

PHARMACEUTICALLY ACCEPTABLE SALT OF A CD47-SIRP ALPHA PATHWAY INHIBITOR

The present application claims priority to and the benefit of Indian Patent Application No. IN202341071231, filed on October 19, 2023, which application is incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

5 The present disclosure is directed to pharmaceutically acceptable salts of compound of formula (I) including its crystalline forms and methods of their preparation. The present disclosure also relates to pharmaceutical compositions comprising said salts of the compound of formula (I), crystalline forms thereof and methods of their use as a therapeutic agent.

BACKGROUND OF THE INVENTION

10 CD47 also known as integrin associated protein (IAP), ovarian cancer antigen (OA3), Rh-related antigen and MER6, is a transmembrane protein that, in humans, is encoded by the CD47 gene. CD47 belongs to the immunoglobulin superfamily and partners with membrane integrins and also binds the ligands thrombospondin-1 (TSP-1) and signal-regulatory protein alpha (SIRP α). CD47 is best known for its pivotal role in preventing
15 phagocytic removal of healthy cells by binding to phagocyte-expressed signal regulatory protein alpha (SIRP α). SIRP α , an inhibitory protein expressed on macrophages, once triggered, suppresses phagocytosis of CD47-expressing cells. This CD47/SIRP α axis is an important homeostatic mechanism preventing removal of healthy normal cells that express CD47. Reversely, down-regulation of CD47 on damaged, aged and superfluous cells ensures their
20 timely removal.

CD47 is expressed on virtually all non-malignant cells, and blocking the CD47 or the loss of CD47 expression or changes in membrane distribution can serve as markers of aged or damaged cells, particularly on red blood cells (RBC). Alternatively, blocking SIRP α also allows engulfment of targets that are not normally phagocytosed, for those cells where pre-
25 phagocytic signals are also present. CD47 is a broadly expressed transmembrane glycoprotein with a single Ig-like domain and five membrane spanning regions, which functions as a cellular ligand for SIRP α with binding mediated through the NH₂-terminal V-like domain of SIRP α . SIRP α is expressed primarily on myeloid cells, including macrophages, granulocytes, myeloid dendritic cells (DCs), mast cells, and their precursors, including hematopoietic stem cells.

CD47 is also constitutively upregulated on a number of cancers such as Non-Hodgkin Lymphoma (NHL), Acute myeloid leukemia (AML), breast, colon, glioblastoma, glioma, ovarian, bladder and prostate cancers. Overexpression of CD47 by tumor cells, which efficiently helps them to escape immune surveillance and killing by innate immune cells.

5 It has been shown that CD47 may be considered as potential target for the treatment of atherosclerosis. Because the process of atherogenesis i.e., the formation of atheromas on the wall of arteries, is associated with upregulation of CD47 which renders malignant cells resistant to programmed cell removal, or 'efferocytosis'. This effect of efferocytosis, is reversed upon administration of CD47-blocking antibodies which normalizes the clearance of diseased
10 vascular tissue, and ameliorates atherosclerosis in multiple mouse models (Kojima Y, et al., Nature. 2016 Aug 4; 536 (7614): 86-90). Further, it has been reported that blockade of CD47 with CD47-Fc fusion protein is effective in regulating Experimental autoimmune encephalomyelitis (EAE) in an animal model for multiple sclerosis (MS) thus provides a potential therapeutic target in preventing and treating MS (Gao Q et al., J Autoimmun. 2016
15 May; 69: 74-85).

International publications, WO2019138367 and WO2020095256 describe inhibitors of CD47-SIRP α signaling pathway, processes for the preparation thereof, pharmaceutical compositions comprising them, their uses as therapeutic agents as monotherapy as well as combination therapy in the treatment of various disorders, particularly in the treatment of
20 cancer and other proliferative disorders, which are incorporated herein by reference for all purposes.

Inhibitors of CD47 are currently being developed for the treatment of cancer. For drug development, it is typically advantageous to employ a form of the drug having desirable properties with respect to its preparation, purification, reproducibility, stability,
25 bioavailability, and other characteristics to prepare a suitable pharmaceutical formulation. However, obtaining a salt or a crystalline form of the CD47 inhibitors reported in the aforesaid literature was difficult because the compounds were not stable at ambient conditions.

WO2019138367 discloses a group of 1,2,4-oxadiazole compounds useful as CD47
30 signalling pathway inhibitors. One of the 1,2,4-oxadiazole compounds disclosed is (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline.

There is a need for new CD47 inhibiting compounds, which, besides possessing the requisite pharmacological properties, also are amenable to preparing pharmaceutically useful formulations and dosage forms with suitable properties, e.g. which allow the manufacture of safe, effective, and high-quality drug products.

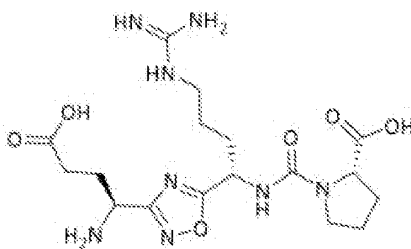
5 SUMMARY OF THE INVENTION

Compound of formula (I) is also known as (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline. In its free acid form, (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline is hygroscopic in nature and pose stability issues.

10 The present disclosure provides processes and synthesis of the pharmaceutically acceptable salts of compound of formula (I) with high yield and purity. The pharmaceutically acceptable salts of compound of formula (I), preferably compound of formula (I) calcium and compound of formula (I) sodium, as invented, exhibit unexpected physicochemical properties, for example, greater stability, greater purity and better suitability for pharmaceutical
15 development.

This disclosure also encompasses the pharmaceutically acceptable salts of the compound of formula (I), and polymorphs, co-crystals, anhydrous, and amorphous forms thereof.

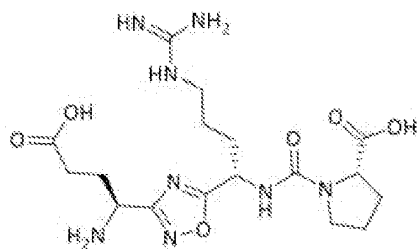
In one aspect, the present disclosure provides a pharmaceutically acceptable salt of
20 compound of formula (I):



(I);

wherein the pharmaceutically acceptable salt is an alkali metal salt or an alkaline earth metal salt.

25 In one aspect, the present disclosure provides a pharmaceutically acceptable salt of compound of formula (I):



(I);

wherein the pharmaceutically acceptable salt is a calcium salt or a sodium salt.

In one aspect, the present disclosure provides a process for preparing the
5 pharmaceutically acceptable salts of compound of formula (I).

In one aspect, the present disclosure provides a crystalline calcium salt of the compound of formula (I).

In one aspect, the present disclosure provides a crystalline sodium salt of the compound of formula (I).

10 In one aspect, the present disclosure provides a pharmaceutical composition comprising the pharmaceutically acceptable salts of the compound of formula (I) and one or more pharmaceutically acceptable carriers or excipients.

In one aspect, the present disclosure provides pharmaceutically acceptable salts of the compound of formula (I) according to the disclosure or a pharmaceutical composition
15 comprising the salt of the compound of formula (I) according to the disclosure for use as a medicament.

In one aspect, the present disclosure provides a method for treating or delaying progression of diseases or disorders wherein the method comprises administering to an individual an effective amount of pharmaceutically acceptable salts of the compound of
20 formula (I).

In one aspect, the present disclosure provides a pharmaceutically acceptable salts of the compound of formula (I) according to the disclosure or a pharmaceutical composition comprising the salt of the compound of formula (I) according to the disclosure for use in a method for treating or delaying progression of diseases or disorders mediated by CD47,
25 wherein the diseases or disorders mediated by CD47 are cancer or other proliferative diseases.

The physicochemical data obtained from the crystal structure of the compound of formula (I) free acid indicated that the compound of formula (I) exists as a Zwitter ion, thereby making the salt formation difficult. In-fact, most salts of the compound of formula (I) were found not to be suitable for pharmaceutical development. However, the salts and forms thereof
5 as disclosed in the present disclosure were surprisingly found to be less hygroscopic, more stable, and substantially pure, thereby rendering them suitable for pharmaceutical development.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows an XRPD pattern of the compound of formula (I) calcium collected at 25°C.

10 **FIG. 2** shows an XRPD Pattern of the compound of formula (I) free acid.

FIG. 3A shows an XRPD pattern of the compound of formula (I) disodium collected at 25°C.

FIG. 3B shows an XRPD pattern of the compound of formula (I) monosodium collected at 25°C.

15 **FIG. 4** shows a differential scanning calorimetry (DSC) thermogram of the compound of formula (I) calcium.

FIG. 5 shows a thermogravimetric analysis (TGA) of the compound of formula (I) calcium.

FIG. 6 shows XRPD overlay of the compound of formula (I) calcium exposed to various conditions.

FIG. 7 shows sorption-desorption isotherm for the compound of formula (I) calcium at 25°C.

20 **FIG. 8** shows Echo detected ^1H MAS NMR spectrum of the compound of formula (I) calcium.

FIG. 9 shows ^1H - ^{13}C CPMAS-NMR spectrum of the compound of formula (I) calcium.

FIG. 10A shows ^{13}C - ^1H 2D-Correlation NMR spectrum (HetCor) of the compound of formula (I) calcium.

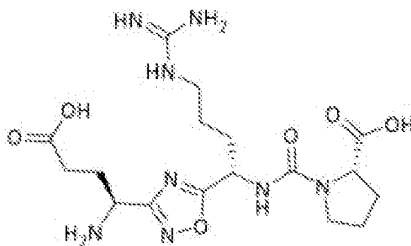
25 **FIG. 10B** shows zoomed ^{13}C - ^1H 2D-Correlation NMR spectrum (HetCor) of the compound of formula (I) calcium.

FIG. 11 shows stick model showing crystal structure of the compound of formula (I) free acid.

DETAILED DESCRIPTION OF THE INVENTION

As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

As used herein, the compound (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline or compound of formula (I) free acid
5 is the compound having the following formula:



(I).

As used herein, the terms “alkali metal salt of formula (I)”, “compound of formula (I) alkali metal salt”, “compound of formula (I) alkali metal” and “pharmaceutically acceptable salt of the compound of formula (I) wherein the salt is an alkali metal” are interchangeable and refer to one or more alkali metal ions with an ionic bond with the compound of formula (I).
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As used herein, the terms “alkaline metal salt of formula (I)”, “compound of formula (I) alkaline metal salt”, “compound of formula (I) alkaline metal” and “pharmaceutically acceptable salt of compound of formula (I) wherein the salt is an alkaline metal” are interchangeable and refer to one or more alkaline metal ions with an ionic bond with the compound of formula (I).
15

As used herein, the terms “calcium salt of formula (I)”, “compound of formula (I) calcium salt”, “compound of formula (I) calcium” and “pharmaceutically acceptable salt of compound of formula (I) wherein the salt is calcium” are interchangeable and refer to one or more calcium ions with an ionic bond with the compound of formula (I).
20

As used herein, the terms “sodium salt of formula (I)”, “compound of formula (I) sodium salt”, “compound of formula (I) sodium” and “pharmaceutically acceptable salt of compound of formula (I) wherein the salt is sodium” are interchangeable and refer to one or more sodium ions with an ionic bond with the compound of formula (I). Sodium salt of formula (I) can include monosodium salts and/or disodium salts.
25

As used herein, the term “alkali metal salt” refers to a salt of an alkali metal selected from Li, Na and K. In one embodiment, the alkali metal salt comprises Na salts or K salts. In one embodiment, the alkali metal salt comprises Na salts. In one embodiment, the alkali metal salt comprises K salts.

- 5 As used herein, the term “alkaline earth metal salt” refers to a salt of an alkaline earth metal selected from Be, Mg, Ca, Sr, and Ba. In one embodiment, the alkaline earth metal salt comprises Mg salts or Ca salts. In one embodiment, the alkaline earth metal salt comprises Ca salts. In one embodiment, the alkaline earth metal salt comprises Mg salts.

- 10 As used herein, the term “pharmaceutically acceptable” refers to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, immunogenicity or other problem or complication, commensurate with a reasonable benefit/risk ratio.

