# SUBSTITUTED AMINOBUTYRIC DERIVATIVES AS NEPRILYSIN INHIBITORS

## FIELD OF THE INVENTION

The present invention relates to novel compounds having neprilysin-inhibition activity. The invention also relates to pharmaceutical compositions comprising such compounds, processes and intermediates for preparing such compounds and methods of using such compounds to treat diseases such as hypertension, heart failure, pulmonary hypertension, and renal disease.

## STATE OF THE ART

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

NEP inhibitors, such as thiorphan, candoxatril, and candoxatrilat, have been studied as potential therapeutics. Compounds that inhibit both NEP and angiotensin-I converting enzyme (ACE) are also known, and include omapatrilat, gempatrilat, and sampatrilat. Referred to as vasopeptidase inhibitors, this latter class of compounds is described in Robl et al. (1999) *Exp. Opin. Ther. Patents* 9(12): 1665-1677.

## SUMMARY ~~OF THE INVENTION~~

The present ~~invention~~disclosure provides novel compounds that have been found to possess neprilysin (NEP) enzyme inhibition activity. Accordingly, compounds of the ~~invention~~present disclosure are expected to be useful and advantageous as therapeutic agents for treating conditions such as hypertension and heart failure.

One aspect of the ~~invention~~present disclosure relates to a compound of formula I:

-$CH(NH_2)CH_2COOCH_3$; $R^{27}$ and $R^{28}$ are independently selected from H, -$C_{1-6}$alkyl, and benzyl; or $R^{27}$ and $R^{28}$ are taken together as -$(CH_2)_{3-6}$-, -C(O)-$(CH_2)_3$-, or -$(CH_2)_2O(CH_2)_2$-; $R^{33}$ is selected from -O-$C_{1-6}$alkyl, -O-benzyl, and -$NR^{27}R^{28}$; and $R^{34}$ is -$C_{1-6}$alkyl or -$C_{0-6}$alkylene-$C_{6-10}$aryl;

$R^{22}$ and $R^{23}$ are independently selected from H, -$C_{1-6}$alkyl, -$CH_2COOH$, -$(CH_2)_2OH$; -$(CH_2)_2OCH_3$, -$(CH_2)_2SO_2NH_2$, -$(CH_2)_2N(CH_3)_2$, -$C_{0-1}$alkylene-$C_{3-7}$cycloalkyl, and -$(CH_2)_2$-imidazolyl; or $R^{22}$ and $R^{23}$ are taken together to form a saturated or partially unsaturated -$C_{3-5}$heterocycle optionally substituted with halo, -OH, -COOH, or -$CONH_2$; and optionally containing an oxygen atom in the ring;

$R^{24}$ is selected from -$C_{1-6}$alkyl; -$C_{0-1}$alkylene-O-$C_{1-6}$alkyl; phenyl optionally substituted with halo or -$OCH_3$; and -$C_{1-9}$heteroaryl;

$R^{36}$ is selected from H, -$CH(CH_3)_2$, phenyl, and benzyl; and

$R^{37}$ is selected from H, -$CH(CH_3)_2$, phenyl, and benzyl;

where each alkyl group in $R^1$, $R^3$, and $R^4$ is optionally substituted with 1 to 8 fluoro atoms; and;

where the methylene linker on the biphenyl is optionally substituted with one or two -$C_{1-6}$alkyl groups or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

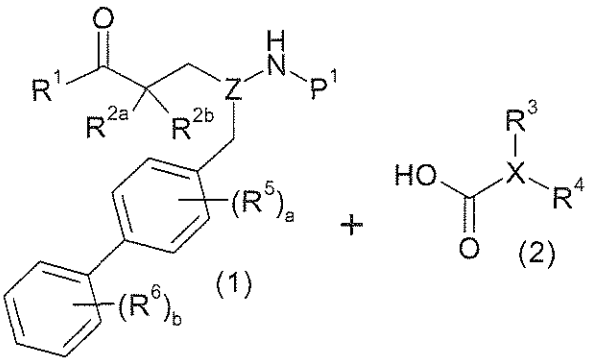
Another aspect of the ~~invention~~present disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the ~~invention~~present disclosure. Such compositions may optionally contain other therapeutic agents. Accordingly, in yet another ~~aspect~~embodiment of the ~~invention~~present disclosure, a pharmaceutical composition comprises a compound of the ~~invention~~present disclosure as the first therapeutic agent, one or more secondary therapeutic agent, and a pharmaceutically acceptable carrier. Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a combination of active agents, comprising a compound of the ~~invention~~present disclosure and a second therapeutic agent. The compound of the ~~invention~~present disclosure can be formulated together or separately from the additional agent(s). When formulated separately, a pharmaceutically acceptable carrier may be included with the additional agent(s). Thus, yet another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a combination of pharmaceutical compositions, the combination comprising: a first pharmaceutical composition comprising a compound of the ~~invention~~present disclosure and a first pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising a second therapeutic agent and a second pharmaceutically acceptable carrier. In another ~~aspect~~embodiment, the ~~invention~~present disclosure relates to a kit containing such pharmaceutical

compositions, for example where the first and second pharmaceutical compositions are separate pharmaceutical compositions.

