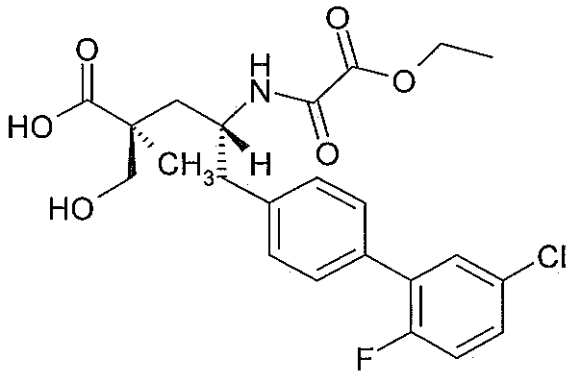
compound will be crystalline. Moreover, no methods exist for predicting which, if any, crystalline form will have the physically properties desired for use as pharmaceutical agents. Accordingly, a need exists for a stable, crystalline form which has a reasonably high melting point.

SUMMARY OF THE INVENTION

The present disclosure provides a novel Compound (**1**) that is converted *in vivo* to form a compound that possesses neprilysin (NEP) enzyme inhibition activity. Accordingly, this compound is expected to be useful and advantageous as a therapeutic agent for treating conditions such as hypertension and heart failure.

One aspect of the present disclosure relates to *(2S,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-(ethoxyoxalylamino)-2-hydroxymethyl-2-methylpentanoic acid (**1**):



(**1**),

or a pharmaceutically acceptable salt thereof. Another aspect of the present disclosure relates to a crystalline form of calcium *(2S,4R)*-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(2-ethoxy-2-oxoacetamido)-2-(hydroxymethyl)-2-methylpentanoate, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 7.18±0.2, 7.38±0.2 and 7.97±0.2. In one embodiment, the present disclosure relates to a crystalline form of Compound **1**. In another embodiment, the crystalline form (**1'**) is a hemi-calcium salt of Compound **1**.

Another aspect of the present disclosure relates to pharmaceutical compositions comprising one or more pharmaceutically acceptable carriers and Compound **1** or a crystalline form thereof. Such compositions may optionally contain other therapeutic agents, including but not limited to, an AT_1 receptor antagonist, an angiotensin-converting enzyme inhibitor, a phosphodiesterase (PDE) inhibitor, a renin inhibitor, a diuretic, or combinations thereof. In another aspect, the present disclosure relates to a pharmaceutical composition comprising the compound as disclosed herein and an AT_1 receptor antagonist,

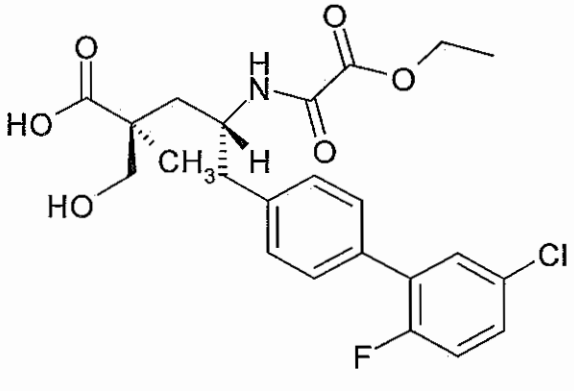
an angiotensin-converting enzyme inhibitor, a phosphodiesterase (PDE) inhibitor, a renin inhibitor, a diuretic, or combinations thereof, and optionally one or more pharmaceutically acceptable carriers. In a further aspect, the present disclosure relates to an oral dosage form comprising the compound as disclosed herein in a capsule, tablet, liquid or suspension. In yet another aspect, the present disclosure relates to an intravenous dosage form comprising the compound as disclosed herein in a buffered solution.

Compound **1** possesses NEP enzyme inhibition activity, and is therefore expected to be useful as a therapeutic agent for treating patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme or by increasing the levels of its peptide substrates. Thus, one aspect of the present disclosure relates to a compound as disclosed herein for use in therapy. In an embodiment, the present disclosure relates to a method of treating patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme, comprising administering to a patient a therapeutically effective amount of Compound **1**.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of the structure:



(1),

or a pharmaceutically acceptable salt thereof.

2. *(2S,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-(ethoxyoxalylamino)-2-hydroxymethyl-2-methylpentanoic acid.

3. A crystalline form of calcium (*2S,4R*)-5-(5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)-4-(2-ethoxy-2-oxoacetamido)-2-(hydroxymethyl)-2-methylpentanoate, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 7.18±0.2, 7.38±0.2 and 7.97±0.2.

