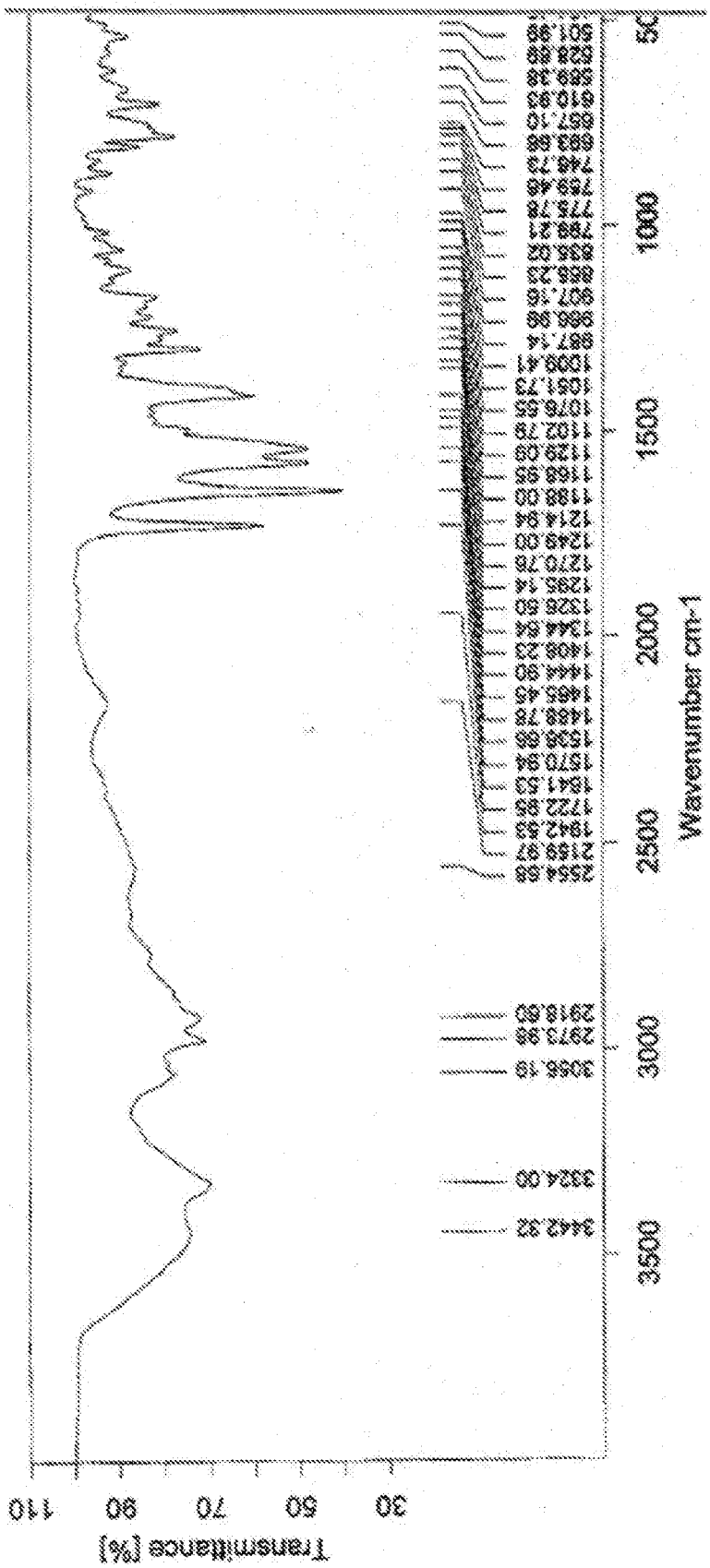

Transmittance [%]
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70
50
30
Wavenumber cm-1
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3000
2500
2000
1500
1000
500
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3056.19
2973.98
2918.60
2554.68
2159.97
1942.63
1723.85
1641.53
1570.94
1503.68
1488.78
1465.45
1444.90
1403.23
1344.84
1326.60
1295.14
1270.78
1249.00
1214.94
1188.00
1168.95
1129.09
1102.78
1076.55
1051.73
1009.41
987.14
969.98
907.16
856.23
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759.46
748.73
693.86
657.10
610.93
589.38
528.69
501.98