- 15 As used herein, the phrase “pharmaceutically acceptable carriers or excipients” refers to pharmaceutically acceptable materials, compositions, or vehicles, such as a liquid or solid filler, diluent, solvent, or encapsulating materials. Excipients or carriers are generally safe, non-toxic, and neither biologically nor otherwise undesirable and include excipients or carriers that are acceptable for veterinary use as well as human pharmaceutical use.

- 20 As used herein, “pharmaceutically acceptable salts” refers to derivatives of the disclosed compounds wherein the parent compound is modified by converting an existing acid or base moiety to its salt form. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts of the present disclosure include the conventional non-toxic salts of the parent compound
25 formed. The pharmaceutically acceptable salts of the present disclosure can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl
30 acetate, alcohols or acetonitrile (ACN) are preferred. In practice, use of the salt form amounts to use of the acid. Appropriate pharmaceutically acceptable salts within the scope of the disclosure are those derived from bases such as sodium hydroxide, sodium bicarbonate,

potassium hydroxide, lithium hydroxide, calcium hydroxide, calcium carbonate, magnesium sulphate and the like. In some embodiments, the cations are sodium, potassium, magnesium, and calcium. In some embodiments, the cations are sodium and calcium. In some embodiments the cation is calcium. In some embodiments the cation is sodium.

5 Depending upon solubility, inorganic salts which may be used include halide salts such as CaCl_2 , CaF_2 , CaBr_2 and CaI_2 , as well as calcium borate (B_4CaO_7), calcium tetrafluoroborate (CaBF_4), calcium carbonate (CaCO_3), monobasic calcium phosphate ($\text{Ca}(\text{H}_2\text{PO}_4)_2$), dibasic calcium phosphate (CaHPO_4) and tribasic calcium phosphate ($\text{Ca}(\text{PO}_4)_2$), calcium sulphate (CaSO_4) and calcium hydroxide ($\text{Ca}(\text{OH})_2$), and hydrates thereof.

10 As used herein, “crystalline” or “crystalline form” is meant to refer to a certain lattice configuration of a crystalline substance. Different crystalline forms of the same substance typically have different crystalline lattices (e.g., unit cells) which are attributed to different physical properties that are characteristic of each of the crystalline forms. In some instances, different lattice configurations have different water or solvent content.

15 As used herein, the term “subject”, “individual” or “patient,” used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

 As used herein, “therapeutically effective amount” refers to an amount that is sufficient to effect treatment, when administered to a mammal in need of such treatment. The
20 therapeutically effective amount will vary depending upon the subject being treated, the weight and age of the subject, the severity of the disease condition, the manner of administration and the like, which can readily be determined by one of ordinary skill in the art.

 The term “substantially pure”, as used herein, refers to a crystalline form, i.e., a polymorph, that is greater than 90% pure, meaning that it contains less than 10% of any other
25 compound, or an alternative polymorph of the crystalline form. In some embodiments, the crystalline form, i.e., polymorph, is greater than 95% pure, or even greater than 98% pure. In some embodiments, crystalline Form A, crystalline Form B, and/or crystalline Form C is greater than 90% pure, greater than 95% pure, greater than 98% pure, greater than 99% pure or greater than 99.5% pure.

30 The phrase “substantially as shown in **FIG.**” refers to a pattern with at least 50%, or at least 60%, or at least 70%, or at least 80%, or at least 90%, or at least 95% or at least 99% of

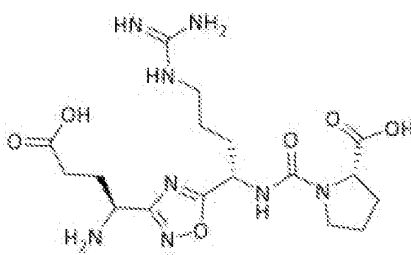
its value appears in the indicated Figure. In some embodiments, when referring to XRPD figures, the phrase “substantially as shown in **FIG.**” refers to a pattern of 2-theta values with at least 3, 4, 5, 6, 7, 8, 9 or greater than 9 peaks.

As used herein, the term “about” when referring to a number or a numerical range
 5 means that the number or numerical range referred to, is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range.

Each embodiment is provided by way of explanation of the disclosure, and not by way of limitation of the disclosure. In fact, it will be apparent to those skilled in the art that various
 10 modifications and variations can be made to the compounds, compositions, and methods described herein without departing from the scope or spirit of the disclosure. For instance, features illustrated or described as part of one embodiment can be applied to another embodiment to yield a still further embodiment. Thus, it is intended that the present disclosure include such modifications and variations and their equivalents. Other objects, features, and
 15 aspects of the present disclosure are disclosed in, or are obvious from, the following detailed description. It is to be understood by one of ordinary skill in the art that the present discussion is a description of exemplary embodiments only and is not to be construed as limiting the broader aspects of the present disclosure.

Compound of formula (I) and pharmaceutically acceptable salt thereof

20 In one embodiment, the present disclosure provides a pharmaceutically acceptable salt of the compound of formula (I):



(I) ;

wherein the pharmaceutically acceptable salt is an alkali metal salt or an alkaline earth
 25 metal salt.

In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 1% to about 5% by weight of the salt. In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 1.5% to about 4% by weight of the salt. In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 2% to about 3% by weight of the salt.

In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 1% to about 10% by weight of the salt. In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 5% to about 10% by weight of the salt. In some embodiments, the pharmaceutically acceptable salt of the compound of formula (I) comprises about 8% to about 10% by weight of the salt.

In one embodiment, the present disclosure provides a pharmaceutically acceptable salt of the compound of formula (I), wherein the salt is an alkaline earth metal salt.

In one embodiment, the alkaline earth metal salt is a calcium salt or a magnesium salt.

In one embodiment, the alkaline earth metal salt is a calcium salt.

In one embodiment, the present disclosure provides a compound of formula (I) calcium. In some embodiments, the calcium content in the compound of formula (I) calcium is from about 1% to about 5% by weight of the salt.

In some embodiments, the calcium content in the compound of formula (I) calcium is from about 1.5% to about 4% by weight of the salt.

In some embodiments, the calcium content in the compound of formula (I) calcium is from about 2% to about 3% by weight of the salt.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is in the range of 5:1 to 1:1.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is 5:1.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is 4:1.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is 3:1.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is 2:1.

In one embodiment, the stoichiometric ratio between the compound of formula (I) and calcium is 1:1.

5

In one embodiment, the compound of formula (I) calcium has a free acid to calcium molar ratio of 1 to <1, 1 to 0.5 – 0.9, 1 to 0.1 – 0.5, 1 to 0.1 – 0.3, or 1 to 0.25, etc.

In one embodiment, the compound of formula (I) calcium has a free acid to calcium molar ratio of 1 to <1 such as 1 to 0.9, 1 to 0.8, 1 to 0.7, 1 to 0.6, 1 to 0.5, 1 to 0.4, 1 to 0.3 or 1 to 0.25, etc.

10

In one embodiment, the compound of formula (I) calcium has a free acid to calcium molar ratio of 1 to <1, for e.g., 1 to 0.25. In some embodiments, the compound of formula (I) calcium is in the form of crystalline Form A. In some embodiments, the crystalline Form A has a free acid to calcium molar ratio of 1 to <1 such as 1 to 0.9, 1 to 0.8, 1 to 0.7, 1 to 0.6, 1 to 0.5, 1 to 0.4, 1 to 0.3 or 1 to 0.25, etc.

15

In some embodiments, the crystalline Form A has a free acid to calcium molar ratio between about 1:1 to about 3:1. In some embodiment, the crystalline Form A has a free acid to calcium molar ratio of about 2:1. In some embodiment, the crystalline Form A has a free acid to calcium molar ratio of about 1:1.

20

In one embodiment, the present disclosure provides a pharmaceutically acceptable salt of the compound of formula (I), wherein the alkali metal salt is a lithium salt, a sodium salt or a potassium salt.

In one embodiment, the alkali metal salt is a sodium salt or a potassium salt.

In one embodiment, the alkali metal salt is a sodium salt.

25

In one embodiment, the alkali metal salt is a monosodium salt or disodium salt.

In one embodiment, the sodium salt is a monosodium salt or a disodium salt.

In one embodiment, the sodium salt is a disodium salt.

In one embodiment, the sodium salt is a monosodium salt.

In one embodiment, the present disclosure provides compound of formula (I) sodium.

In some embodiments, the sodium content in the compound of formula (I) sodium is from about 1% to about 10% by weight of the salt.

In some embodiments, the sodium content in the compound of formula (I) sodium is from about 5% to about 10% by weight of the salt.

- 5 In some embodiments, the sodium content in the compound of formula (I) sodium is from about 8% to about 10% by weight of the salt.

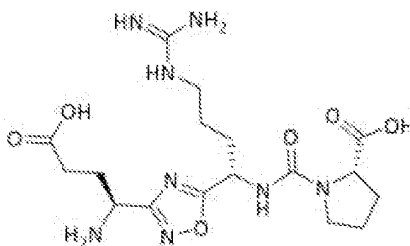
In one embodiment, the compound of formula (I) sodium may have a free acid to sodium molar ratio of 1 to <1 such as 1 to 0.9, 1 to 0.8, 1 to 0.7, 1 to 0.6, 1 to 0.5, 1 to 0.4, 1 to 0.3 or 1 to 0.25 etc.

- 10 In some embodiments, the compound of formula (I) sodium is in the form of crystalline Form B. In some embodiments, Form B is the crystalline form of the compound of formula (I) disodium. In some embodiments, the crystalline Form B has a free acid to sodium molar ratio of 1 to <1, of 1 to <1 such as 1 to 0.9, 1 to 0.8, 1 to 0.7, 1 to 0.6, 1 to 0.5, 1 to 0.4, 1 to 0.3 or 1 to 0.25, etc. In some embodiments, the compound of formula (I) sodium is in the form of
- 15 crystalline Form C. In some embodiments, Form C is the crystalline form of the compound of formula (I) monosodium. In some embodiments, the crystalline Form C has a free acid to sodium molar ratio of 1 to <1, of 1 to <1 such as 1 to 0.9, 1 to 0.8, 1 to 0.7, 1 to 0.6, 1 to 0.5, 1 to 0.4, 1 to 0.3 or 1 to 0.25.

Methods of preparing pharmaceutically acceptable salts of the compound of formula (I)

- 20 In one embodiment, the present disclosure provides a process for preparing the pharmaceutically acceptable salt of the compound of formula (I), the process comprising the steps of:

a) providing a mixture comprising compound of formula (I) and a solvent A;



(I);

b) reacting the mixture with a cation source and precipitating the salt of compound of formula (I) by using a solvent B; and

c) isolating the salt of compound of formula (I);

5 wherein the solvent A and the solvent B are independently selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.

In one embodiment, the solvent A is water.

In one embodiment, the compound of formula (I) in step (a) is in a free acid form.

10 In one embodiment, the compound of formula (I) in step (a) is a sodium salt of the compound of formula (I).

In one embodiment, the solvent B is ethanol. In another embodiment, the solvent B is an anti-solvent.

15 In one embodiment, the cation source is selected from calcium carbonate, calcium hydroxide, calcium methoxide, calcium chloride, magnesium carbonate, magnesium chloride or combinations thereof.

In some embodiment, the cation source in step (b) is calcium carbonate.

In one embodiment of the process for preparing the pharmaceutically acceptable salt of compound of formula (I), the compound of formula (I) is provided as a free acid. In one
20 embodiment of the process for preparing the pharmaceutically acceptable salt of the compound of formula (I), the compound of formula (I) is provided in a salt form wherein the cation is different from the cation of the cation source provided to prepare the salt. In one embodiment of the process for preparing the pharmaceutically acceptable salt of the compound of formula (I), the compound of formula (I) is provided as a sodium salt thereof. In one embodiment of
25 step a) in the process for preparing pharmaceutically acceptable salt of the compound of formula (I), the compound of formula (I) is a free acid. In one embodiment of step a) in the process for preparing the pharmaceutically acceptable salt of the compound of formula (I), the compound of formula (I) is present in salt form wherein the cation is different from the cation of the cation source provided to prepare the salt. In one embodiment of step a) in the process
30 for preparing the pharmaceutically acceptable salt of the compound of formula (I), the

compound of formula (I) of step a) is a free acid. In one embodiment of step a) in the process for preparing the pharmaceutically acceptable salt of the compound of formula (I), the compound of formula (I) is a sodium salt thereof.

