# 5-BIPHENYL-4-HETEROARYLCARBONYLAMINO-PENTANOIC ACID DERIVATIVES AS NEPRILYSIN INHIBITORS

## BACKGROUND OF THE INVENTION

### FIELD OF THE INVENTION

The present invention relates to novel compounds having neprilysin-inhibition activity. The invention also relates to pharmaceutical compositions comprising these compounds, processes and intermediates for preparing these compounds and methods of using these 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.

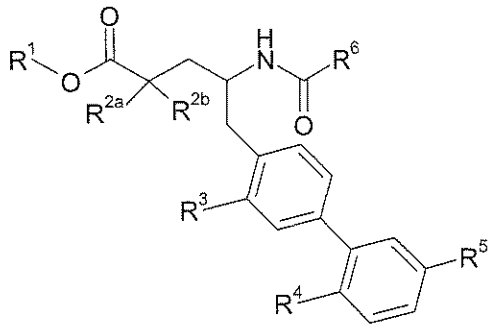
In spite of these compounds however, there remains a need for NEP inhibitors that have improved potency, different metabolic and cleavage properties, and/or having improved oral absorption. This invention is directed to that need.

## 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:



(I)

where:

$R^1$ is H, -$C_{1-8}$alkyl, -$CH(CH_3)OC(O)$-O-cyclohexyl, -$(CH_2)_2$-morpholinyl, or -$CH_2$-5-methyl-[1,3]dioxol-2-one;

$R^{2a}$ is -$C_{1-2}$alkyl and $R^{2b}$ is -$C_{0-2}$alkylene-$NH_2$, -$C(O)NH_2$, -COOH, -$CH_2$-O-$C_{1-6}$alkyl, -CN, or pyridine; or $R^{2a}$ is-$CH_2OH$ and $R^{2b}$ is -$CH_2CH_3$, -$(CH_2)_2CH_3$, -$C_{1-2}$alkylene-OH, -$(CH_2)_2NH_2$, -$(CH_2)_2$-$NHC(O)CH_3$, or -$CH_2CH{=}CH_2$; or $R^{2a}$ and $R^{2b}$ are taken together to form -O-$(CH_2)_2$-, -$(CH_2)_2$-O-$CH_2$-, -$CH_2$-NH-$CH_2$-, -NH-$(CH_2)_2$-, -$(CH_2)$-NH-$(CH_2)_2$-, or -$(CH_2)$-N[$C(O)CH_3$]-$(CH_2)_2$-;

$R^3$, $R^4$ and $R^5$ are independently H or halo; and

$R^6$ is a heterocycle selected from the group consisting of 3H-oxazol-2-one, [1,2,4]oxadiazol-5-one, [1,2,3,5]oxatriazole, [1,2,4]triazolo[1,5-α]pyridine, triazole, pyrazole, imidazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, and pyrimidine; the heterocycle is attached at a carbon atom; and each nitrogen atom in the heterocycle is unsubstituted or substituted with an $R^{60}$ group selected from the group consisting of -OH, -$(CH_2)_2OH$, -$C_{0-2}$alkylene-O-$C_{1-6}$alkyl, -$C_{1-6}$alkyl, -$CHF_2$, and -$CF_3$; and each carbon atom in the heterocycle is unsubstituted or substituted with an $R^{61}$ group independently selected from the group consisting of halo, -OH, -$C_{1-6}$alkyl, -$C_{0-2}$alkylene-O-$C_{1-6}$alkyl, -$C(O)CH_3$, -$C(O)NH(CH_3)$, -$C(O)N(CH_3)_2$, -$C_{3-6}$cycloalkyl, -$CF_3$, -$CH_2SO_2CH_3$, -$NH_2$, -$CH_2NH_2$, -$CH_2N(CH_3)_2$, and phenyl substituted with methyl or halo;

with the proviso that when $R^{2a}$ is -$CH_3$ and $R^{2b}$ is -$CH_2$-O-$C_{1-6}$alkyl, then $R^6$ is not unsubstituted 3H-oxazol-2-one; unsubstituted [1,2,3]triazole; [1,2,3]triazole substituted with an $R^{60}$ group selected from the group consisting of -OH, -$C_{0-2}$alkylene-O-$C_{1-6}$alkyl, and -$C_{1-6}$alkyl; [1,2,4]triazole substituted with an $R^{61}$ group selected from the group consisting of halo and -OH; pyrazole substituted with an $R^{60}$ group that is -$C_{1-6}$alkyl;

pyrazole substituted with an $R^{61}$ group selected from the group consisting of -OH, -$C_{1-6}$alkyl, -$C_{0-2}$alkylene-O-$C_{1-6}$alkyl, and -C(O)$CH_3$; or isoxazole substituted with an $R^{61}$ group selected from the group consisting of -OH, -$C_{1-6}$alkyl, and -$C_{0-2}$alkylene-O-$C_{1-6}$alkyl;