Compounds of the ~~invention~~present disclosure possess NEP enzyme inhibition activity, and are therefore expected to be useful as therapeutic agents 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~~embodiment of the ~~invention~~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 a compound of the ~~invention~~present disclosure. Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a method of treating hypertension, heart failure, or renal disease, comprising administering to a patient a therapeutically effective amount of a compound of the ~~invention~~present disclosure. Still another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a method for inhibiting a NEP enzyme in a mammal comprising administering to the mammal, a NEP enzyme-inhibiting amount of a compound of the ~~invention~~present disclosure.

Since compounds of the ~~invention~~present disclosure possess NEP inhibition activity, they are also useful as research tools. Accordingly, one ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a method of using a compound of the ~~invention~~present disclosure as a research tool, the method comprising conducting a biological assay using a compound of the ~~invention~~present disclosure. Compounds of the ~~invention~~present disclosure can also be used to evaluate new chemical compounds. Thus another ~~aspect~~embodiment of the ~~invention~~present 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 a compound of the ~~invention~~present disclosure 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 ~~aspect~~embodiment of the ~~invention~~present 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 a compound of the ~~invention~~present disclosure; and (b) determining the effects caused by the compound on the biological system or sample.

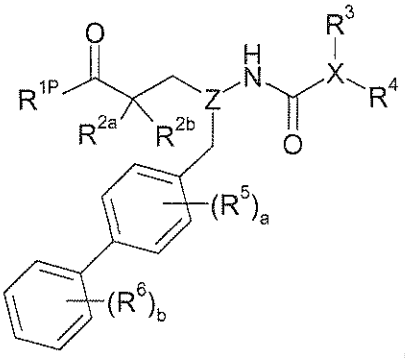
Yet another aspect of the ~~invention~~present disclosure relates to processes and intermediates useful for preparing compounds of the ~~invention~~present disclosure. Accordingly, another aspect of the ~~invention~~present disclosure relates to a process of preparing compounds of formula I as disclosed herein, comprising the step of coupling a compound of formula 1 with a compound of formula 2:



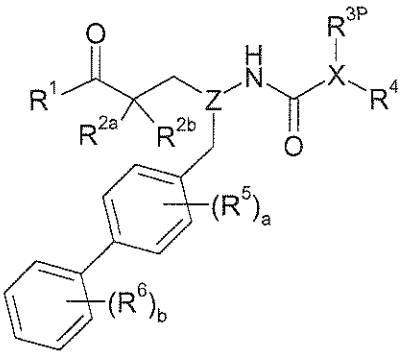
(1) + (2)

to produce a compound of formula I; where $P^1$ is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises deprotecting the compound of formula 1 when $P^1$ is an amino protecting group; and where $R^1$-$R^6$, a, b, Z, and X are as defined for formula I. Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to a process of preparing a pharmaceutically acceptable salt of a compound of formula I, comprising contacting a compound of formula I in free acid or base form with a pharmaceutically acceptable base or acid.

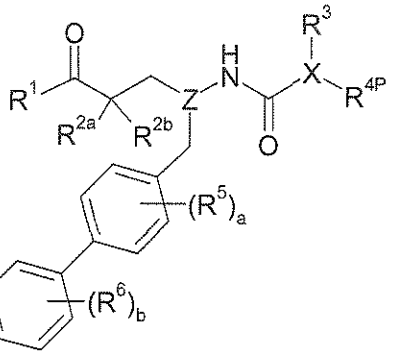
Another aspect of the present disclosure relates to a process for preparing a compound as defined above, comprising the step of deprotecting a compound selected from:



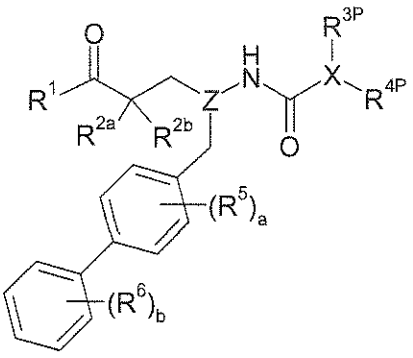
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(10),



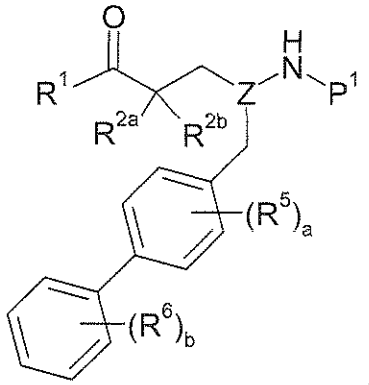
(11), and



(12),

or a salt thereof; where $R^{1P}$ is selected from -O-$P^3$, -NH$P^2$, and -NH(O-$P^4$); $R^{3P}$ is selected from -$C_{0-5}$alkylene-O-$P^4$, -$C_{0-1}$alkylene-COO-$P^3$, and phenyl substituted with -O-$P^4$; $R^{4P}$ is selected from -O-$P^4$; -$C_{1-2}$alkylene-COO-$P^3$; and phenyl or benzyl substituted with -COO-$P^3$; $P^2$ is an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; $P^3$ is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; and $P^4$ is a hydroxyl-protecting group selected from -$C_{1-6}$alkyl, tri$C_{1-6}$alkylsilyl, -$C_{1-6}$alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl.

