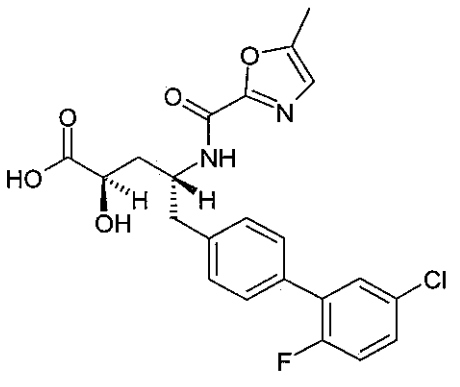
Additionally, to effectively use a NEP inhibitor compound as a therapeutic agent, it would be desirable to have a solid-state form that can be readily manufactured and that has acceptable chemical and physical stability. For example, it would be highly desirable to have a physical form that is thermally stable at reasonably high temperature, thereby facilitating processing and storage of the material. Crystalline solids are generally preferred over amorphous forms, for enhancing purity and stability of the manufactured product. However, the formation of crystalline forms of organic compounds is highly unpredictable. No reliable methods exist for predicting which, if any, form of an organic 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

The present disclosure provides a novel Compound (**1**) that has been found to possess 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, pulmonary hypertension, heart failure and renal disease.

One aspect of the disclosure relates to *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid (**1**):



(**1**),

or a pharmaceutically acceptable salt thereof. Another aspect of the disclosure relates to a crystalline form of Compound **1**, wherein the crystalline form is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 8.48±0.20, 14.19±0.20, 17.03±0.20, 21.15±0.20, and 25.41±0.20. In one embodiment, the crystalline form (**1'**) is

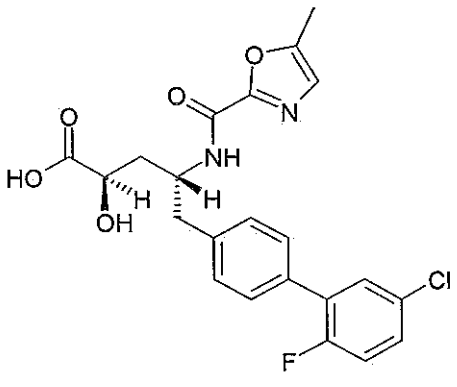
non-solvated.

Another aspect of the disclosure relates to pharmaceutical compositions comprising one or more pharmaceutically acceptable carriers and Compound **1** or a crystalline form

CLAIMS

WHAT IS CLAIMED IS:

1. A compound having the structure:



(1),

or a pharmaceutically acceptable salt thereof.

2. *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid.

3. A crystalline form of *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid, wherein the crystalline form is characterized by a powder x-ray diffraction pattern comprising diffraction peaks at 2θ values of 8.48±0.20, 14.19±0.20, 17.03±0.20, 21.15±0.20, and 25.41±0.20.

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 7.51±0.20, 8.48±0.20, 14.19±0.20, 17.03±0.20, 17.62±0.20, 17.87±0.20, 20.59±0.20, 21.15±0.20, 21.88±0.20, 24.45±0.20, 24.78±0.20, 25.41±0.20, 25.67±0.20, 27.67±0.20, and 28.22±0.20.

5. The crystalline form of Claim 4, wherein the crystalline form is further characterized by having one or more additional diffraction peaks at 2θ values selected from 16.09±0.20, 18.70±0.20, 19.21±0.20, 19.40±0.20, 21.64±0.20, 22.25±0.20, 26.43±0.20, 28.55±0.20, 30.73±0.20, 31.10±0.20, 32.64±0.20, 33.14±0.20, and 34.46±0.20.

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 165 °C and 169 °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 of 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 of 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 of 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 Claim 1 or 2 in a buffered solution.

18. A process for preparing the compound of Claim 1, the process comprising coupling *(2R,4R)*-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxypentanoic acid ethyl ester with 2-methyloxazole-2-carboylic acid to yield the compound of Claim 1.

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

(a) combining 2-methyloxazole-2-carboylic acid and *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU) in *N,N*-dimethylformamide (DMF) and stirring at room temperature;

(b) adding *(2R,4R)*-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxypentanoic acid ethyl ester and *N,N*-diisopropylethylamine and stirring at room temperature;

(c) isolating and then dissolving the resulting solids in dry ethanol and dry tetrahydrofuran;

(d) adding a solution of lithium hydroxide in water; and

(e) isolating the resulting solids to yield the compound of Claim 1.

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

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

(a) dissolving *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid in ethyl acetate and hexanes to complete dissolution; and

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

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

(a) coupling *(2R,4R)*-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxypentanoic acid ethyl ester with sodium 5-methyloxazole-2-carboylate to yield *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid;

(b) treating *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid with ethyl acetate and hexanes to complete dissolution; and

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

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

24. The use of a compound according to 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 the compound of any one of Claims 1 to 8 for the manufacture of a medicament 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.

27. The use according to Claim 26, where atrial natriuretic peptide (ANP) or cyclic guanosine monophosphate (cGMP) levels in a subject increase .

28. The use according to Claim 27, wherein levels of ANP and cGMP are measured in either urine or plasma or both in a subject.