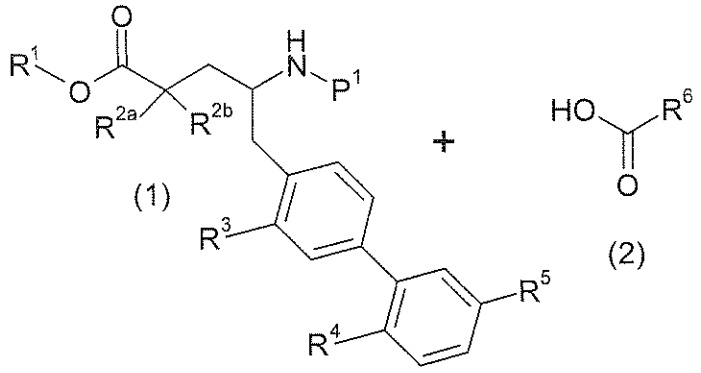
or a pharmaceutically acceptable salt thereof.

Another aspect of the ~~invention~~ present disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the invention. Such compositions may optionally contain other therapeutic agents.

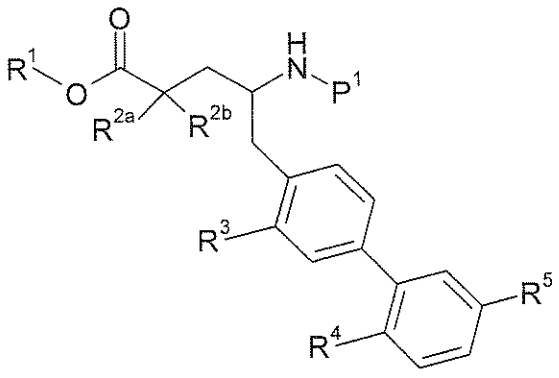
Compounds of the invention possess NEP enzyme inhibition activity, and are therefore expected to be useful as therapeutic agents for treating patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme or by increasing the levels of its peptide substrates. Thus, one ~~aspect~~ embodiment of the present disclosure ~~invention~~ 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. Another ~~aspect~~ embodiment of the present disclosure ~~invention~~ 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. Still another ~~aspect~~ embodiment of the present disclosure ~~invention~~ 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.

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

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




to produce a compound of formula I; where $P^1$ is H or an amino-protecting group selected from the group consisting of *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 $R^1$, $R^{2a}$, $R^{2b}$, and $R^3$-$R^6$ are as defined for formula I. In other ~~aspects~~embodiments, the present disclosure ~~invention~~ 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 present disclosure ~~invention~~ novel intermediates have formula 1, or a salt thereof, as defined herein. In another aspect, there is provided a compound of formula 5:




(5),

where: $R^1$ is H, -$C_{1-8}$alkyl, -$CH(CH_3)OC(O)$-O-cyclohexyl, -$(CH_2)_2$-morpholinyl, or -$CH_2$-5-methyl-[1,3]dioxol-2-one; $R^{2a}$ is-$C_{1-2}$alkyl and $R^{2b}$ is -$C_{0-2}$alkylene-$NH_2$, -$C(O)NH_2$, -COOH, -CN, or pyridine; or $R^{2a}$ is-$CH_2OH$ and $R^{2b}$ is -$CH_2CH_3$, -$(CH_2)_2CH_3$, -$C_{1-2}$alkylene-OH,

-$(CH_2)_2NH_2$, -$(CH_2)_2$-NHC(O)$CH_3$, or -$CH_2CH{=}CH_2$; or $R^{2a}$ and $R^{2b}$ are taken together to form -O-$(CH_2)_2$-, -$(CH_2)_2$-O-$CH_2$-, -$CH_2$-NH-$CH_2$-, -NH-$(CH_2)_2$-, -$(CH_2)$-NH-$(CH_2)_2$-, or -$(CH_2)$-N[C(O)$CH_3$]-$(CH_2)_2$-; $P^1$ is H or an amino-protecting group selected from the group consisting of *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; or a salt thereof.

In another aspect, there is provided a compound of formula I as disclosed herein 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, 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 present disclosure ~~invention~~ relates to use of a compound of the invention for inhibiting a NEP enzyme in a mammal. Still another ~~aspect~~ embodiment of the present disclosure ~~invention~~ relates to the use of a compound of the invention as a research tool. Other ~~aspects and~~ embodiments of the present disclosure ~~invention~~ are disclosed herein.

## DETAILED DESCRIPTION OF THE INVENTION

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