combining AT_1 receptor antagonism and NEP inhibition, as evidenced by AT_1 receptor antagonist/NEP inhibitor combinations described in WO 9213564 to Darrow et al (Schering Corporation); US20030144215 to Ksander et al.; Pu et al., Abstract presented at the Canadian Cardiovascular Congress (October 2004); and Gardiner et al. (2006) *JPET* 319:340-348; and WO 2007/045663 (Novartis AG) to Glasspool et al.

Recently, WO 2007/056546 (Novartis AG) to Feng et al. has described complexes of an AT_1 receptor antagonist and a NEP inhibitor, where an AT_1 receptor antagonist compound is non-covalently bound to a NEP inhibitor compound, or where the antagonist compound is linked to the inhibitor compound by a cation.

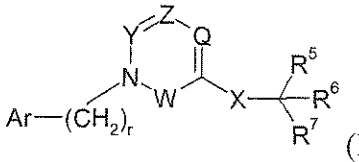
In spite of the advances in the art, there remains a need for a highly efficacious monotherapy with multiple mechanisms of action leading to levels of blood pressure control that can currently only be achieved with combination therapy. Thus, although various hypertensive agents are known, and administered in various combinations, it would be highly desirable to provide compounds having both AT_1 receptor antagonist activity and NEP inhibition activity in the same molecule. Compounds possessing both of these activities are expected to be particularly useful as therapeutic agents since they would exhibit antihypertensive activity through two independent modes of action while having single molecule pharmacokinetics.

In addition, such dual-acting compounds are also expected to have utility to treat a variety of other diseases that can be treated by antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme.

SUMMARY ~~OF THE INVENTION~~

The present disclosure~~invention~~ provides novel compounds that have been found to possess AT_1 receptor antagonist activity and 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 embodiment~~aspect~~ of the present disclosure~~invention~~ is directed to a compound of formula I:

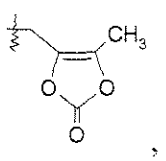
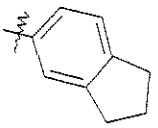
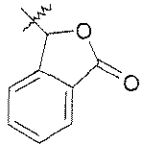


(I)

wherein: r is 0, 1 or 2;

Ar is selected from:

-C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,


, 
, or 
;

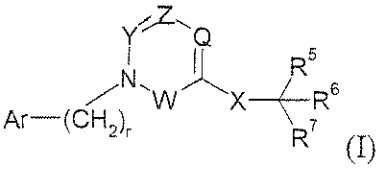
R^{5ea} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, $-NR^{5eb}R^{5ec}$, or $-CH(NH_2)CH_2COOCH_3$; R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl, or are taken together as -$(CH_2)_{3-6}$-; R^{5f} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$; R^{5fa} and R^{5fb} are independently selected from H and -C_{1-4}alkyl; R^{5g} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or $-CH_2$-O-$(CH_2)_2$-O-CH_3; R^{5h} is H or -C_{1-4}alkyl; R^{5i} is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl; and R^{5j} is -C_{1-6}alkyl, aryl, or $-CH_2CH(NH_2)COOH$;

R^6 is selected from -C_{1-6}alkyl, $-CH_2O(CH_2)_2$-O-CH_3, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl;

wherein: each $-CH_2$- group in $-(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro; each ring in Ar and each aryl and heteroaryl in R^{1-3} and R^{5-6} is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, $-S(O)_2$-C_{1-4}alkyl, -phenyl, $-NO_2$, $-NH_2$, -NH-C_{1-6}alkyl and $-N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms; each carbon atom in X is optionally substituted with one or more R^{4b} groups and one $-CH_2$- moiety in X may be replaced with a group selected from -C_{4-8}cycloalkylene-, $-CR^{4d}$=CH-, and $-CH=CR^{4d}$-; wherein R^{4b} is selected from -C_{0-5}alkylene-$COOR^{4c}$, -C_{1-6}alkyl, -C_{0-1}alkylene-$CONH_2$, -C_{1-2}alkylene-OH, -C_{0-3}alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or -C_{1-4}alkyl; and R^{4d} is selected from $-CH_2$-thiophene and phenyl; each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} is optionally substituted with 1 to 7 fluoro atoms; and pharmaceutically acceptable salts thereof.