4. The crystalline form of Claim 3, wherein the crystalline form is characterized by a powder X-ray diffraction pattern comprising diffraction peaks at 2θ values of 3.98±0.2, 5.00±0.2, 7.18±0.2, 7.38±0.2, 7.97±0.2, 8.87±0.2, and 10.91±0.2.

5. The crystalline form of Claim 4, wherein the crystalline form is further characterized by having one or more additional difrraction peaks at 2θ values selected from 3.47±0.2, 9.99±0.2, 15.74±0.2, 15.98±0.2, and 18.98±0.2.

6. The crystalline form of Claim 3, wherein the crystalline form is characterized by a powder X-ray diffraction pattern in which the peak positions are substantially in accordance with the peak positions of the pattern shown in FIG. 1.

7. The crystalline form of Claim 3, wherein the crystalline form is characterized by a differential scanning calorimetry trace recorded at a heating rate of 10 °C per minute which shows a maximum in endothermic heat flow at a temperature between about 237 °C and about 241 °C.

8. The crystalline form of Claim 3, wherein the crystalline form is characterized by a differential scanning calorimetry trace substantially in accordance with that shown in FIG. 2.

9. A pharmaceutical composition comprising the compound as claimed in any one of Claims 1 to 8 and one or more pharmaceutically acceptable carriers.

10. The pharmaceutical composition of Claim 9, wherein the pharmaceutically acceptable carrier is magnesium stearate.

11. A pharmaceutical composition comprising the compound as claimed in any one of Claims 1 to 8 and an AT_1 receptor antagonist, an angiotensin-converting enzyme inhibitor, a phosphodiesterase (PDE) inhibitor, a renin inhibitor, a diuretic, or combinations thereof, and optionally one or more pharmaceutically acceptable carriers.

12. An oral dosage form comprising the compound as claimed in any one of Claims 1 to 8 in a capsule, tablet, liquid or suspension.

13. The oral dosage form of Claim 12 wherein a release of the compound in a subject is an immediate, controlled or delayed release.

14. The oral dosage form of Claim 12, wherein the capsule material is gelatin, polysaccharide, chitosan or synthetic polymers.

15. The oral dosage form of Claim 12, wherein the hard capsule comprises gelatin, polysaccharides, or synthetic polymers.

16. The oral dosage form of Claim 12, wherein the capsule comprises

hydroxypropyl methylcellulose.

17. An intravenous dosage form comprising the compound as claimed in Claims 1 or 2 in a buffered solution.

18. A process for preparing the compound of Claim 1, the process comprising (a) mixing ethanol and oxalyl chloride to form a solution; (b) reacting *(2S,4R)*-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethyl-2-methylpentanoic acid benzyl ester with the solution; and (c) combining resulting mixture with palladium on carbon under hydrogen to yield the compound of Claim 1.

19. A process for preparing the compound of Claim 1, the process comprising:

(a) dissolving ethanol in dicloromethane;

(b) adding oxalyl chloride to form a solution and stirring at room temperature;

(c) evaporating solvent from solution;

(d) adding remaining solution to *(2S,4R)*-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethyl-2-methylpentanoic acid benzyl ester that is first dissolved in dicloromethane;

(e) adding *N,N*-diisopropylethylamine and stirring a room temperature;

(f) evaporating solvent to form a solid;

(g) combining solid with palladium 10 wt% on carbon in solvent to form a mixture;

(h) placing mixture under hydrogen with stirring; and

(i) filtering off palladium on carbon and vacuum drying to yield the compound of Claim 1.

20. The process according to Claim 19, wherein the resulting solids in steps (f) and (i) are purified by chromatography.

21. A process for preparing the crystalline form of Claim 3, the process comprising:

(a) dissolving *(2S,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-(ethoxyoxalylamino)-2-hydroxymethyl-2-methylpentanoic acid in ethanol and *N,N*-

diisopropylethylamine to form solution A;

(b) dissolving calcium trifluoromethane sulfonate in ethanol to form solution B;

(c) adding dropwise solution B to solution A to form a slurry;

(d) stirring at room temperature; and

(e) isolating the resulting solids to yield the crystalline form.

22. The process according to Claim 21, the process further comprising:

(f) cooling the crystalline form to about 5 °C and adding a cold ethanol:water mixture under vigorous stirring; and

(g) filtering and drying at room termperature to yield crystalline form.

23. A compound as claimed in any one of Claims 1 to 8 for use in therapy.

24. The use of a compound as claimed in any one of Claims 1 to 8 for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.

25. The use of claim 24 for treating a renally-impaired subject.

26. The use according to claim 25, wherein the renally-impaired subject has chronic kidney disease with an estimated glomerular filtration rate (eGFR) between 60 mL/min/1.73 m^2 and 15 mL/min/1.73 m^2.