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

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

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; and

R^{36} 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.

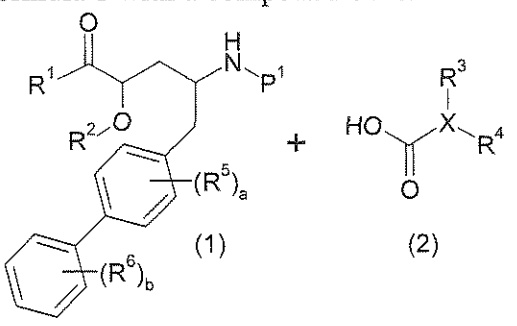
Another aspect of the present disclosure~~invention~~ relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound as disclosed herein~~of the invention~~. Such compositions may optionally contain other therapeutic agents. Accordingly, in yet another embodiment~~aspect~~ of the present disclosure~~invention~~, a pharmaceutical composition comprises a compound of the present disclosure~~invention~~ as the first therapeutic agent, one or more secondary therapeutic agent, and a pharmaceutically acceptable carrier. Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a combination of active agents, comprising a compound of the present disclosure~~invention~~ and a second therapeutic agent. The compound of the present disclosure~~invention~~ 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 embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a combination of pharmaceutical compositions, the combination comprising: a first pharmaceutical composition comprising a compound of the present disclosure~~invention~~ and a first pharmaceutically acceptable carrier; and a second pharmaceutical composition comprising a second therapeutic agent and a second pharmaceutically acceptable carrier. In another embodiment~~aspect~~, the present disclosure~~invention~~ relates to a kit containing such pharmaceutical compositions, for example where the first and second pharmaceutical compositions are separate pharmaceutical compositions.

Compounds of the present disclosure~~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

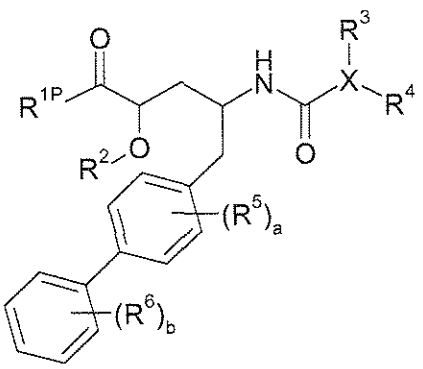
of its peptide substrates. Thus, one embodimentaspect of the present disclosureinvention relates to a method of treating patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme, comprising administering to a patient a therapeutically effective amount of a compound of the inventionpresent disclosure. Another aspectembodiment of the inventionpresent 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 inventionpresent disclosure. Still another aspectembodiment of the inventionpresent 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 inventionpresent disclosure.

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

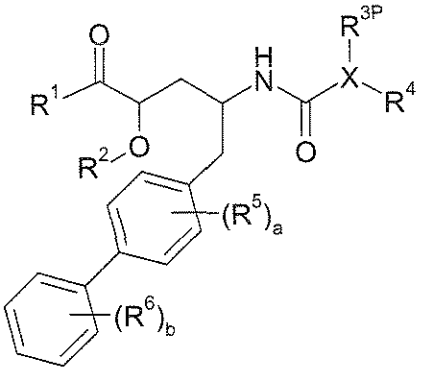
Yet another aspectembodiment of the inventionpresent disclosure relates to processes and intermediates useful for preparing compounds of the inventionpresent disclosure. Accordingly, another aspect of the inventionpresent disclosure relates to a process of preparing compounds of formula I as disclosed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



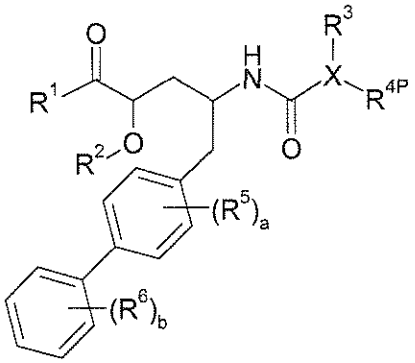
to produce a compound of formula I; where P^1 is H or amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises deprotecting the compound of formula 1 when P^1 is an amino protecting group; and where R^1-R^6, a, b, and X are as defined for formula I. In another aspect, there is provided a process for preparing a compound as defined herein, comprising the step of deprotecting a compound selected from:



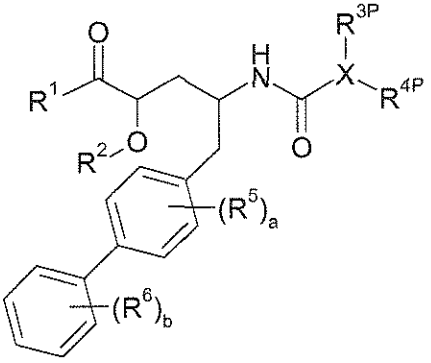
(6),



(7),



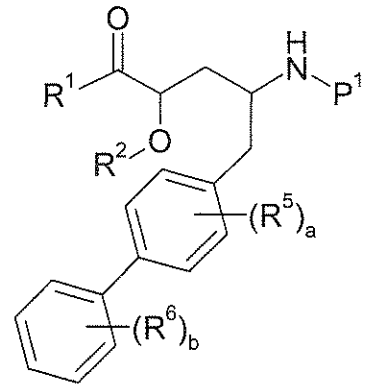
(8), and



(9),

or a salt thereof; where R^{1P} is selected from -O-P^3, -NHP^2, and -NH(O-P^4); R^{3P} is selected from -$C_{0\text{-}5}$alkylene-O-P^4, -$C_{0\text{-}1}$alkylene-COO-P^3, and phenyl substituted with -O-P^4; R^{4P} is selected from -O-P^4; -$C_{1\text{-}2}$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 -$C_{1\text{-}6}$alkyl, tri$C_{1\text{-}6}$alkylsilyl, -$C_{1\text{-}6}$alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl. Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a process of preparing a pharmaceutically acceptable salt of a compound of formula I, comprising contacting a

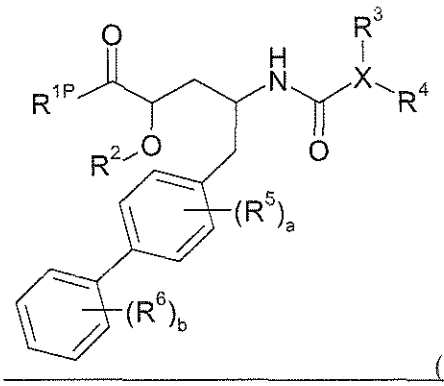
compound of formula I in free acid or base form with a pharmaceutically acceptable base or acid. In other embodimentaspects, the present disclosureinvention relates to products prepared by any of the processes described herein, as well as novel intermediates used in such process. In one embodimentaspect of the present disclosureinvention novel intermediates have formula 1, 6, 7, 8, or 9, or a salt thereof, as defined herein. In one aspect, there is provided an intermediate useful in the synthesis of a compound as defined herein, having formula 1:



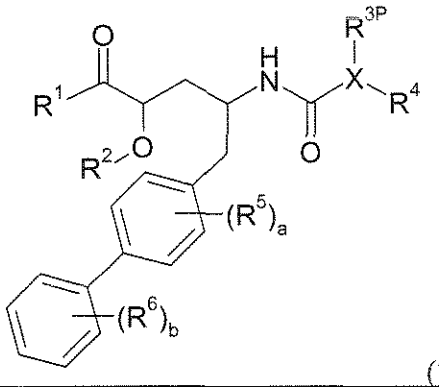
(1),

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.

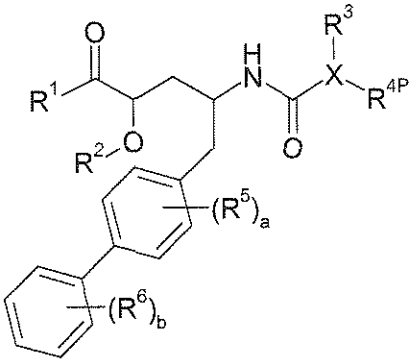
In another aspect, there is provided an intermediate useful in the synthesis of a compound as defined herein, selected from:



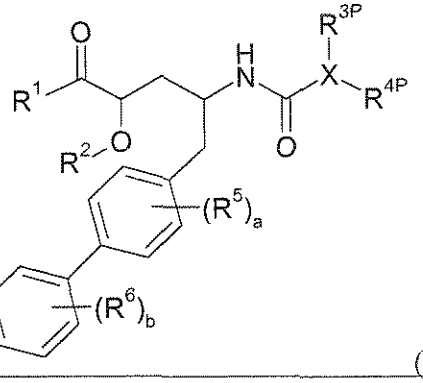
(6),



(7),



(8), and



(9),

or a salt thereof; where R^{1P} is selected from -O-P^3, -NHP^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, triC_{1-6}alkylsilyl, -C_{1-6}alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl.

In another aspect, there is provided a compound as defined herein, for use in therapy.

Yet another aspect of the present disclosure~~invention~~ relates to the use of a compound of formula I as disclosed herein 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 embodiment~~aspect~~ of the present disclosure~~invention~~ relates to use of a compound of the present disclosure~~invention~~ for inhibiting a NEP enzyme in a mammal. Still another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to the use of a compound of the present disclosure~~invention~~ as a research tool. Other ~~aspects and~~ embodiments of the present disclosure~~invention~~ 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 quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used herein are to be understood as being modified in all instances by the term "about," unless otherwise indicated. Accordingly, the numbers set forth herein are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each number should at least be construed in light of the reported significant digits and by applying ordinary rounding techniques.