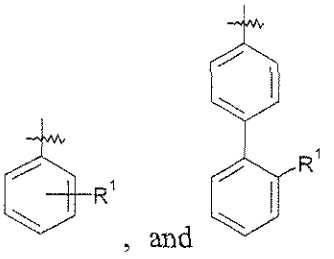
In a first aspect, there is provided a compound of formula I:


(I)

wherein:

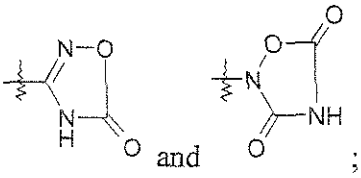
r is 1;

Ar is selected from:

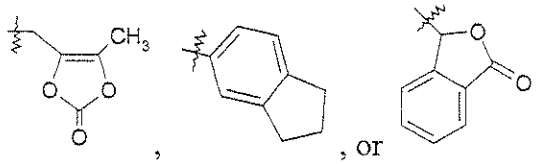

, and

;

R^1 is selected from -$COOR^{1a}$, -$NHSO_2R^{1b}$, -SO_2NHR^{1d}, -SO_2OH, -C(O)NH-SO_2R^{1c}, -$P(O)(OH)_2$, -CN, -O-$CH(R^{1e})$-COOH, tetrazol-5-yl,


and ;

R^{1a} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(C_{1-4}alkyl)OC(O)R^{1aa}$, -$C_{0-6}$alkylenemorpholine,



R^{1aa} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{1ab}R^{1ac}$, or -$CH(NH_2)CH_2COOCH_3$; R^{1ab} and R^{1ac} are independently selected from H, -C_{1-6}alkyl, and benzyl, or are taken together as -$(CH_2)_{3-6}$-; R^{1b} is R^{1c} or -$NHC(O)R^{1c}$; R^{1c} is -C_{1-6}alkyl, -C_{0-6}alkylene-O-R^{1ca}, -C_{1-5}alkylene-$NR^{1cb}R^{1cc}$, -C_{0-4}alkylenearyl or -C_{0-4}alkyleneheteroaryl; R^{1ca} is H, -C_{1-6}alkyl, or -C_{1-6}alkylene-O-C_{1-6}alkyl; R^{1cb} and R^{1cc} are independently selected from H and -C_{1-6}alkyl, or are taken together as -$(CH_2)_2$-O-$(CH_2)_2$- or -$(CH_2)_2$-N[$C(O)CH_3$]-$(CH_2)_2$-; R^{1d} is H, R^{1c}, -$C(O)R^{1c}$, or -$C(O)NHR^{1c}$; R^{1e} is -C_{1-4}alkyl or aryl;

Y is -$C(R^3)$-, Z is -N-, Q is -$C(R^2)$- and W is a bond; Y is -N-, Z is -$C(R^3)$-, Q is -$C(R^2)$- and W is a bond; or Y is -$C(R^3)$-, Z is -CH-, Q is -N- and W is a bond;

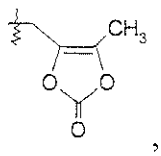
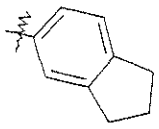
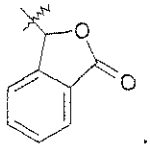
R^2 is selected from H, halo, -NO_2, -C_{1-6}alkyl, -C_{2-6}alkenyl, -C_{3-6}cycloalkyl, -CN, -$C(O)R^{2a}$, -C_{0-5}alkylene-OR^{2b}, -C_{0-5}alkylene-$NR^{2c}R^{2d}$, -C_{0-3}alkylenearyl, and -C_{0-3}alkylene-heteroaryl; where R^{2a} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, -OR^{2b} and -$NR^{2c}R^{2d}$; R^{2b} is selected from H, -C_{1-6}alkyl, -C_{3-6}cycloalkyl, and -C_{0-1}alkylenearyl; and R^{2c} and R^{2d} are independently selected from H, -C_{1-4}alkyl, and -C_{0-1}alkylenearyl;