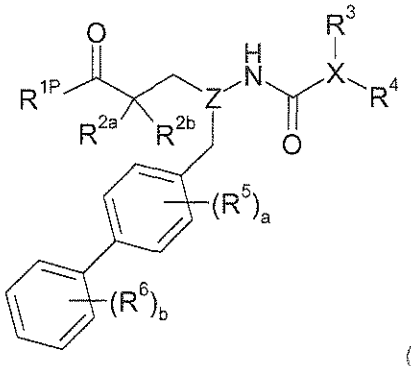
Another aspect of the present disclosure relates to an intermediate useful in the synthesis of a compound as defined above, having formula 1:



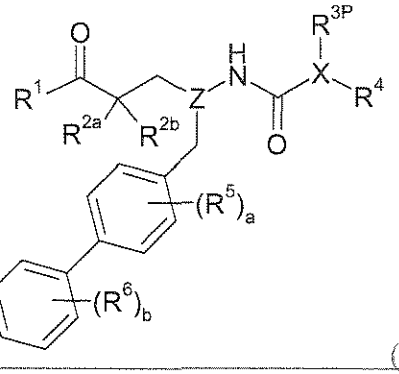
(1),

where $P^1$ is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; or a salt thereof.

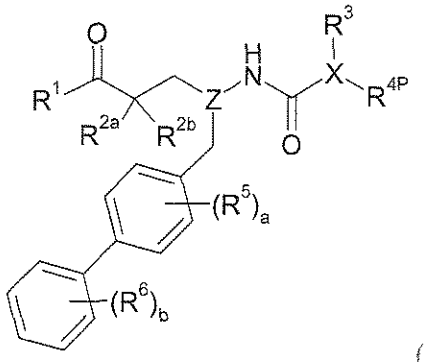
Another aspect of the present disclosure relates to an intermediate useful in the synthesis of a compound as defined above, selected from:



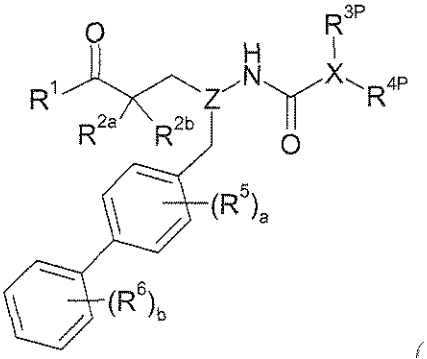
(9),



(10),



(11), and



(12),

or a salt thereof; where $R^{1P}$ is selected from -O-$P^3$, -NH$P^2$, and -NH(O-$P^4$); $R^{3P}$ is selected from -$C_{0-5}$alkylene-O-$P^4$, -$C_{0-1}$alkylene-COO-$P^3$, and phenyl substituted with -O-$P^4$; $R^{4P}$ is selected from -O-$P^4$; -$C_{1-2}$alkylene-COO-$P^3$; and phenyl or benzyl substituted with -COO-$P^3$; $P^2$ is an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; $P^3$ is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; and $P^4$ is a hydroxyl-protecting group selected from -$C_{1-6}$alkyl, tri$C_{1-6}$alkylsilyl, -$C_{1-6}$alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl.

In other ~~aspect~~embodiments, the ~~invention~~present disclosure relates to products prepared by any of the processes described herein, as well as novel intermediates used in such process. In one ~~aspect~~embodiment of the ~~invention~~present disclosure novel intermediates have formula 1, 9, 10, 11, 12, or a salt thereof, as defined herein. Another aspect of the present disclosure relates to a compound as defined above, for use in therapy.

Yet another aspect of the ~~invention~~present disclosure relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof as disclosed herein, for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating hypertension, heart failure, or renal disease. Another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to use of a compound of the ~~invention~~present disclosure for inhibiting a NEP enzyme in a mammal. Still another ~~aspect~~embodiment of the ~~invention~~present disclosure relates to the use of a compound of the ~~invention~~present disclosure as a research tool. Other ~~aspects and~~ embodiments of the ~~invention~~present disclosure are disclosed herein.

## DETAILED DESCRIPTION OF THE INVENTION

### DEFINITIONS

When describing the compounds, compositions, methods and processes of the invention, the following terms have the following meanings unless otherwise indicated. Additionally, as used herein, the singular forms "a," "an," and "the" include the corresponding plural forms unless the context of use clearly dictates otherwise. The terms "comprising", "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements. All numbers expressing