5 In some embodiments, the process for preparing the pharmaceutically acceptable salt of the compound of formula (I) comprises treating a mixture of step (a) with metal ion exchange resin under aqueous conditions. In some embodiments, the process for preparing the pharmaceutically acceptable salt of the compound of formula (I), wherein the cation is selected from sodium, potassium, magnesium and lithium. In some embodiment, the cation is sodium.

10 In one embodiment, the process of preparing pharmaceutically acceptable salt of compound of formula (I) further comprises treating a mixture of step (a) with metal ion exchange resin, under aqueous conditions, thereby eliminating sodium ion from the mixture.

In one embodiment, the process of preparing pharmaceutically acceptable salt of compound of formula (I) further comprising optional step of treating a mixture of step (a) with metal ion exchange resin under aqueous conditions.

15 In one embodiment, the process of preparing pharmaceutically acceptable salt of compound of formula (I) further comprising optional step of treating a mixture of step (a) with metal ion exchange resin under aqueous conditions, thereby eliminating sodium ion from the mixture.

20 In one embodiment, the precipitation in step (b) is performed by addition of the solvent B.

In one embodiment, the process of preparing compound of formula (I) calcium, comprises treating a mixture comprising compound of formula (I) sodium with metal ion exchange resin under aqueous conditions. In one embodiment, the treatment of compound of formula (I) sodium with metal ion exchange resin is to eliminate the sodium ion from the mixture, thereby purifying the mixture comprising the compound of formula (I).

25 In one embodiment, the compound of formula (I) is isolated as a pharmaceutically acceptable salt. In some embodiments, the compound of formula (I) is isolated as sodium salt, wherein the compound of formula (I) is dissolved in a suitable solvent and passed through cation exchange resin. In some other embodiments, the compound of formula (I) is dissolved in TFA: TIPS: water mixture and then the mixture is treated with sodium ion source and the compound of formula (I) is isolated as sodium salt. In some embodiments, the compound of formula (I) sodium is passed through the column packed with cation exchange resin such as

sodium ion exchange resin. In some embodiments, the compound of formula (I) sodium is passed through the column packed with cation exchange resin wherein the cation exchange resin is selected from but not limited to Dowex 50WX8 200 Sodium resin, Indion 225 Sodium resin and the like. In some embodiments, the compound of formula (I) sodium is dissolved in
5 a suitable solvent such as acetone, tetrahydrofuran, ethanol, isopropanol, acetonitrile, and the like, and treated with calcium carbonate or any other alkaline earth metal ion source to provide a corresponding calcium or other alkaline earth metal salt of compound of Formula (I).

In one embodiment, the process of preparing the compound of formula (I) calcium, comprises treating a mixture comprising the compound of formula (I) sodium with metal ion
10 exchange resin under aqueous conditions. In one embodiment, treatment of the compound of formula (I) sodium with metal ion exchange resin is to eliminate the sodium ion from the mixture.

In one embodiment, the metal ion exchange resin is a cation exchange resin. In one embodiment, cation exchange resins are based on the cations such as hydrogen, ammonium, sodium, potassium and calcium. In one embodiment, the metal ion exchange resin is
15 sodium ion exchange resin. In one embodiment, the metal ion exchange resin is Indion resin. In one embodiment, the metal ion exchange resin is Indion 225Hresin.

In one embodiment, in step b) of the process for preparing the compound of formula (I) calcium, the precipitation of the salt is performed by addition of the solvent B. In one
20 embodiment, solvent B is an antisolvent.

In one embodiment of step b) of the process for preparing the compound of formula (I) calcium, the precipitation of the salt is carried out through the addition of an antisolvent and the antisolvent is solvent B.

In one embodiment, the solvent B is selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water, and mixtures thereof. In
25 one embodiment, the solvent B is ethanol.

In one embodiment, in step b) of the process for preparing the salt of the compound of formula (I), the cation source is selected from calcium carbonate, calcium hydroxide, calcium
30 methoxide, calcium chloride, magnesium carbonate, magnesium chloride, NaOH, Na₂CO₃ or combinations thereof.

According to the preceding embodiment, the salt is a pharmaceutically acceptable salt.

In one embodiment, the cation source is the calcium ion source.

In one embodiment, the cation source is the sodium ion source.

5 In one embodiment of step b) of the process for preparing the compound of formula (I) calcium, the cation source is selected from calcium carbonate, calcium hydroxide, calcium methoxide and calcium chloride.

In one embodiment of step b) of the process for preparing compound of formula (I) calcium, the calcium ion source is selected from calcium carbonate, calcium hydroxide, calcium methoxide and calcium chloride.

10 In one embodiment, the cation source in step (b) is calcium carbonate.

In one embodiment, the calcium source in (b) is calcium carbonate.

In one embodiment, in step b) of the process for preparing compound of formula (I) sodium, the cation source is selected from NaOH or Na₂CO₃.

15 In one embodiment, in step b) of the process for preparing compound of formula (I) sodium, the sodium ion source is selected from NaOH or Na₂CO₃.

In one embodiment, the isolating in (c) comprises filtering the mixture and precipitated salt of compound of formula (I) of (b) and, washing and drying the precipitated salt of compound of formula (I) obtained from the filtration.

20 In one embodiment, the step c) of isolation of calcium salt of compound of formula (I) from the mixture comprises filtering the mixture comprising the salt, washing and drying the salt obtained from the filtration.

25 In one embodiment, the step (c) of isolating the salt of compound of formula (I) further comprises sub-steps of i) filtering the mixture and precipitating the salt of compound of formula (I) from step (b); and ii) washing and drying the precipitated salt of compound of formula (I) obtained from the filtration.

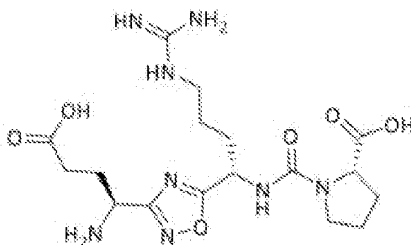
In one embodiment, step c) of isolation of calcium salt of the compound of formula (I) from the mixture further comprises sub-steps of i) filtering the mixture comprising the salt; and ii) washing and drying the salt obtained from the filtration.

In one embodiment, the process of preparing the compound of formula (I) calcium comprises reacting sodium salt of the compound of formula (I) with a calcium ion source under aqueous conditions, wherein the calcium ion source is calcium carbonate.

The term as used herein, “anti-solvent” or “antisolvent” means a solvent in which the compound crystals are insoluble, minimally soluble, or partially soluble, (i.e. solubility less than 1 mg/mL). In practice, the addition of an antisolvent to a solution in which crystals are dissolved reduces the solubility of the crystals in solution, i.e., supersaturation, thereby stimulating precipitation of the subject compound. In one embodiment, the crystals are washed with a combination of antisolvent and the organic solvent. In one embodiment, the antisolvent is water, while in other embodiments, it is an alkane solvent, such as hexane or pentane, or an aromatic hydrocarbon solvent, such as 1,2-dichloroethane, benzene, toluene, methylcyclohexane or xylene.

In one embodiment, the antisolvent is dichloromethane, dichloroethane, ethanol, methanol, propanol, butanol, pentanol, isobutyl acetate, isobutylene acetate, methylcyclohexane, n-hexane, n-heptane, tetrahydrofuran, and mixtures thereof.

In one embodiment, the present disclosure provides a process for preparing the calcium salt of the compound of formula (I) comprising reacting a compound of formula (I) with a cation source in the presence of solvent C:



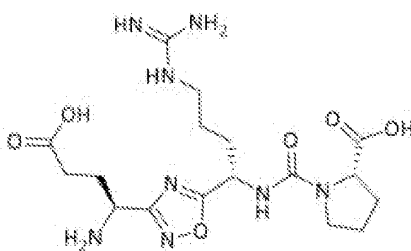
(I)

wherein the solvent C is selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.

In one embodiment, the cation source comprises calcium carbonate, calcium hydroxide, calcium methoxide, calcium chloride or a combinations thereof.

In one embodiment, the reaction is carried out at about 20 °C to about 40 °C. In another embodiment, the reaction is carried out at a temperature of about 20 °C, about 25 °C, about 30 °C, about 35 °C or about 40 °C. In one embodiment, the salt obtained is a crystalline compound of formula (I) calcium.

- 5 In another embodiment, the present disclosure provides a process for preparing the sodium salt of the compound of formula (I) comprising reacting a compound of formula (I) with a cation source in the presence of solvent C:



(I);

- 10 wherein the solvent C is selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.

In some embodiments, the cation source is NaOH or Na₂CO₃. In another embodiment, the cation source is NaOH.

- 15 In one embodiment, the reaction is carried out at a temperature of about 20 °C, about 25 °C, about 30 °C, about 35 °C or about 40 °C.

In one embodiment, the salt of compound of formula (I) obtained is a crystalline compound of formula (I) calcium or a crystalline compound of formula (I) sodium.

In one embodiment, the salt obtained is a crystalline compound of formula (I) sodium.

- 20 In some embodiments, the salts of the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have improved solubility in a solvent, e.g., improved solubility in an aqueous environment, e.g., *in vivo*. In some embodiments, the salts of the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have an increased dissolution rate in an aqueous environment, e.g., *in vivo*. In some
25 embodiments, the salts of the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have improved bioavailability. In some embodiments, the salts of

the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have improved physical stability. In some embodiments, the salts of the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have improved chemical stability, e.g., have reduced formation of degradation products. In some embodiments, the salts
5 of the compound of formula (I) described herein, e.g., alkali metal salts and/or alkaline metal salts, have reduced oxidation.

In one embodiment, the salts are present in crystalline form. In another embodiment, the salts are present in an amorphous form.

In one embodiment, these salts may be present either in substantially crystalline forms
10 or as partially crystalline forms.

In one embodiment, the salts may be present in substantially crystalline form. The term “substantially crystalline” as used herein refers to salts of the compound of formula (I) in which it is from 50% to 100% crystalline. Within this range, the salt of the compound of formula (I) may be at least 55% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at
15 least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.

In one embodiment, the term “substantially crystalline” as used herein refers to salts of the compound of formula (I) calcium in which it is from 50% to 100% crystalline. Within this
20 range, the salt of the compound of formula (I) calcium may be at least 55% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.

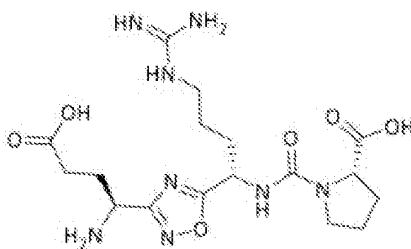
In one embodiment, the term “substantially crystalline” as used herein refers to salts of
25 the compound of formula (I) sodium in which it is from 50% to 100% crystalline. Within this range, the salt of compound of formula (I) sodium may be at least 55% crystalline, or at least 60% crystalline, or at least 70% crystalline, or at least 80% crystalline, or at least 90% crystalline, or at least 95% crystalline, or at least 98% crystalline, or at least 99% crystalline, or at least 99.5% crystalline, or at least 99.9% crystalline, for example 100% crystalline.

30 In some embodiments, the crystalline forms described herein, e.g., Form A, Form B and/or Form C, have improved solubility in a solvent, e.g., improved solubility in an aqueous

solvent. In some embodiments, the crystalline forms described herein, e.g., Form A, Form B and/or Form C, have an increased dissolution rate in an aqueous environment, e.g., improved solubility in an aqueous solvent. In some embodiments, the crystalline forms described herein, e.g., Form A, Form B and/or Form C, have improved physical stability, e.g., the crystal structure is stable for an extended period of time. In some embodiments, the crystalline forms described herein, e.g., Form A, Form B and/or Form C, have improved chemical stability, e.g., have reduced formation of degradation products. In one embodiment, the salts of the present disclosure may be present in an amorphous form. In some embodiments, the salts of the present disclosure may be present in amorphous form, for example, contain up to 30% of a crystalline form. In some embodiments, salts of the present disclosure, may be present in an amorphous form which may also for example, contain up to 25%, 20%, 15%, 10%, 5%, or 2% of a crystalline solid. In some embodiments, salts of the present disclosure contains a mixture of crystalline solids and amorphous solids, the characterizing data, such as XRPD, may contain indicators of both crystalline and amorphous forms. In one embodiment, the salts of the present disclosure may be present in substantially amorphous form. As used herein, the term “substantially amorphous” refers to a solid material having little or no long-range order in the position of its molecules. For example, substantially amorphous materials have less than 15% crystallinity (e.g., less than 10% crystallinity, less than 5% crystallinity, or less than 2% crystallinity). In one embodiment, the salts are present in non-solvated form or in a solvent free form. In another embodiment, the salts are present in solvated/hydrated form.