R^3 is selected from -C_{1-10}alkyl, -C_{2-10}alkenyl, -C_{3-10}alkynyl, -C_{0-3}alkylene-C_{3-7}cycloalkyl, -C_{2-3}alkenylene-C_{3-7}cycloalkyl, -C_{2-3}alkynylene-C_{3-7}cycloalkyl, -C_{0-5}alkylene-NR^{3a}-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-O-C_{0-5}alkylene-R^{3b}, -C_{0-5}alkylene-S-C_{1-5}alkylene-R^{3b}, and -C_{0-3}alkylenearyl; where R^{3a} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, and -C_{0-3}alkylenearyl; and R^{3b} is selected from H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, and aryl;

X is -C_{1-12}alkylene-, where at least one -CH_2- moiety in the alkylene is replaced with a -NR^{4a}-C(O)- or -C(O)-NR^{4a}- moiety, where R^{4a} is selected from H, -OH, and -C_{1-4}alkyl;

R^5 is selected from -C_{0-3}alkylene-SR^{5a}, -C_{0-3}alkylene-$C(O)NR^{5b}R^{5c}$, -C_{0-3}alkylene-NR^{5b}-$C(O)R^{5d}$, -NH-C_{0-1}alkylene-$P(O)(OR^{5e})_2$, -C_{0-3}alkylene-$P(O)OR^{5e}R^{5f}$, -C_{0-2}alkylene-CHR^{5g}-COOH, -C_{0-3}alkylene-$C(O)NR^{5h}$-CHR^{5i}-COOH, and -C_{0-3}alkylene-S-SR^{5j}; R^{5a} is H or -C(O)-R^{5aa}; R^{5aa} is -C_{1-6}alkyl, -C_{0-6}alkylene-C_{3-7}cycloalkyl,

-C_{0-6}alkylenearyl, -C_{0-6}alkyleneheteroaryl, -C_{0-6}alkylenemorpholine, -C_{0-6}alkylenepiperazine-CH_3, -$CH(NH_2)$-$CH(CH_3)_2$, -2-pyrrolidine, -C_{0-6}alkylene-OR^{5ab}, -O-C_{0-6}alkylenearyl, -C_{1-2}alkylene-OC(O)-C_{1-6}alkyl, -C_{1-2}alkylene-OC(O)-C_{0-6}alkylenearyl, or -O-C_{1-2}alkylene-OC(O)O-C_{1-6}alkyl; R^{5ab} is H or -C_{1-6}alkyl; R^{5b} is H, -OH, -$OC(O)R^{5ba}$, -CH_2COOH, -O-benzyl, -pyridyl, or -$OC(S)NR^{5bb}R^{5bc}$; R^{5ba} is H, -C_{1-6}alkyl, aryl, -OCH_2-aryl, -CH_2O-aryl, or -$NR^{5bb}R^{5bc}$; R^{5bb} and R^{5bc} are independently selected from H and -C_{1-4}alkyl; R^{5c} is H, -C_{1-6}alkyl, or -C(O)-R^{5ca}; R^{5ca} is H, -C_{1-6}alkyl, -C_{3-7}cycloalkyl, aryl, or heteroaryl; R^{5d} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -$NR^{5da}R^{5db}$, -CH_2SH, or -O-C_{1-6}alkyl; R^{5da} and R^{5db} are independently selected from H and -C_{1-4}alkyl; R^{5e} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, -C_{1-3}alkyleneheteroaryl, -C_{3-7}cycloalkyl, -$CH(CH_3)$-O-$C(O)R^{5ea}$,


, 
, or 
;

R^{5ea} is -O-C_{1-6}alkyl, -O-C_{3-7}cycloalkyl, -$NR^{5eb}R^{5ec}$, or -$CH(NH_2)CH_2COOCH_3$; R^{5eb} and R^{5ec} are independently selected from H, -C_{1-4}alkyl, and -C_{1-3}alkylenearyl, or are taken together as -$(CH_2)_{3-6}$-; R^{5f} is H, -C_{1-4}alkyl, -C_{0-3}alkylenearyl, -C_{1-3}alkylene-$NR^{5fa}R^{5fb}$, or -C_{1-3}alkylene(aryl)-C_{0-3}alkylene-$NR^{5fa}R^{5fb}$; R^{5fa} and R^{5fb} are independently selected from H and -C_{1-4}alkyl; R^{5g} is H, -C_{1-6}alkyl, -C_{1-3}alkylenearyl, or -CH_2-O-$(CH_2)_2$-O-CH_3; R^{5h} is H or -C_{1-4}alkyl; R^{5i} is H, -C_{1-4}alkyl, or -C_{0-3}alkylenearyl; and R^{5j} is -C_{1-6}alkyl, aryl, or -$CH_2CH(NH_2)COOH$;

