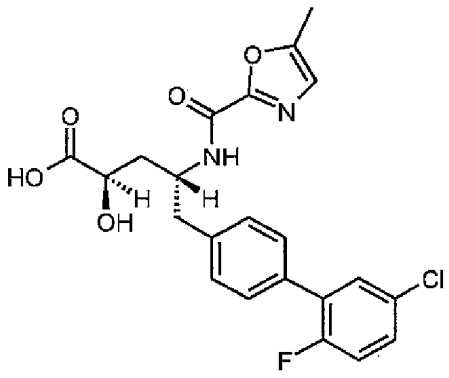
Additionally, to effectively use a NEP inhibitor compound as a therapeutic agent, it would be desirable to have a solid-state form that can be readily manufactured and that has acceptable chemical and physical stability. For example, it would be highly desirable to have a physical form that is thermally 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**. 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

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.

Compound **1** of the disclosure 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 embodiment of the 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**. Another embodiment of the disclosure relates to a method of treating hypertension, pulmonary hypertension, heart failure, or renal disease, comprising administering to a subject a therapeutically effective amount of Compound **1**. Still another embodiment of the disclosure relates to a method for inhibiting a NEP enzyme in a subject comprising administering to the subject, a NEP enzyme-inhibiting amount of Compound **1**.

Since Compound **1** of the disclosure possesses NEP inhibition activity, it is also useful as a research tool. Accordingly, one embodiment of the disclosure relates to a method of using Compound **1** of the disclosure as a research tool, the method comprising conducting a biological assay using Compound **1**. Compound **1** can also be used to evaluate new chemical compounds. Thus another embodiment of the disclosure relates to a method of evaluating a test compound in a biological assay, comprising: (a) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with Compound **1** to provide a second assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include a NEP enzyme inhibition assay. Still another embodiment of the disclosure relates to a method of studying a biological system or sample comprising a NEP enzyme, the method comprising: (a) contacting the biological system or sample with Compound **1**; and (b) determining the effects caused by Compound **1** on the biological system or sample.

Yet another aspect of the disclosure relates to processes useful for preparing Compound **1** or a crystalline form thereof.

Another aspect of the disclosure relates to Compound **1** or a crystalline form thereof for use in therapy. Yet another aspect of the disclosure relates to the use of Compound **1** or a crystalline form thereof for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating hypertension, heart failure, or renal

disease. Another aspect of the disclosure relates to use of Compound **1** or crystalline form thereof for inhibiting a NEP enzyme in a subject. Another aspect of the disclosure relates to an oral dosage form comprising Compound **1** or crystalline form thereof in a capsule, tablet, liquid or suspension. Another aspect of the disclosure relates to an intravenous dosage form comprising Compound **1** or crystalline form thereof in a buffered solution. Other aspects and embodiments of the invention are disclosed herein.

BRIEF DESCRIPTION OF THE DRAWINGS

Various aspects of the present invention are illustrated by reference to the accompanying drawings.

FIG. 1 shows a powder x-ray diffraction (PXRD) pattern of the crystalline non-solvated *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid (**1'**).

FIG. 2 shows a differential scanning calorimetry (DSC) thermogram of the crystalline non-solvated form (**1'**).

FIG. 3 shows a thermal gravimetry profile for the crystalline non-solvated form (**1'**).

FIG. 4 shows a dynamic moisture sorption (DMS) isotherm of the crystalline non-solvated form (**1'**).

FIG. 5 is a polarized light microscope (PLM) image of the crystalline non-solvated form (**1'**).

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the invention relates to *(2R,4R)*-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid (**1**), or a pharmaceutically acceptable salt thereof.

Compound **1** of the invention contains two chiral centers and therefore, a compound of such a structure may exist in various stereoisomeric forms. Specificially, the carbon atoms may have a particular *(R,R)*, *(S,S)*, *(S,R)*, or *(R,S)* configuration or are enriched in a stereoisomeric form having such configuration. Compound **1**, as shown and named is in the (*R, R*) configuration. It will be understood by those skilled in the art that minor amounts of the other stereoisomers may be present in the compositions of the invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual stereoisomers may be obtained by numerous methods that are well known in the art, including chiral chromatography using a suitable chiral stationary phase or support, or by chemically

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

23. 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.

24. A compound according to any one of Claims 1 to 9 for use in therapy.

25. The use of a compound according to any one of Claims 1 to 9, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.

26. The use of the compound of any one of Claims 1 to 9 for the manufacture of a medicament for treating a renally- impaired subject.

27. The use according to claim 26, 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.

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

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