In one embodiment, there is provided certain forms of compound of formula (I) calcium which are in partially crystalline form. In an embodiment, the calcium salts may be present either in partially crystalline forms, crystalline form or amorphous form. In an embodiment, partially crystalline form of a compound of formula (I) calcium is having crystalline purity in the range of 10-90%, preferably crystalline purity 10-80%, or crystalline purity of at least 10-70%, or crystalline purity of at least 10-60%, or crystalline purity of at least 10-50%, or crystalline purity of at least 10-40%, or crystalline purity of 10-30%, or crystalline purity of 10-20% and including all values in between the defined ranges.

In one embodiment, the present disclosure provides a crystalline form of a compound of formula (I) calcium:



(I).

In one embodiment, the crystalline form is characterized by X-ray powder diffraction analysis.

5 In some embodiments, the crystalline form of the compound of formula (I) calcium is Form A.

In some embodiments, the crystalline form is Form A characterized by an X-ray powder diffraction (XRPD) pattern comprising at least 3 peaks with 2-theta values selected from 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

15 In some embodiments, the crystalline form is Form A characterized by an X-ray powder diffraction (XRPD) pattern comprising at least 4 peaks with 2-theta values selected from 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

25 In some embodiments, the crystalline form is Form A characterized by an XRPD pattern comprising at least 5 peaks with 2-theta values selected from 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

0.2, 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

In some embodiments, the crystalline form is Form A characterized by an XRPD pattern comprising at least 6 peaks, at least 7 peaks, at least 8 peaks, at least 9 peaks, or at least 10 peaks as described in the previous embodiments.

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 9.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 13.2 ± 0.2 .

10 In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 19.8 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 .

15 In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9 , 13.2 ± 0.2 and 19.8 ± 0.2 and 23.9 ± 0.2 .

20 In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9 , 13.2 ± 0.2 and 19.8 ± 0.2 and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 and 23.9 ± 0.2 .

25 In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9

± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 21.5 ± 0.2 and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 21.5 ± 0.2 and 23.9 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

In one embodiment, the crystalline Form A is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

In one embodiment, crystalline Form A is characterized by X-ray powder diffraction (XRPD) pattern substantially as shown in **FIG. 1**.

Table 1: Exemplary peaks of compound of formula (I) Calcium

Index	Pos. [$^{\circ}$ 2-Theta (2 θ)]	d-spacing [$\text{\AA}$]
1	8.0983	10.92
2	9.5452	9.27
3	9.8765	8.96
4	10.6616	8.30
5	11.8148	7.49
6	12.9385	6.84
7	13.1970	6.71
8	13.8046	6.42
9	14.1226	6.27
10	15.0182	5.90
11	16.2787	5.45
12	16.4909	5.38
13	17.6691	5.02
14	19.1769	4.63
15	19.4344	4.57
16	19.8448	4.47
17	20.5361	4.32
18	20.9281	4.24
19	21.5961	4.12
20	22.1102	4.02
21	23.4349	3.80
22	23.9127	3.72
23	24.3936	3.65
24	25.7131	3.46
25	26.7197	3.34
26	27.8234	3.21
27	29.1545	3.06
28	29.9225	2.99

Provided herein is characterizing information to describe any solid forms of crystalline Form A. It should be understood, however, that not all such information is required for one skilled in the art to determine that such particular form is present in a given composition, but that the determination of a particular form can be achieved using any portion of the characterizing information that one skilled in the art would recognize as sufficient for establishing the presence of a particular form, e.g., even a distinguishing peak can be sufficient for one skilled in the art to appreciate that such particular form is present.

In one embodiment, the compound of formula (I) calcium, e.g., Form A, by differential scanning calorimetry (DSC) shows an endotherm with a peak temperature from about 145 °C to about 160 °C corresponding to the melting. In some embodiments, the compound of formula (I) calcium, e.g., Form A, shows an endotherm with a peak temperature in the range selected from about 145 °C to about 155 °C corresponding to the melting. In some embodiment, Form A having an endotherm with a peak temperature at about 145 °C to about 155 °C, as measured by differential scanning calorimetry (DSC). In some embodiments, the compound of formula (I) calcium, e.g., Form A, shows an endotherm with a peak temperature in the range selected from about 145 °C to about 155 °C, about 150 °C to about 155 °C and about 150 °C to about 153 °C as determined by DSC corresponding to the melting. In some embodiment, Form A having an endotherm with a peak temperature at about 145 °C to about 155 °C, preferably about 150 °C to about 155 °C, or more preferably about 150 °C to about 153 °C as determined by DSC. In one embodiment, the compound of formula (I) calcium shows an endotherm with a peak temperature at 153 °C $\pm$ 3 °C as determined by DSC. In some embodiment, Form A having an endotherm with a peak temperature at about 153 °C $\pm$ 3 °C as determined by DSC. See, **FIG. 4**.

In one embodiment, the compound of formula (I) calcium, e.g., Form A, is having endotherm with a peak temperature as shown in **FIG. 4**.

In one embodiment, the compound of formula (I) calcium, e.g., Form A, is having a thermogravimetric analysis (TGA) pattern substantially as shown in **FIG. 5**.

In an embodiment, the present disclosure provides a crystalline form of compound of formula (I) calcium or calcium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline having at least one of the following characteristics:

- a) an XRPD pattern substantially as shown in **FIG.1**; and
- b) at least one XRPD peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 .

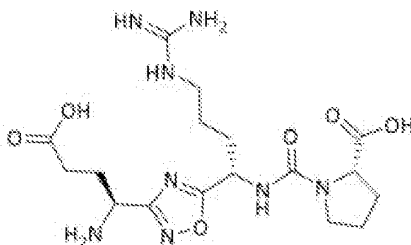
In an embodiment, the present disclosure provides a crystalline form of the compound of formula (I) calcium or calcium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline having at least one of the following characteristics:

- a) a XRPD pattern substantially as shown in **FIG.1**;
- b) at least one XRPD peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 ; and
- c) an endotherm with a peak temperature at $153 \text{ }^{\circ}\text{C} \pm 3 \text{ }^{\circ}\text{C}$ as determined by DSC.

In an embodiment, the present disclosure provides a crystalline form of compound of formula (I) calcium or calcium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline having at least one of the following characteristics:

- a) a XRPD pattern substantially as shown in **FIG.1**;
- b) at least one XRPD peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 ;
- c) an endotherm with a peak temperature at $153 \text{ }^{\circ}\text{C} \pm 3 \text{ }^{\circ}\text{C}$ as determined by DSC; and
- d) a TGA pattern as substantially as shown in **FIG.5**.

In one embodiment, the present disclosure provides a crystalline compound of formula (I) sodium:



(I).

In one embodiment, the present disclosure provides a crystalline compound of formula (I) monosodium. In some embodiments, the present disclosure provides a crystalline compound of monosodium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline. In one embodiment, the present disclosure provides a crystalline compound of formula (I) disodium.

In one embodiment, the present disclosure provides a crystalline form of a compound of formula (I) disodium or a disodium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline.

In one embodiment, the crystalline form of a compound of formula (I) disodium
5 characterized by X-ray powder diffraction analysis.

In some embodiments, the crystalline form of the compound of formula (I) disodium is Form B.

In some embodiments, the disodium crystalline form is Form B characterized by an XRPD pattern comprising at least 3 peaks with 2-theta values selected from 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2
10 and 42.4 ± 0.2 .

In some embodiments, the disodium crystalline form is Form B characterized by an XRPD pattern comprising at least 4 peaks with 2-theta values selected from 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2
15 and 42.4 ± 0.2 .

In some embodiments, the disodium crystalline form is Form B characterized by an XRPD pattern comprising at least 5 peaks with 2-theta values selected from 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2
and 42.4 ± 0.2 .

In some embodiments, the crystalline form is Form B characterized by an XRPD
20 pattern comprising at least 6 peaks, at least 7 peaks, at least 8 peaks, at least 9 peaks, or at least 10 peaks as described in the previous embodiments.

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 31.7 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction
25 pattern comprising at least one peak with 2-theta values 33.9 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 22.5 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction
30 pattern comprising at least one peak with 2-theta values 23.5 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 25.4 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 27.9 ± 0.2 .

5 In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 28.9 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 37.7 ± 0.2 .

10 In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 42.4 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 22.5 ± 0.2 , 23.5 ± 0.2 , 31.7 ± 0.2 and 33.9 ± 0.2 .

15 In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 and 37.7 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 and 37.7 ± 0.2 .

20 In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .

25 In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values: 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern comprising peaks with 2-theta values: 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .

In one embodiment, the crystalline Form B is characterized by X-ray powder diffraction pattern substantially as shown in **FIG. 3A**.

Table 2: Exemplary peaks of compound of formula (I) disodium

Index	Pos. [°2-Theta (2θ)]	d-spacing [Å]
1	18.538	4.78249
2	18.918	4.68711
3	22.512	3.94637
4	23.505	3.78176
5	25.410	3.50245
6	27.939	3.19088
7	28.906	3.08636
8	31.788	2.81276
9	33.931	2.63988
10	37.776	2.37954
11	42.403	2.12995

In one embodiment, the present disclosure provides a crystalline form of a compound of formula (I) monosodium or a monosodium salt of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline.

In one embodiment, the crystalline form of a compound of formula (I) monosodium characterized by X-ray powder diffraction analysis.

In one embodiment, the crystalline form of the compound of formula (I) monosodium is Form C.

In one embodiment, the crystalline compound of formula (I) monosodium is Form C characterized by X-ray powder diffraction pattern comprising at least one peak with 2-theta values 42.3 ± 0.2 , 42.9 ± 0.2 , 43.2 ± 0.2 and 43.8 ± 0.2 .

In one embodiment, Form C is characterized by X-ray powder diffraction pattern substantially as shown in **FIG. 3B**.

Table 3: Exemplary peaks of compound of formula (I) monosodium

Index	Pos. [$^{\circ}$ 2-Theta (2 θ)]	d-spacing [$\text{\AA}$]
1	18.593	4.76841
2	22.558	3.93845
3	23.543	3.77579
4	25.472	3.49403
5	31.781	2.81334
6	33.943	2.63892
7	37.795	2.37838
8	42.357	2.13218
9	42.983	2.10255
10	43.275	2.08904
11	43.875	2.06184

5 In one embodiment, the present disclosure provides a compound obtainable by a process which comprises:

- i) providing an aqueous mixture comprising compound of formula (I);
- ii) reacting the mixture with calcium carbonate;
- iii) filtering the mixture obtained in (ii) and adding an antisolvent to the filtrate; and
- 10 iv) isolating the compound so obtained from the mixture; wherein the antisolvent is ethanol.

In one embodiment, the present disclosure provides a compound obtainable by a process, the process comprising the steps of:

- i) providing an aqueous mixture comprising a compound of formula (I);
- 15 ii) reacting the mixture with calcium carbonate;
- iii) filtering the mixture of step (ii) to obtain a filtrate;
- iv) adding a solvent B to the filtrate to form a reaction mixture, wherein the solvent B is ethanol; and
- v) isolating the compound from the reaction mixture.

In some embodiments, the disclosure provides a compound obtainable by a process which comprises:

- i) providing an aqueous mixture comprising a compound of formula (I);
- ii) reacting the mixture with calcium carbonate and then filtering the mixture to obtain
5 a filtrate;
- iii) adding an antisolvent to the filtrate to form a reaction mixture, wherein the antisolvent is ethanol; and
- iv) isolating the compound from the reaction mixture.

10 In some embodiments, the disclosure provides a compound obtainable by a process which comprises:

- i) providing an aqueous mixture comprising a compound of formula (I);
- ii) reacting the mixture with calcium carbonate;
- iii) filtering the mixture of step (ii) to obtain a filtrate;
- 15 iv) adding a solvent B to the filtrate to form a reaction mixture, wherein the solvent B is ethanol; and
- v) isolating the compound from the reaction mixture.