R^6 is selected from -C_{1-6}alkyl, -$CH_2O(CH_2)_2$-O-CH_3, -C_{1-6}alkylene-O-C_{1-6}alkyl, -C_{0-3}alkylenearyl, -C_{0-3}alkyleneheteroaryl, and -C_{0-3}alkylene-C_{3-7}cycloalkyl; and

R^7 is H or is taken together with R^6 to form -C_{3-8}cycloalkyl;

wherein:

each -CH_2- group in -$(CH_2)_r$- is optionally substituted with 1 or 2 substituents independently selected from -C_{1-4}alkyl and fluoro;

each ring in Ar and each aryl and heteroaryl in R^{1-3} and R^{5-6} is optionally substituted with 1 to 3 substituents independently selected from -OH, -C_{1-6}alkyl, -C_{2-4}alkenyl, -C_{2-4}alkynyl, -CN, halo, -O-C_{1-6}alkyl, -S-C_{1-6}alkyl, -S(O)-C_{1-6}alkyl, -$S(O)_2$-C_{1-4}alkyl, -phenyl, -NO_2, -NH_2, -NH-C_{1-6}alkyl and -$N(C_{1-6}alkyl)_2$, wherein each alkyl, alkenyl and alkynyl is optionally substituted with 1 to 5 fluoro atoms;

each carbon atom in X is optionally substituted with one or more R^{4b} groups and one $-CH_2-$ moiety in X may be replaced with a group selected from $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, and $-CH=CR^{4d}-$; wherein R^{4b} is selected from $-C_{0-5}$alkylene-$COOR^{4c}$, $-C_{1-6}$alkyl, $-C_{0-1}$alkylene-$CONH_2$, $-C_{1-2}$alkylene-OH, $-C_{0-3}$alkylene-C_{3-7}cycloalkyl, 1H-indol-3-yl, benzyl, and hydroxybenzyl, where R^{4c} is H or $-C_{1-4}$alkyl; and R^{4d} is selected from $-CH_2$-2-thiophene and phenyl;

each alkyl and each aryl in R^{1-3}, R^{4a-4d}, and R^{5-6} is optionally substituted with 1 to 7 fluoro atoms;

wherein each aryl in R^1, R^2, R^3, R^5, and R^6 contains 6 to 10 carbon ring atoms; and each heteroaryl in R^1, R^2, R^5, and R^6 contains 2 to 9 carbon ring atoms and 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur;

and pharmaceutically acceptable salts thereof.

Another aspect of the present disclosure~~invention~~ relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound according to the first aspect~~of the invention~~. Such compositions may optionally contain other therapeutic agents such as diuretics, β_1 adrenergic receptor blockers, calcium channel blockers, angiotensin-converting enzyme

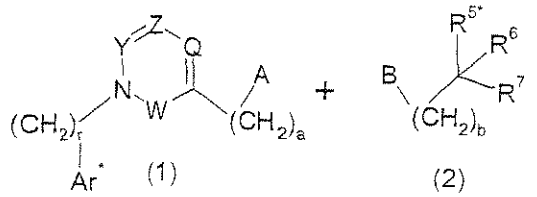
inhibitors, AT_1 receptor antagonists, neprilysin inhibitors, non-steroidal anti-inflammatory agents, prostaglandins, anti-lipid agents, anti-diabetic agents, anti-thrombotic agents, renin inhibitors, endothelin receptor antagonists, endothelin converting enzyme inhibitors, aldosterone antagonists, angiotensin-converting enzyme/neprilysin inhibitors, vasopressin receptor antagonists, and combinations thereof. Accordingly, in yet another ~~aspect~~embodiment of the ~~invention~~present disclosure, a pharmaceutical composition comprises a compound of the ~~invention~~present disclosure, a second therapeutic agent, and a pharmaceutically acceptable carrier. Another ~~aspect~~embodiment of the ~~invention~~present disclosure pertains 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. The ~~invention~~present disclosure also 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 both AT_1 receptor antagonist activity and 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 antagonizing the AT_1 receptor and/or inhibiting the NEP enzyme. Thus, one ~~aspect~~embodiment of the ~~invention~~present disclosure is directed to a method of treating patients suffering from a disease or disorder that is treated by antagonizing the AT_1 receptor and/or 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 is directed to a method of treating hypertension or heart failure, 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 pertains to a method for antagonizing an AT_1 receptor in a mammal comprising administering to the mammal, an AT_1 receptor-antagonizing amount of a compound of the ~~invention~~present disclosure. Yet another ~~aspect~~embodiment of the ~~invention~~present disclosure pertains 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.

