

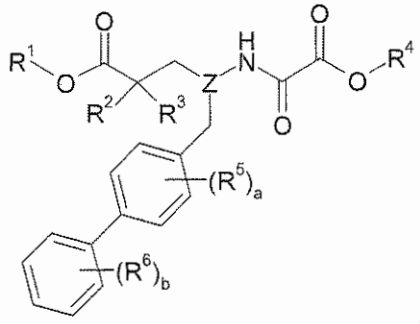
Compound	R	IC_{50} (nM)
21g	-C(O)-CH_2-COOH	92
21a (R,S)	-C(O)-$(CH_2)_2$-COOH	5
21b (S,R)	-C(O)-$(CH_2)_2$-COOH	190
21c (R,R)	-C(O)-$(CH_2)_2$-COOH	700
21d (S,S)	-C(O)-$(CH_2)_2$-COOH	27
21e	-C(O)-$(CH_2)_3$-COOH	90
21f	-C(O)-$(CH_2)_4$-COOH	324

Compound 21a, which has a succinic acid substituent, is the most active compound, with an IC_{50} of 5 nM. The authors observed that "the succininc acid in the P_2' site appears to be optimal since extension of the carboxylic acid chain by one (21e) and two (21f) methylene units decreased activity 18- and 65-fold." The authors further noted that "decreasing the chain length by one methylene (21g) also showed an 18-fold decrease in activity." (page 1692, 2nd column).

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



(I)

where:

R^1 is selected from H, -C_{1-8}alkyl, -C_{1-3}alkylene-C_{6-10}aryl, -C_{1-3}alkylene-C_{1-9}heteroaryl, -C_{3-7}cycloalkyl, -$[(CH_2)_2O]_{1-3}CH_3$, -C_{1-6}alkylene-$OC(O)R^{10}$, -C_{1-6}alkylene-

$-(CH_2)_2O(CH_2)_2-$; R^{43} is selected from -O-C_{1-6}alkyl, -O-benzyl, and $-NR^{41}R^{42}$; and R^{44} is -C_{1-6}alkyl or -C_{0-6}alkylene-C_{6-10}aryl; R^{45} is H, $-CH_3$, $-CH(CH_3)_2$, phenyl, or benzyl;

a is 0 or 1; R^5 is selected from halo, $-CH_3$, $-CF_3$, and -CN;

b is 0 or an integer from 1 to 3; each R^6 is independently selected from halo, -OH, $-CH_3$, $-OCH_3$, -CN, and $-CF_3$;

where each alkyl group in R^1 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.

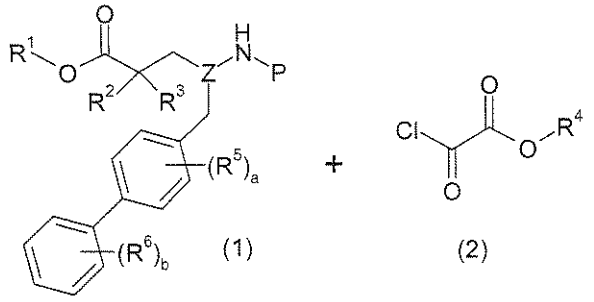
Another aspect of the present disclosure ~~invention~~ relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the present disclosure~~invention~~. Such compositions may optionally contain other therapeutic agents. Accordingly, in yet another ~~aspect~~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

Since compounds of the present disclosure ~~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 present disclosure ~~invention~~ as a research tool, the method comprising conducting a biological assay using a compound of the present disclosure~~invention~~. Compounds of the present disclosure ~~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 present disclosure ~~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 present disclosure~~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 present disclosure~~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:

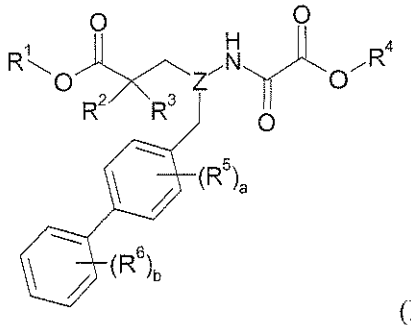


to produce a compound of formula I; where P is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises

deprotecting the compound of formula 1 when P is an amino protecting group; and where R^1-R^6, a, b, and Z are as defined for formula I. Another ~~aspect~~ embodiment 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 ~~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.

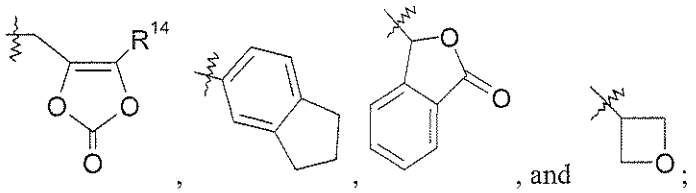
Yet another aspect of the present disclosure ~~invention~~ relates to the use of a compound of formula I or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament, especially for the manufacture of a medicament useful for treating hypertension, heart failure, or renal disease. Another aspect relates to a compound as disclosed herein for use in therapy. Another ~~aspect~~ embodiment 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 ~~aspect~~ embodiment 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.

A particular group of compounds of formula I are those disclosed in U.S. Provisional Application No. 61/554,625, filed on November 2, 2011. This group includes compounds of formula I'; wherein:



(I')

where: R^1 is selected from H, -C_{1-8}alkyl, -C_{1-3}alkylene-C_{6-10}aryl, -C_{1-3}alkylene-C_{1-9}heteroaryl, -C_{3-7}cycloalkyl, -$[(CH_2)_2O]_{1-3}CH_3$, -C_{1-6}alkylene-$OC(O)R^{10}$, -C_{1-6}alkylene-$NR^{11}R^{12}$, -C_{1-6}alkylene-$C(O)R^{13}$, -C_{0-6}alkylenemorpholinyl, -C_{1-6}alkylene-SO_2-C_{1-6}alkyl,



, , , and ;

R^{10} is selected from -C_{1-6}alkyl, -O-C_{1-6}alkyl, -C_{3-7}cycloalkyl, -O-C_{3-7}cycloalkyl, phenyl, -O-phenyl, -$NR^{11}R^{12}$, -$CH[CH(CH_3)_2]$-NH_2, -$CH[CH(CH_3)_2]$-NHC(O)O-C_{1-6}alkyl, and