In one embodiment, adding a solvent B to the filtrate to form a reaction mixture, wherein the calcium salt crystallizes out of the reaction mixture.

20 In one embodiment, adding a solvent B to the filtrate to form a reaction mixture, wherein the calcium salt of the compound of formula (I) crystallizes out of the reaction mixture.

According to the preceding embodiment, the solvent B is an anti-solvent facilitating the crystallization of the calcium salt of the compound of formula (I) from the filtrate.

25 In one embodiment of a compound obtainable by a process, of the action of isolation of the compound comprises filtering the compound from the reaction mixture, washing and drying the compound obtained from the reaction mixture under vacuum condition.

30 In one embodiment, the compound obtainable by a process wherein the step (v) of isolating the compound further comprises sub-steps of i) filtering the compound from the reaction mixture; and ii) washing and drying the compound obtained from the reaction mixture under vacuum condition.

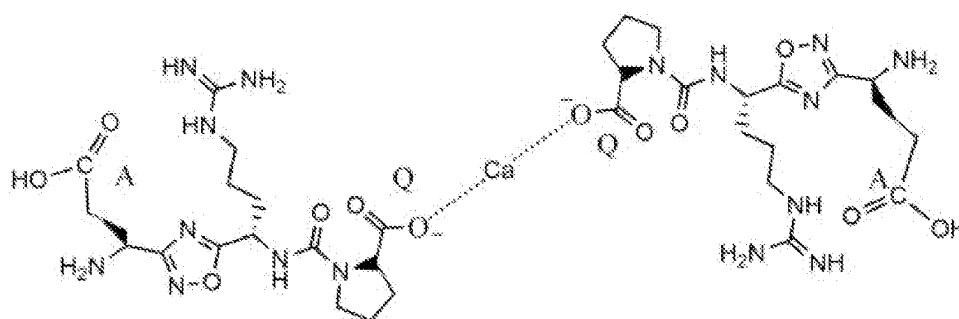
In one embodiment, the crystalline compound of formula (I) calcium is the crystalline calcium salt of compound of formula (I) as described herein.

In some embodiments, the compound of formula (I) calcium or compound of formula (I) sodium is substantially isolated.

5 By “substantially isolated” is meant that the salt, cocrystal or compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the salts described herein. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at
 10 least about 97%, or at least about 99% by weight of the salts described herein, or salt thereof. Methods for isolating compounds and their salts are conventional techniques routine in the art.

In one embodiment, the preparation method further comprises inducing crystallization. The method can also comprise drying the crystals, for example, under reduced pressure. In one embodiment, inducing precipitation or crystallization comprises secondary nucleation, wherein
 15 nucleation occurs in the presence of seed crystals or interactions with the environment (crystallizer walls, stirring impellers, sonication, etc.).

In some embodiments, the compound of formula (I) calcium is represented by formula (IA):



20 (IA).

The calcium salt of the compound of formula (I) according to the preceding embodiment, wherein the compound is in a crystalline form.

25

Pharmaceutical compositions

In one embodiment, the disclosure relates to a pharmaceutical composition comprising a pharmaceutically acceptable salt of the compound of formula (I) and one or more pharmaceutically acceptable carriers or excipients.

5 In one embodiment, a pharmaceutically acceptable salt of the compound of formula (I) is a compound of formula (I) calcium. In one embodiment, a pharmaceutically acceptable salt of the compound of formula (I) is a compound of formula (I) disodium.

In one embodiment, the disclosure relates to a pharmaceutical composition comprising a compound of formula (I) calcium and one or more pharmaceutically acceptable excipients.

10 In one embodiment, the disclosure relates to a pharmaceutical composition comprising a compound of formula (I) calcium (1:0.25) and one or more pharmaceutically acceptable excipients.

In one embodiment, the present disclosure relates to a pharmaceutical composition comprising a compound of formula (I) calcium thereof in combination with at least one other
15 therapeutic agent and a pharmaceutically acceptable carrier or excipient.

In one embodiment, the present disclosure provides a use of pharmaceutical composition comprising a compound of formula (I) calcium or compound of formula (I) sodium, and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). In one embodiment, the present disclosure provides a use of
20 a pharmaceutical composition comprising a compound of formula (I) calcium as described herein and at least one pharmaceutically acceptable excipient (such as a pharmaceutically acceptable carrier or diluent). The compound of formula (I) calcium or compound of formula (I) sodium, described in the present disclosure may be associated with a pharmaceutically acceptable excipient (such as a carrier or a diluent) or be diluted by a carrier or enclosed within
25 a carrier which can be in the form of a capsule, sachet, paper or other container.

The compounds described in the present disclosure are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared using procedures well known in the pharmaceutical art and comprise at least one compound of the present disclosure. The pharmaceutical composition of the present disclosure comprises one or more
30 compounds described herein and one or more pharmaceutically acceptable excipients. Typically, the pharmaceutically acceptable excipients are approved by regulatory authorities or are generally regarded as safe for human or animal use. The pharmaceutically acceptable excipients include, but are not limited to, carriers, diluents, glidants and lubricants,

preservatives, buffering agents, chelating agents, polymers, gelling agents, viscosifying agents, solvents and the like.

The pharmaceutical composition can be administered by oral, parenteral or inhalation routes. Examples of parenteral administration include administration by injection,
5 percutaneous, transmucosal, transnasal and transpulmonary administrations.

Examples of suitable carriers include, but are not limited to, water, salt solutions, alcohols, polyethylene glycols, lactose, sucrose, dextrin, magnesium carbonate, sugar, amylose, magnesium stearate, talc, stearic acid, lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, fatty acid esters and
10 polyoxyethylene.

The pharmaceutical composition may also include one or more pharmaceutically acceptable auxiliary agents, wetting agents, suspending agents, preserving agents, buffers, sweetening agents, flavouring agents, colorants or any combination of the foregoing.

The pharmaceutical compositions may be in conventional forms, for example, tablets,
15 capsules, solutions, suspensions, injectables or products for topical application. Further, the pharmaceutical composition of the present disclosure may be formulated to provide desired release profile.

Administration of compounds of the disclosure, in pure form or in an appropriate pharmaceutical composition, can be carried out using any of the accepted routes of
20 administration. The route of administration may be any route which effectively transports the compound of the present disclosure to the appropriate or desired site of action. Suitable routes of administration include, but are not limited to, oral, nasal, buccal, dermal, intradermal, transdermal, parenteral, rectal, subcutaneous, intravenous, intraurethral, intramuscular or topical.

25 Solid oral formulations include, but are not limited to, tablets, capsules (soft or hard gelatin), dragees (containing the active ingredient in powder or pellet form), troches and lozenges.

Liquid formulations include, but are not limited to, syrups, emulsions and sterile injectable liquids, such as suspensions or solutions.

Topical dosage forms of the compounds include ointments, pastes, creams, lotions, powders, solutions, eye or ear drops, impregnated dressings and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration.

5 The pharmaceutical compositions of the present disclosure may be prepared by conventional techniques known in literature.

In another embodiment, the present disclosure provides a product comprising a compound of formula (I) sodium for use as a medicament.

10 In another embodiment, the present disclosure provides a product comprising a compound of formula (I) calcium for use in a method of treating diseases and/or disorders mediated by CD47-SIRP alpha signaling pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) calcium.

15 In another embodiment, the present disclosure provides a product or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) calcium or compound of formula (I) sodium, described herein, for use in a method of treating diseases and/or disorder mediated by CD47-SIRP alpha pathway in a subject comprising administering to the subject in need thereof.

20 In another embodiment, the present disclosure provides a product or a pharmaceutical composition comprising a compound of formula (I) calcium or compound of formula (I) sodium, described herein, for use in a method of treating diseases and/or disorder mediated by CD47-SIRP alpha pathway in a subject, the method comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) calcium or or a compound of formula (I) sodium.

25 In another embodiment, the present disclosure provides a product or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) calcium or compound of formula (I) sodium, described herein, for use in a method of treating diseases and/or disorder mediated by CD47-SIRP alpha pathway in a subject, comprising administering the product or pharmaceutical composition to the subject.

30 In another embodiment, the present disclosure provides a product or a pharmaceutical composition comprising a compound of formula (I) calcium or compound of formula (I) sodium, described herein, for use as a medicament.

In another embodiment, the present disclosure provides a product or a pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) calcium or compound of formula (I) sodium, described herein, for use as a medicament.

In another embodiment, the present disclosure provides a product comprising a
5 compound of formula (I) sodium for use in a method of treating diseases and/or disorders mediated by CD47-SIRP alpha signaling pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) sodium. In another embodiment, the present disclosure provides a product for use in a method of treating diseases and/or disorders, wherein the disease and/or disorder mediated by CD47-SIRP alpha
10 signaling pathway is cancer.

In another embodiment, the present disclosure provides a method of treating diseases and/or disorder mediated by CD47-SIRP alpha pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) calcium or crystalline form thereof described herein.

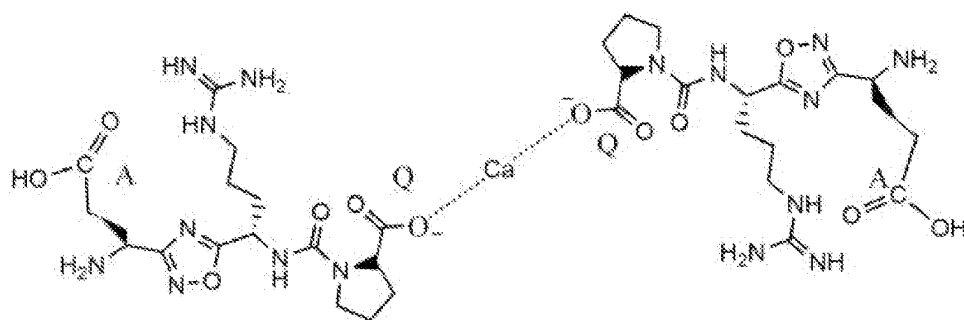
15 In another embodiment, the present disclosure provides a method of treating diseases and/or disorder mediated by CD47-SIRP alpha pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) sodium or crystalline form described herein.

In one embodiment, the disease or disorder mediated by CD47-SIRP alpha pathway is
20 cancer.

In one embodiment, the cancer is selected from melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular
25 cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus, cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute
30 leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), non-small cell lung cancer (NSCLC), primary CNS

lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, B-cell lymphomas, environmentally induced cancers including those induced by asbestos (e.g., mesothelioma), and combinations of said cancers.

5 In one embodiment, a compound of formula (I) calcium represented by formula (IA):



(IA).

EXPERIMENTAL

The present disclosure provides methods for the preparation of pharmaceutically acceptable salts of the compound of formula (I) according to the procedures of the following examples, using appropriate materials and conditions. Those skilled in the art will understand that known variations of the conditions and processes of the following preparative procedures can be used to prepare these compounds of the present disclosure. Moreover, by utilizing the procedures described in detail, one of ordinary skill in the art can prepare additional compounds of the present disclosure.

ABBREVIATIONS:

The abbreviations used in the entire specification is summarized below with their meaning.

IPA- Isopropyl alcohol; DMSO- *N,N*-Dimethyl sulfoxide; DMF- *N,N*-Dimethyl formamide; NaOH- sodium hydroxide; EtOAc- Ethyl acetate; TFA- Trifluoro acetic acid; MTBE- Methyl tert-butyl ether; TIPS- Triisopropyl silane; XRPD-X-Ray Powder Diffraction; ICP-MS- Inductively Coupled Plasma Mass Spectrometry; LCMS- Liquid chromatography-mass spectrometry; HPLC- High-performance liquid chromatography; NMR-Nuclear magnetic resonance; RT- Room temperature; C- Celsius; N- Normality; g- Grams; h- Hour(s); SSNMR-solid state nuclear magnetic resonance; NMR- nuclear magnetic resonance.