Compounds of formula I and pharmaceutically acceptable salts thereof, that are of particular interest include those that exhibit an inhibitory constant (pK_i) for binding to an AT_1 receptor greater than or equal to about 5.0; in particular those having a pK_i greater than or equal to about 6.0; in one embodiment those having a pK_i greater than or equal to about 7.0; more particularly those having a pK_i greater than or equal to about 8.0; and in yet another embodiment, those having a pK_i within the range of about 8.0-10.0. Compounds of particular interest also include those having a NEP enzyme inhibitory concentration (pIC_{50}) greater than or equal to about 5.0; in one embodiment those having a pIC_{50} greater than or equal to about 6.0; in particular those having a pIC_{50} greater than or equal to about 7.0; and most particularly those having a pIC_{50} within the range of about 7.0-10.0. Compounds of further interest include those having a pK_i for binding to an AT_1 receptor greater than or equal to about 7.5 and having a NEP enzyme pIC_{50} greater than or equal to about 7.0.

Since compounds of the ~~invention~~present disclosure possess AT_1 receptor antagonist activity and NEP inhibition activity, such compounds are also useful as research tools. Accordingly, one ~~aspect~~embodiment of the ~~invention~~present disclosure pertains 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 an AT_1 receptor binding assay and a NEP enzyme inhibition assay. Still another ~~aspect~~embodiment of the ~~invention~~present disclosure is directed to a method of studying a biological system or sample comprising an AT_1 receptor, a NEP enzyme, or both, 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.

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

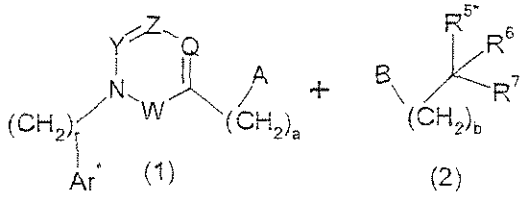


(1) (2)

where: A is $-NH_2$ and B is -COOH or A is -COOH and B is $-NH_2$; the sum of a and b is in the range of 0 to 11; Ar* represents Ar-R^{1*}, where R^{1*} is R^1 or a protected form of R^1; and R^{5*} represents R^5 or a protected form of R^5; the carbon atoms in the $-(CH_2)_a$ and $-(CH_2)_b$ groups may be substituted with one or more R^{4b} groups; and one $-CH_2-$ group in the $-(CH_2)_a$ or the $-(CH_2)_b$ group may be replaced with $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, or $-CH=CR^{4d}-$; and optionally deprotecting the product when R^{1*} is a protected form of R^1 and/or R^{5*} is a protected form of R^5.

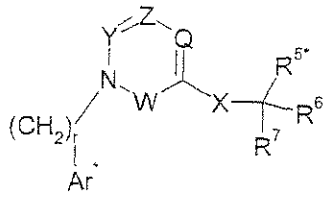
In another aspect, there is provided a process for preparing the compound according to the first aspect, comprising:

(a) coupling a compound of formula 1 with a compound of formula 2:



(1) (2)

to produce a compound having the formula:



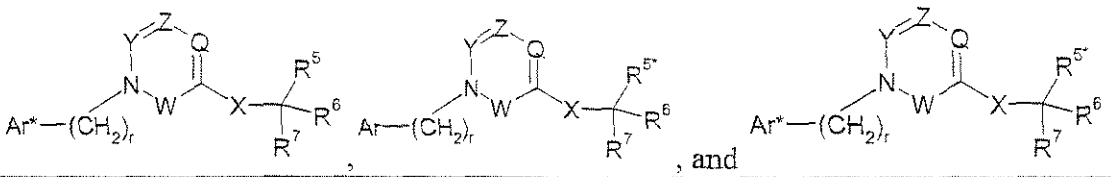
where: A is $-NH_2$ and B is -COOH or A is -COOH and B is $-NH_2$; the sum of a and b is in the range of 0 to 11; r is 1; Ar* represents Ar-R^{1*}, where R^{1*} is R^1 or a protected form of R^1; and R^{5*} represents R^5 or a protected form of R^5; the carbon atoms in the $-(CH_2)_a$ and $-(CH_2)_b$ groups may be substituted with one or more R^{4b} groups; and one $-CH_2-$ group in the $-(CH_2)_a$ or the $-(CH_2)_b$ group may be replaced with $-C_{4-8}$cycloalkylene-, $-CR^{4d}=CH-$, or $-CH=CR^{4d}-$; and