FIG. 11

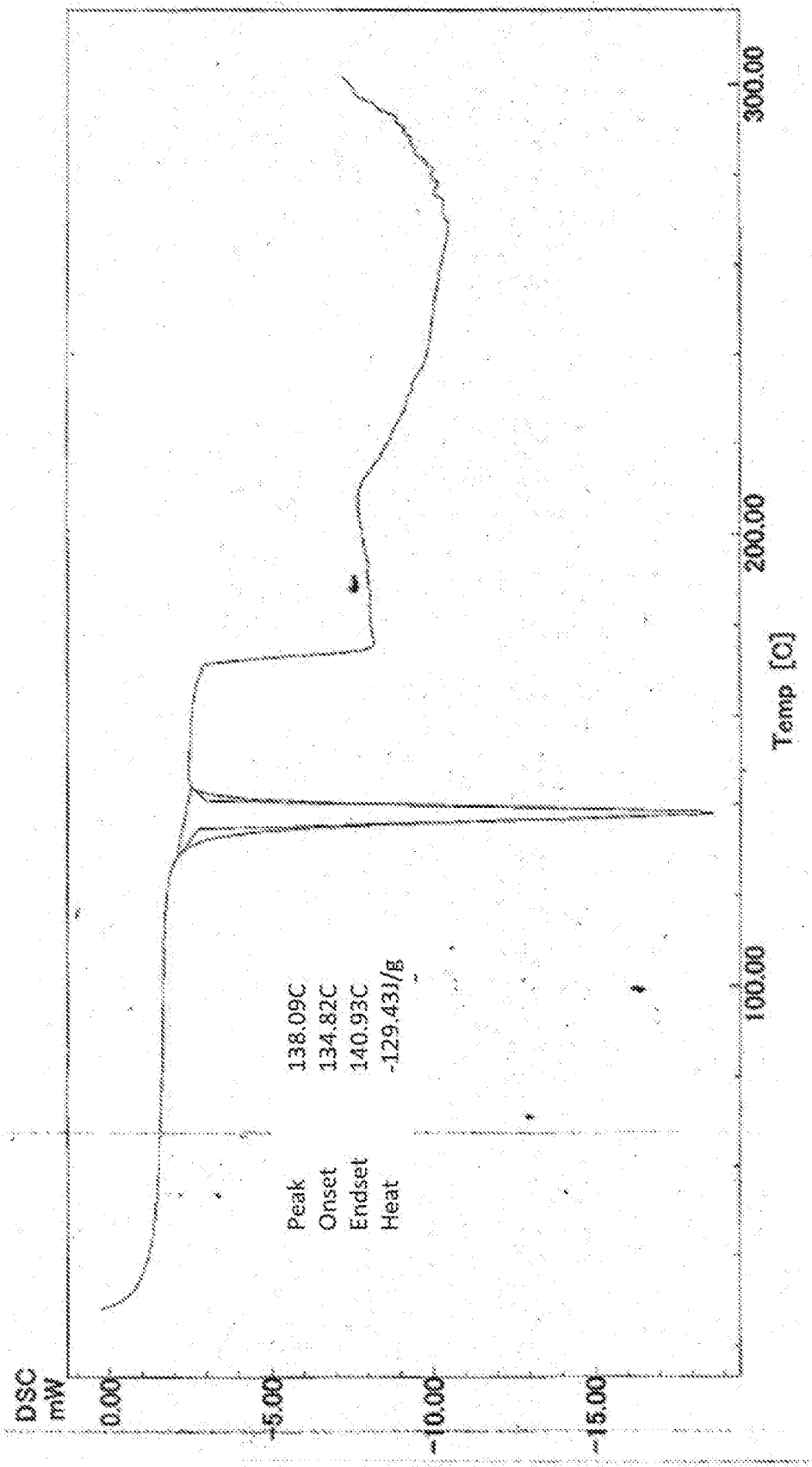

DSC
mW
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-5.00
-10.00
-15.00
100.00
200.00
300.00
Temp [C]
Peak 138.09C
Onset 134.82C
Endset 140.93C
Heat -129.43J/g

FIG. 12

INTERNATIONAL SEARCH REPORT

International application No
PCT/IS2016/050012

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C233/47 C07C231/02 C07C231/24 C07C211/07 C07C211/27
C07C211/30 C07C215/10 A61K31/216 A61K31/41 A61P9/12
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)
A61K C07C C07B

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, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GARY M KSANDER ET AL: "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US , vol. 38, no. 10 1 May 1995 (1995-05-01), pages 1689-1700, XP008154341, ISSN: 0022-2623, DOI: 10.1021/JM00010A014 Retrieved from the Internet: URL:http://pubs.acs.org/journals/jmcmar/index.html [retrieved on 1995-05-01] figure 3; compounds 18,19,20 page 1697; compounds 18,19,20 ----- -/--	1-7,9, 15-17, 19,25, 45-47

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 December 2016	09/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Kardinal, Siegmar

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/IS2016/050012

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 8 877 938 B2 (FENG LILI [US] ET AL) 4 November 2014 (2014-11-04) cited in the application claims; examples -----	1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IS2016/050012

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-6, 45-47(completely); 7, 9, 15-17, 19, 25(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-6, 45-47(completely); 7, 9, 15-17, 19, 25(partially)

   Preparation/purification of the compound of formula I, in particular using certain salts of the compound of formula II as starting material, whereby claims 7-9, 13-16 and 17-19, 23-27 are covered in so far as the "amine" used is pyridine (see claims 9, 19); Corresponding use and a pharmaceutical composition.

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2. claims: 8, 10-14, 18, 20-24, 26-44, 48(completely); 7, 9, 15-17, 19, 25(partially)

   Preparation/purification of the compound of formula I involving the intermediate formation of an amine salt III of an amine NR1R2R3 as defined in claims 7 and 17 or of an amine as defined in claims 12 and 22; Certain amine salts of the compound of formula I.
   Process of preparing trisodium N-(3-carboxy-1-oxopropyl)-(4S)-(p-phenylphenylmethyl)-4-amino-(2R)-methylbutanoic acid ethyl ester - valsartan hemipentahydrate.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IS2016/050012

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