Analytical Methods:

X-Ray Powder Diffraction (XRPD):

5 X-Ray powder diffraction patterns were collected on an X’Pert3 PRO MPD diffractometer using CuK α radiation (45 kV, 40 mA). The details of the data collection are summarized below in table 4:

Table 4: X-Ray Powder Diffraction Parameters

Instrument	PANalytical
Model	X’ Pert3 PRO MPD diffractometer (Transmission Mode)
X-Ray wavelength	Cu, k α , K α 1 (Å): 1.540598, K α 2/K α 1 intensity ratio: 0.50
X-Ray tube setting	45 kV, 40 mA
Divergence slit	Fixed 1/2°
Scan mode	Continuous
Scan range (°2 Theta)	3° - 40°
Scan speed [°/min]	1.2
Step size (°2 Theta)	0.017
Test Time (s)	2078 s
Temperature	25 °C (Ambient Temperature)

One of ordinary skill in the art will appreciate that an X-ray diffraction pattern may be obtained with a measurement error that is dependent upon the measurement conditions employed. It is generally known that intensities in X-ray diffraction pattern may fluctuate depending upon measurement conditions employed. It should be further understood that relative intensities may also vary depending upon experimental conditions, sample texture, and wavelength of X-ray radiation used. The agreement in the 2-theta-diffraction angles between specimen and reference is within 0.2° for the same crystal form and such degree of measurement error should be considered as relevant to the diffraction angles disclosed herein.

10

15 Consequently, it is to be understood that the crystal forms of the instant disclosure are not limited to the crystal forms that provide X-ray diffraction patterns completely identical to the X-ray diffraction patterns depicted in the accompanying Figures disclosed herein. Any crystal forms that provide X- ray diffraction patterns substantially identical to those disclosed in the accompanying Figures fall within the scope of the present disclosure. The ability to ascertain

substantial identities of X-ray diffraction patterns is within the purview of one of ordinary skill in the art.

HPLC method:

Analytical HPLC was performed using on ZIC HILIC 200A column (4.6 mm × 250 mm, 5 µm), Flow rate: 1.0 mL / min. The elution conditions used are: Buffer A: 5 mmol ammonium acetate, Buffer B: Acetonitrile, Equilibration of the column with 80 % buffer B and elution by a gradient of 80 % to 50 % buffer B during 32 min. LCMS was performed on AP1 2000 LC/MS/MS triple quad (Applied biosystems) with Agilent 1100 series HPLC with G1315 B DAD, using Mercury MS column or using Agilent LC/MSD VL single quad with Agilent 1100 series HPLC with G1315 B DAD, using Mercury MS column or using Shimadzu LCMS 2020 single quad with Prominence UFLC system with SPD-20 A DAD. Sodium content was analysed using AAS Agilent technologies 240 AA and Calcium content was analysed by either ICP-OES using Perkin Elmer Inc. (Optima 5300 DV) or via ICP-MS method using Agilent Technologies 7800X ICP-MS system.

Thermogravimetric Analysis and Differential Scanning Calorimetry:

Thermogravimetric analysis (TGA) data were collected using a Q5000 TGA from TA Instruments. Differential scanning calorimetry (DSC) was performed using a TA Q2000 DSC from TA Instruments. Method parameters are provided below in the table 5.

Table 5: TGA and DSC Parameters

Parameters	TGA	DSC
Method	Ramp	Ramp
Pan	Platinum (100µL), open	Aluminium plate, crimped
Temperature	RT-Target Temperature	25 °C-Target Temperature
Ramp rate	10 °C/min to 300°C	10 °C/min
Purge gas	N ₂	N ₂

From the XRPD studies of the compound of formula (I) as a free acid which was obtained using the procedure described in Example 1 of WO201938367, it was found to be amorphous. Such free acid in amorphous form is unstable at ambient conditions. The XRPD is shown in **FIG.2**.

In any drug product preparations, it is essential for the drug compound to exhibit adequate stability and possess suitable physicochemical properties for its development as a drug product. The compound of formula (I) as free acid was observed to be hygroscopic under ambient conditions and, as a result, was deemed unsuitable for further pharmaceutical development. Therefore, it was imperative to improve the physicochemical properties of the compound of formula (I) free acid.

With the objective of obtaining a compound of formula (I) with improved physicochemical properties for further pharmaceutical development, the inventors performed several experiments including salt screening studies, co-lyophilization, chelates conversion, pro-drug approach by using various reagents, solvent systems and reaction conditions, however none of the methods were successful. The salt screening methods by using various salts/amines such as sodium citrate, sodium phosphate, ammonium chloride etc., with different solvents systems such as ethanol, methanol, IPA, DMSO, DMF, etc., and with different temperature ranges did only result in hygroscopic compounds and failed to result in any suitable yield for the further pharmaceutical development.

It was found that compound of formula (I) calcium salt and compound of formula (I) sodium salt were surprisingly stable and found to be crystalline in nature. Further, these salts of the compound of formula (I) have unexpected advantages in various desired properties such as filterability, stability, and solubility compared to other salts as well as the product of other methodologies experimented in compound of formula (I) free acid. Further, the compound of formula (I) calcium salt and compound of formula (I) sodium salt as described in the present disclosure showed crystalline nature.

Compound of formula (I) as a free acid is prepared using the procedure described in Example 1 of WO2019138367, which is hereby incorporated by reference in their entirety.

Example -1: Preparation of compound of formula (I) Sodium

Synthesis of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline Sodium

Method A:

(((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline (12 g) was dissolved in water and the resulting solution was cooled to 5-10 °C. To this solution, a cold solution of 0.5N NaOH was added until pH is greater than 9.3.

The resulting solution was stirred for 10-20 mins and extracted with EtOAc. The aqueous layer was concentrated under high vacuum at 28°C and co-evaporated with acetonitrile. The gummy syrup, so obtained, was triturated with acetonitrile to yield off-white solid which was dried under vacuum to yield 12.5 g of title sodium salt. LCMS: 441.4 (M+H)⁺; 463.2 (M+Na)⁺; 485.4 (M+2Na)⁺.

Alternatively, the title compound was also isolated through work up procedure via anti-solvent addition using solvents such as IPA. Atomic absorption spectroscopy confirmed the presence of sodium salt with a sodium content of 9.6%.

Method B:

(((S)-1-(3-((S)-4-(tert-butoxy)-1-((tert-butoxycarbonyl)amino)-4-oxobutyl)-1,2,4-oxadiazol-5-yl)-4-(3-((2,2,4,6,7-pentamethyl-2,3-dihydrobenzofuran-5-yl)sulfonyl)guanidino)butyl)carbamoyl)-L-proline (200 g, 0.235 mol) was added slowly to a stirring solution of TFA (4.5 vol), TIPS (0.25 vol) and water (0.25 vol) at 10±5°C. The reaction temperature was slowly raised to 30±5°C and the mixture was stirred for 3.5 hours. The reaction mass was quenched by the addition of water. The aqueous layer was washed with MTBE. The pH of the aqueous layer was adjusted to 4.5 to 6.6 with sodium bicarbonate at 30±5°C. The aqueous layer was concentrated, and isopropyl alcohol (10 vol) was added. The reaction mixture was stirred for 20-24h and filtered. The crude solid was washed with methanol water mixture (7:0.5 vol), filtered and dried under vacuum to yield the (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline sodium salt (41 g).

Resin treatment:

(((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline sodium salt was dissolved in water and the aqueous solution was treated with water washed sodium ion exchange resin (e.g. Indion 225H resin) three times (each time with 1 w/w) and filtered, and filtrate so obtained was used in the further steps.

Example -2: Preparation of compound of formula (I) Calcium

Calcium carbonate (41 g) at 0 °C to 10 °C was added to an aqueous solution of (((S)-1-(3-((S)-1-amino-3-carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline (Compound of formula (I), 150 g) or resin treated (((S)-1-(3-((S)-1-amino-3-

carboxypropyl)-1,2,4-oxadiazol-5-yl)-4-guanidinobutyl)carbamoyl)-L-proline sodium salt. The reaction mixture was stirred for 24 hours at room temperature, filtered and washed with water. The filtrate containing compound of formula (I) calcium was precipitated from the solution using ethanol as an antisolvent and filtered at room temperature. The solid, so
5 obtained, was washed with MTBE and dried under vacuum to yield 120 g of title compound (LCMS: 440.46 (M+H)⁺; Mass observed 441.2).

Differential scanning calorimetry

Differential scanning calorimetry (DSC) of the compound of formula (I) calcium showed an endotherm at 152.9 °C (peak temperature) before melting/decomposition with an
10 onset at 150.92 °C (FIG. 4).

Thermogravimetric analysis

TGA analysis of the compound of formula (I) calcium was performed in Q5000 TA TGA instrument. Accurately weighed 23.6 mg sample was loaded in Platinum pan and heated at a rate of 10 °C/min over a temperature range of 30 to 300 °C under a nitrogen purge of 50
15 mL/min. TGA thermogram showed the weight loss initiation after 26 °C, and the weight loss corresponds to the adsorbed moisture or residual solvents (FIG. 5).

Solubility measurement for compound of formula (I) calcium

Equilibrium solubility of the compound of formula (I) calcium was measured in water at 20°C and 30°C. All samples are equilibrated at temperature for 6h and is highly soluble in
20 water with 82.59 ± 3.341 mg/ml as solubility at 24 hrs. The compound showed pH independent solubility in aqueous pH buffer solutions across the range of pH 1.2 – 9.0.

Stability and forced degradation studies

Stability and forced degradation studies were performed under a number of stressed conditions for a certain period to understand the advantages of compound of formula (I)
25 calcium over its free acid form and the influence of temperature and humidity on the compound of formula (I) calcium. The samples prepared according to the procedures described above were packed in polyethylene bags and placed in a stability chamber. Various storage conditions were tried including 25°C ± 2°C/60 % Relative Humidity (RH) ±5% RH and 5°C ± 3°C for up to 3 months. The samples were analysed at pre-determined time intervals for HPLC purity and
30 water content. The compound of formula (I) calcium was shown to be stable to degradation

and remained unchanged in terms of its physical form after the storage for 3 months at 25°C ± 2°C/60% Relative Humidity (RH), and 5°C ± 3°C. Contrastingly, Formula (I) free acid was stable at room temperature for around 7 days only. The forced degradation results for the compound of formula (I) calcium are tabulated below in **Table 6**.

5 **Table 6: Forced degradation results**

Condition	Parameter	Months			
		0	1	2	3
5°C ± 3°C	Water content (KF)	7.5	7.9	8.4	8.6
	Compound purity (HPLC)	98.9	99.2	99.0	98.8
25°C ± 2°C / 60% RH ± 5% RH	Water content (KF)	7.5	9.0	9.3	9.4
	Compound purity (HPLC)	98.9	99.0	98.7	98.4

Solid form stability

Compound of formula (I) calcium was exposed to different stability conditions (5°C, 25°C ± 2°C/60% RH, 30°C/75% RH and 40°C/75% RH) for 3 months in stability chambers, after which XRPD analysis was performed on the samples of different conditions and compared with solid form of the compound of formula (I) calcium. XRPD patterns of the samples of different conditions were found to be matching with the XRPD pattern of the compound of formula (I) calcium (**FIG. 6**).

Dynamic Vapor Sorption Studies

Dynamic Vapor Sorption analysis of compound of formula (I) calcium was performed to evaluate the physical stability in presence of moisture and its tendency to absorb the same. Sorption-desorption isotherm for the compound of formula (I) calcium was investigated at 25°C. It was observed that the sample weight increased with an increase in the humidity indicating moisture uptake and showed typical ‘S’ shaped curve without hysteresis upon desorption, indicating the moisture ‘picked-up’ at higher humidity is absorbed onto the surface of the solid and does not affect its internal structure, as the sorption and desorption curve did not show any step change corresponding to hydrate formation. Nearly, 7.81% w/w was gained by compound of formula (I) calcium at 80% RH. (**FIG.7**).

Mass spectroscopy:

Molecular weight of the compound of formula (I) calcium was analyzed by mass spectroscopy. Experimental condition to determine mass involves dissolving the compound of formula (I) calcium in a suitable buffer that has appropriate solubility for the analyte, in this case the compound of formula (I) calcium dissociates into the compound of formula (I) free acid and calcium ions showing that the compound of formula (I) calcium do not exist in its chelated form. In mass spectroscopic analysis, it was observed the mass of free acid (Molecular weight 441) which is typical for any salt form. Hence, mass spectroscopy data supports that the calcium exists as a salt in the compound of formula (I) calcium and is not chelated. Hence molecular weight of the compound of formula (I) calcium cannot be determined.