(b) when R^{1*} is a protected form of R^1 and/or R^{5*} is a protected form of R^5, deprotecting the product of step (a) to produce a compound of formula I.

In another aspect, there is provided a compound prepared by the process as defined above.

In another aspect, there is provided an intermediate useful in the synthesis of the compound according to the first aspect, selected from

the group comprising:



, and

wherein: r is 1; Ar* is Ar-R^{1}*; R^{1}* is selected from -C(O)O-P^2, -SO_2O-P^5, -SO_2NH-P^6, -P(O)(O-P^7)$_2$, -OCH(CH_3)-C(O)O-P^2, -OCH(aryl)-C(O)O-P^2, and tetrazol-5-yl-P^4; R^{5*} is selected from -C_{0-3}alkylene-S-P^3, -C_{0-3}alkylene-C(O)NH(O-P^5), -C_{0-3}alkylene-N(O-P^5)-C(O)R^{5d}, -C_{0-1}alkylene-NHC(O)CH_2S-P^3, -NH-C_{0-1}alkylene-P(O)(O-P^7)$_2$, -C_{0-3}alkylene-P(O)(O-P^7)-R^{5e}, -C_{0-2}alkylene-CHR^{5f}-C(O)O-P^2 and -C_{0-3}alkylene-C(O)NR^{5g}-CHR^{5h}-C(O)O-P^2; P^2 is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; P^3 is a-C(O)CH_3; P^4 is a tetrazole-protecting group selected from trityl and diphenylmethyl; P^5 is a hydroxyl-protecting group selected from C_{1-6}alkyl, trimethylsilyl, triethylsilyl, *tert*-butyldimethylsilyl, formyl, acetyl, pivaloyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl; P^6 is a sulfonamide-protecting group selected from *t*-butyl, formyl, acetyl, phenylacetyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl, benzoyl, and 4-acetoxybenzoyl; and P^7 is a phosphate-protecting group selected from C_{1-4}alkyl, phenyl, chlorophenyl, and methylphenyl; and salts thereof.

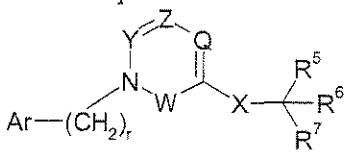
Another embodiment~~aspect~~ of the present disclosure~~invention~~ relates to a process of preparing a pharmaceutically acceptable salt of a compound of formula I, comprising contacting a compound of formula I in free acid or base form with a pharmaceutically acceptable base or acid. In other embodiments~~aspects~~, the present disclosure~~invention~~ is directed to products prepared by any of the processes described herein, as well as novel intermediates used in such process. In one embodiment~~aspect~~ of the present disclosure~~invention~~ novel intermediates have formula VIII, IX or X.

Another aspect of the present disclosure is directed to the compound according to the first aspect for use as a medicament.

Yet another aspect of the present disclosure~~invention~~ is directed to the use of a compound according to the first aspect~~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 or heart failure. Other~~Another~~ aspects of the present disclosure~~invention~~ are~~is~~ directed to use of a compound according to the first aspect for the manufacture of a medicament~~of the invention~~ for antagonizing an AT_1 receptor or for inhibiting a NEP enzyme in a mammal. Still another embodiment~~aspect~~ of the present disclosure~~invention~~ pertains 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

The invention is directed to compounds of formula I:



(I)

and pharmaceutically acceptable salts thereof.

As used herein, the term "compound of the invention" is intended to include compounds of formula I as well as the species embodied in formulas II-VI. In addition, the compounds of the invention may also contain several basic or acidic groups (for example, amino or carboxyl groups) and therefore, such compounds can exist as a free base, free