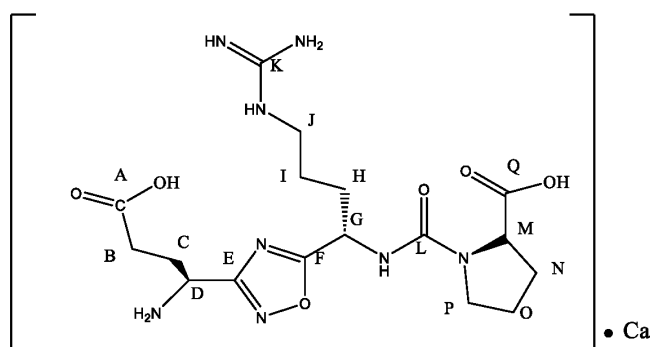
Determination of the structure, molecular formula and molecular weight of compound of formula (I) calcium:

The compound of formula (I) calcium is highly soluble in water and very poorly soluble in organic solvents. Due to the high solubility of the compound of formula (I) calcium in water, it dissociates into the compound of formula (I) free acid and calcium cations. Therefore, a single crystal of compound of formula (I) calcium could not be generated.

Due to the lack of single crystal data, the molecular structure or molecular formula of the compound of formula (I) calcium cannot be determined. However, to address the problem associated with the potency of drug, which is connected to the molecular weight, the correction factor method was used. In this method, the molecular formula of compound of formula (I) free acid is corrected with percentage of the calcium which is determined experimentally by ICP-MS. By using this approach even though molecular formula or molecular weight of the salt is not available, the potency of the drug can be determined.

Solid state nuclear magnetic resonance (SSNMR)

All the experiments of SSNMR were performed at 400 MHz (9.4 T) solid-state NMR spectrometer. The compound of formula (I) calcium sample in powdered form was packed in a 1.9 mm rotor at room temperature. The sample was spun at 35 kHz at the magic angle (54.70) relative to the main magnetic field. On the ^1H and the ^{13}C channels, the pulse lengths of 1.35 ms and 2.5 ms were used for 900 rotations. As mentioned in the structure below, carbon atoms are labelled as "A" to "Q" for understanding the SSNMR and single crystal XRD data.



i) Echo detected ^1H MAS-NMR spectrum

Echo detected ^1H MAS-NMR spectrum of compound of formula (I) calcium is shown in FIG.

8. Echo detection was used to overcome the baseline distortion in ^1H spectra and to enhance spectral resolution by suppressing unwanted background signals. The spectrum in FIG. 8 shows a clear resolution between the aliphatic and acidic protons of the compound of formula (I) calcium. The peaks centered around 9-10 ppm correspond to the acidic protons, the presence or absence of these peaks is directly related to the stoichiometry of the compound with Ca.

10

ii) ^1H - ^{13}C CPMAS-NMR spectrum

FIG. 9 shows the ^1H - ^{13}C CPMAS-NMR spectrum of the compound of formula (I) calcium.

This experiment involves a transfer of ^1H polarization to ^{13}C and the detection of a ^{13}C signal.

The peak assignment was performed using information from the chemical structure, electronic

15 environment, stereo, and regiochemistry. The region between 150 and 190 ppm shows four kinds of peaks that belong to acid carbonyls (A, Q), imine bonds (E + F + K), and amide carbonyls (L). The relative intensity of the peak corresponding to "Q" is lower than the peak for "A", which indicates that the Q site has fewer neighboring protons, i.e., weaker ^1H - ^{13}C interaction, compared to the "A" site. The same trend is followed in the case of imine and amide peaks as well. In order to obtain more concrete evidence, 2D Heteronuclear Correlation (HetCor) spectroscopy was also used.

20

iii) 2D Heteronuclear Correlation (HetCor) spectroscopy

^{13}C - ^1H 2D-Correlation NMR spectrum (HetCor) of the compound of formula (I) calcium is

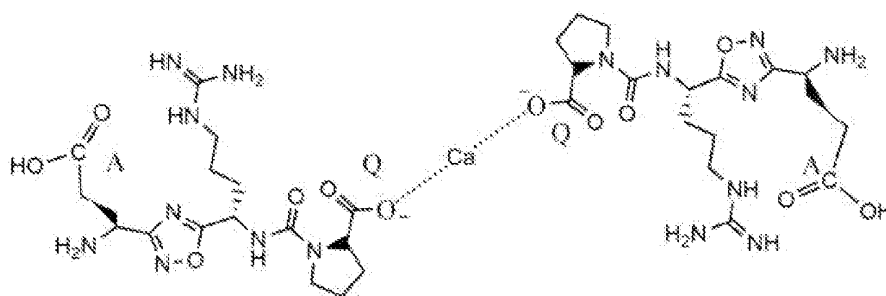
25 shown in FIG. 10A and 10B. FIG. 10A shows the total correlation spectra and the FIG.10B shows zoomed-in spectra of the ^{13}C carbonyl/acidic region to clearly highlight the differences in the cross-peak intensities involving the "A" and "Q" sites of ^{13}C .

From the peak marked in the oval box in Figure 10B, it is clearly evident that “A” sites strongly correlate with the acidic protons, which means those are in the -COOH form. But the region marked with a rectangle box signifies that “Q” is weakly correlating with acidic protons. Therefore, it should be in ionic [i.e., -COO⁻] form. From this experiment, it is evident that Ca²⁺ is bonded between two “Q” carbonyls as depicted in formula (IA), and in that case the stoichiometry is Ca:compound of formula (I) = 1:2.

Determination of crystal structure of compound of formula (I) free acid

Crystal structure of the compound of formula (I) free acid is shown in FIG.11. The asymmetric unit of the single crystal structure was comprised of two independent free acid molecules (zwitterion) of the compound of formula (I), two water molecules and three acetone molecules. Data indicated that one of the acetone molecules was seriously disordered, so it was omitted from the structure model by solvent mask analysis and only two acetone molecules were shown in FIG 11, which indicated the crystal is acetone water co-solvate of the compound of formula (I) free acid. These findings also support the observation of SSNMR experiments that only one carboxylic acid group is involved in salt formation i.e. Q Carbon atom.

The low intensity of the Q-sites in ¹³C CP spectrum relative to the A-sites indicated that Q-sites are relatively proton-deficient sites. This claim was verified using 2D HetCor MAS-NMR spectroscopy that clearly showed ¹³C-¹H cross peaks for A-¹³C sites and the acidic ¹H sites however, the cross-peaks between Q ¹³C sites with the acidic ¹H were missing (See below structure). These observations confirm that the Q ¹³C sites are not correlated with the acidic ¹Hs, which implies that these protons are replaced by Ca²⁺ ions. Based on the experimental data, the structure of compound of formula (I) calcium was found to be as below formula (IA):



(IA).

Incorporation by Reference

All publications and patents mentioned herein are hereby incorporated by reference in their entirety as if each individual publication or patent was specifically and individually

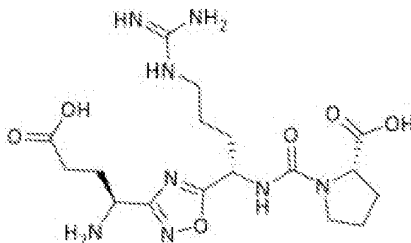
indicated to be incorporated by reference. In case of conflict, the present application, including any definitions herein, will control.

Equivalents

5 While specific embodiments of the subject disclosure have been discussed, the above specification is illustrative and not restrictive. Many variations of the disclosure will become apparent to those skilled in the art upon review of this specification and the claims below. The full scope of the disclosure should be determined by reference to the claims, along with their full scope of equivalents, and the specification, along with such variations.

We claim:

1. A pharmaceutically acceptable salt of compound of formula (I):



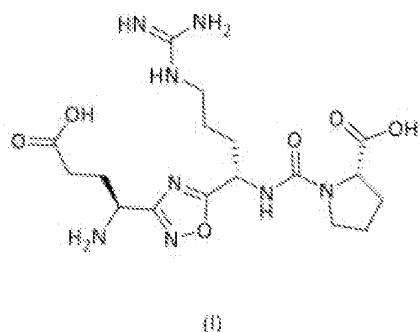
(I) ;

- 5 wherein the pharmaceutically acceptable salt is an alkali metal salt or an alkaline earth metal salt.
2. The pharmaceutically acceptable salt of claim 1, wherein the alkali metal salt is a sodium salt or a potassium salt.
3. The pharmaceutically acceptable salt of claim 1, wherein the alkaline earth metal salt is a calcium salt or a magnesium salt.
- 10 4. The pharmaceutically acceptable salt of claim 1, wherein the alkaline earth metal salt is a calcium salt.
5. The pharmaceutically acceptable salt of claim 4, wherein the stoichiometric ratio between the compound of formula (I) and calcium is 2:1.
- 15 6. The pharmaceutically acceptable salt of claim 3 to 5, wherein the calcium content is from about 1% to about 5% by weight of the salt.
7. The pharmaceutically acceptable salt of claim 3 to 5, wherein the calcium content is from about 1.5% to about 4% by weight of the salt.
8. The pharmaceutically acceptable salt of claim 3 to 5, wherein the calcium content is from about 2% to about 3% by weight of the salt.
- 20 9. The pharmaceutically acceptable salt of claim 1, wherein the alkali metal salt is a sodium salt.
10. The pharmaceutically acceptable salt of claim 9, wherein the sodium content is from about 1% to about 10% by weight of the salt.

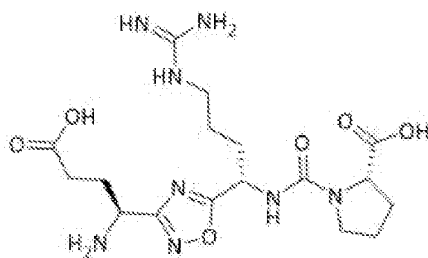
11. The pharmaceutically acceptable salt of claim 9, wherein the sodium content is from about 5% to about 10% by weight of the salt.
12. The pharmaceutically acceptable salt of claim 9, wherein the sodium content is from about 8% to about 10% by weight of the salt.
- 5 13. The pharmaceutically acceptable salt of any one of claims 9 to 12, wherein the alkali metal salt is a monosodium salt or disodium salt.
14. A process for preparing the pharmaceutically acceptable salt of claim 1, the process comprising the steps of:
 - a) providing a mixture comprising a compound of formula (I) and a solvent A;
 - 10 b) reacting the mixture with a cation source and precipitating the salt of compound of formula (I) by using a solvent B; and
 - c) isolating the salt of compound of formula (I);

wherein the solvent A and the solvent B are independently selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.
- 15 15. The process of claim 14, wherein the solvent A is water.
16. The process of claim 14, wherein the compound of formula (I) in step (a) is in a free acid form.
- 20 17. The process of claim 14, wherein the compound of formula (I) in step (a) is a sodium salt of compound of formula (I).
18. The process of claim 17, further comprises treating a mixture of step (a) with metal ion exchange resin, under aqueous conditions, thereby eliminating sodium ion from the mixture.
- 25 19. The process of any one of the claims 14-18, wherein the precipitation in step (b) is performed by addition of the solvent B.
20. The process of claim 19, wherein the solvent B is ethanol.

21. The process of claim 14, wherein the cation source is selected from calcium carbonate, calcium hydroxide, calcium methoxide, calcium chloride, magnesium carbonate, magnesium chloride or combinations thereof.
22. The process of claim 14, wherein the cation source in step (b) is calcium carbonate.
- 5 23. The process of any one of the claims 14-22, wherein the step (c) of isolating the salt of compound of formula (I) further comprises sub steps of:
- i) filtering the mixture and precipitating the salt of compound of formula (I) from step (b); and
- ii) washing and drying the precipitated salt of compound of formula (I) obtained from the filtration.
- 10 24. A process for preparing the sodium salt of any one of the claims 9 to 13, comprising reacting a compound of formula (I) with a cation source in the presence of a solvent C:



- 15 wherein the solvent C is selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.
25. The process of claim 24, wherein the cation source is NaOH or Na₂CO₃.
- 20 26. The process of claim 25, wherein the cation source is NaOH.
27. A process for preparing the calcium salt of any one of the claims 4 to 8, comprising a step of reacting a compound of formula (I) with a cation source in the presence of solvent C:



(I) ;

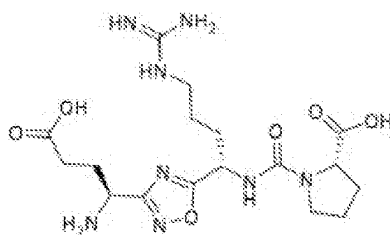
wherein the solvent C is selected from tetrahydrofuran, acetonitrile, methanol, anisole, diethyl ether, ethanol, 1,4-dioxane, acetonitrile, acetone, dichloromethane, isopropyl alcohol, methyl tert-butyl ether (MTBE), n-heptane, water and mixtures thereof.

28. The process of claim 27, wherein the cation source comprises calcium carbonate, calcium hydroxide, calcium methoxide, calcium chloride or a combination thereof.

29. The process of any one of claims 14 to 28, wherein the reaction is carried out at about 20 °C to about 40 °C.

30. The process of any one of claims 14 to 29, wherein the salt of compound of formula (I) obtained is a crystalline compound of formula (I) calcium or a crystalline compound of formula (I) sodium.

31. A crystalline form of a compound of formula (I) calcium



(I)

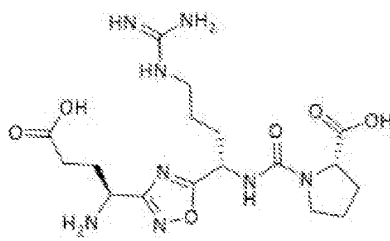
32. The crystalline form of claim 31, wherein the crystalline form is Form A characterized by an X-ray powder diffraction (XRPD) pattern comprising at least 3 peaks with 2-theta values selected from 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , $20.5 \pm$

0.2, 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

33. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising at least 5 peaks with 2-theta values selected from 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .
34. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 .
35. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 19.8 ± 0.2 and 23.9 ± 0.2 .
36. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 9.9 ± 0.2 , 11.8 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 and 23.9 ± 0.2 .
37. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 and 23.9 ± 0.2 .
38. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 8.1 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 19.2 ± 0.2 , 19.8 ± 0.2 , 20.1 ± 0.2 , 21.5 ± 0.2 and 23.9 ± 0.2 .
39. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern comprising peaks with 2-theta values: 6.5 ± 0.2 , 6.8 ± 0.2 , 8.1 ± 0.2 , 9.5 ± 0.2 , 9.9 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 12.9 ± 0.2 , 13.2 ± 0.2 , 13.8 ± 0.2 , 14.1 ± 0.2 , 15.1 ± 0.2 , 16.3 ± 0.2 , 16.5 ± 0.2 , 17.7 ± 0.2 , 18.0 ± 0.2 , 18.7 ± 0.2 , 19.2 ± 0.2 , 19.5 ± 0.2 , 19.8 ± 0.2

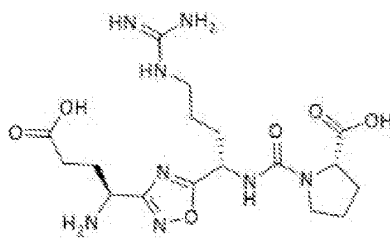
0.2, 20.1 ± 0.2 , 20.5 ± 0.2 , 21.5 ± 0.2 , 22.1 ± 0.2 , 22.7 ± 0.2 , 23.5 ± 0.2 , 23.9 ± 0.2 , 24.4 ± 0.2 , 24.9 ± 0.2 , 25.7 ± 0.2 , 26.7 ± 0.2 , 27.2 ± 0.2 , 27.8 ± 0.2 , 28.5 ± 0.2 , 29.1 ± 0.2 , 29.9 ± 0.2 , 31.2 ± 0.2 , 32.2 ± 0.2 , 33.4 ± 0.2 , 35.1 ± 0.2 , 37.6 ± 0.2 and 38.4 ± 0.2 .

40. The crystalline form of claim 32, wherein Form A is characterized by an XRPD pattern substantially as shown in FIG. 1.
41. The crystalline form of claim 31, having an endotherm with a peak temperature at about 145°C to about 155°C , as measured by differential scanning calorimetry (DSC).
42. The crystalline form of claim 31, having an endotherm with a peak temperature at about 145°C to about 155°C , preferably about 150°C to about 155°C , or more preferably about 150°C to about 153°C as determined by DSC.
43. The crystalline form of claim 31, having an endotherm with a peak temperature at about $153^{\circ}\text{C} \pm 3^{\circ}\text{C}$ as determined by DSC.
44. The crystalline form of claim 31, having a thermogravimetric analysis (TGA) pattern substantially as shown in FIG. 5.
45. The crystalline form of claim 31, having at least one of the following characteristics:
- a) an XRPD pattern substantially as shown in FIG. 1;
 - b) at least one XRPD peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 ; and
 - c) an endotherm with a peak temperature at $153^{\circ}\text{C} \pm 3^{\circ}\text{C}$ as determined by DSC.
46. The crystalline form of claim 31, having at least one of the following characteristics:
- a) an XRPD pattern substantially as shown in FIG.1;
 - b) at least one XRPD peak with 2-theta values: 9.9 ± 0.2 , 13.2 ± 0.2 and 19.8 ± 0.2 ;
 - c) an endotherm with a peak temperature at $153^{\circ}\text{C} \pm 3^{\circ}\text{C}$ as determined by DSC; and
 - d) a TGA pattern substantially as shown in FIG.5.
47. A crystalline form of a compound of formula (I) disodium



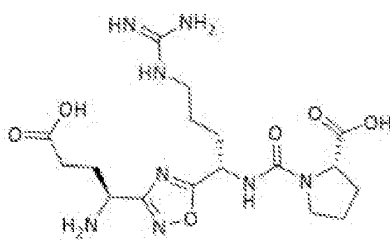
(I)

48. The crystalline form of claim 47, wherein the crystalline form is Form B characterized by an XRPD pattern comprising at least 3 peaks with 2-theta values selected from 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .
49. The crystalline form of claim 47, wherein the crystalline form is Form B characterized by an XRPD pattern comprising at least 5 peaks with 2-theta values selected from 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .
50. The crystalline form of claim 47, wherein the crystalline form is Form B characterized by an XRPD pattern comprising peaks with 2-theta values: 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 and 37.7 ± 0.2 .
51. The crystalline form of claim 48, wherein the crystalline form is Form B characterized by an XRPD pattern comprising peaks with 2-theta values: 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .
52. The crystalline form of claim 48, wherein the crystalline form is Form B characterized by an XRPD pattern comprising peaks with 2-theta values: 18.5 ± 0.2 , 18.9 ± 0.2 , 22.5 ± 0.2 , 23.5 ± 0.2 , 25.4 ± 0.2 , 27.9 ± 0.2 , 28.9 ± 0.2 , 31.7 ± 0.2 , 33.9 ± 0.2 , 37.7 ± 0.2 and 42.4 ± 0.2 .
53. The crystalline form of claims 47 to 52, wherein the crystalline form is Form B characterized by an XRPD pattern substantially as shown in FIG. 3A.
54. A crystalline form of a compound of formula (I) monosodium



(I)

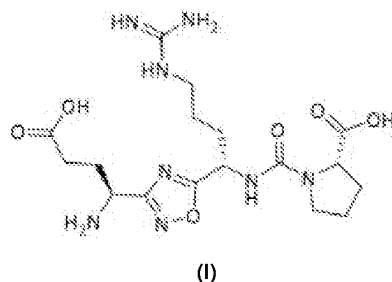
55. The crystalline form of claim 54, wherein the crystalline form is Form C characterized by a XRPD pattern comprising peaks with 2-theta values: 42.3 ± 0.2 , 42.9 ± 0.2 , 43.2 ± 0.2 and 43.8 ± 0.2 .
56. The crystalline form of any one of claims 54 or 55, characterized by an XRPD pattern substantially as shown in FIG. 3B.
57. A compound obtainable by a process, the process comprising the steps of:
- providing an aqueous mixture comprising a compound of formula (I)



(I)

- reacting the mixture with calcium carbonate;
 - filtering the mixture of step (ii) to obtain a filtrate;
 - adding a solvent B to the filtrate to form a reaction mixture, wherein the solvent B is ethanol; and
 - isolating the compound from the reaction mixture.
58. The compound of claim 57, wherein the step (v) of isolating the compound further comprises sub-steps of:
- filtering the compound from the reaction mixture; and
 - washing and drying the compound obtained from the reaction mixture under vacuum condition.

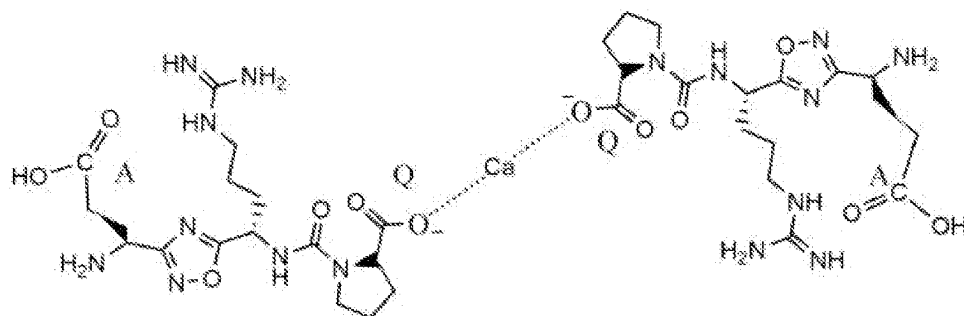
59. A pharmaceutical composition comprising the pharmaceutically acceptable salt of any one of claims 1 to 13 or the crystalline form of any one of the claims 31 to 56 and one or more pharmaceutically acceptable carriers or excipients.
60. A product comprising a compound of formula (I) calcium or a compound of formula (I) sodium for use as a medicament, wherein the compound of formula (I) is:



61. A product comprising a compound of formula (I) calcium for use in a method of treating diseases and/or disorders mediated by CD47-SIRP alpha signaling pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) calcium according to any one of claims 4 to 8 or a crystalline form thereof according to anyone of claims 31 to 46.
62. A product comprising a compound of formula (I) sodium for use in a method of treating diseases and/or disorders mediated by CD47-SIRP alpha signaling pathway in a subject comprising administering to the subject in need thereof a therapeutically effective amount of a compound of formula (I) sodium according to any one of claims 9 to 13 or a crystalline form thereof according to anyone of claims 47 to 56.
63. The product for use of claim 61 or 62, for use in a method of treating diseases and/or disorders, wherein the disease and/or disorder mediated by CD47-SIRP alpha signaling pathway is cancer.
64. The product for use of claim 63, wherein the cancer is selected from melanoma, renal cancer, prostate cancer, breast cancer, colon cancer and lung cancer, bone cancer, pancreatic cancer, skin cancer, cancer of the head or neck, cutaneous or intraocular malignant melanoma, uterine cancer, ovarian cancer, rectal cancer, cancer of the anal region, stomach cancer, testicular cancer, carcinoma of the fallopian tubes, carcinoma of the endometrium, carcinoma of the cervix, carcinoma of the vagina, carcinoma of the vulva, Hodgkin's Disease, non-Hodgkin's lymphoma, cancer of the esophagus,

cancer of the small intestine, cancer of the endocrine system, cancer of the thyroid gland, cancer of the parathyroid gland, cancer of the adrenal gland, sarcoma of soft tissue, cancer of the urethra, cancer of the penis, chronic or acute leukemias including acute myeloid leukemia, chronic myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, solid tumors of childhood, lymphocytic lymphoma, cancer of the bladder, cancer of the kidney or ureter, carcinoma of the renal pelvis, neoplasm of the central nervous system (CNS), non-small cell lung cancer (NSCLC), primary CNS lymphoma, tumor angiogenesis, spinal axis tumor, brain stem glioma, pituitary adenoma, Kaposi's sarcoma, epidermoid cancer, squamous cell cancer, T-cell lymphoma, B-cell lymphomas, environmentally induced cancers including those induced by asbestos (Example, mesothelioma), and combinations of said cancers.

65. A compound of formula (I) calcium represented by formula (IA):



(IA).

66. The compound of claim 65, wherein the compound is in a crystalline form.