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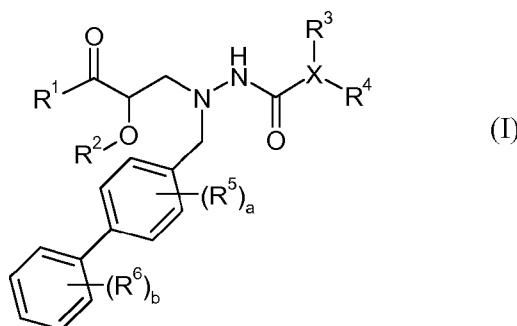
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(54) Title: NEPRILYSIN INHIBITORS



(57) Abstract: In one aspect, the invention relates to compounds having the formula: (I) where R¹-R⁶, a, b, and X are as defined in the specification, or a pharmaceutically acceptable salt thereof. These compounds have neprilysin inhibition activity. In another aspect, the invention relates to pharmaceutical compositions comprising such compounds; methods of using such compounds; and processes and intermediates for preparing such compounds.

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NEPRILYSIN INHIBITORS

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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 10 using such compounds to treat diseases such as hypertension, heart failure, pulmonary hypertension, and renal disease.

STATE OF THE ART

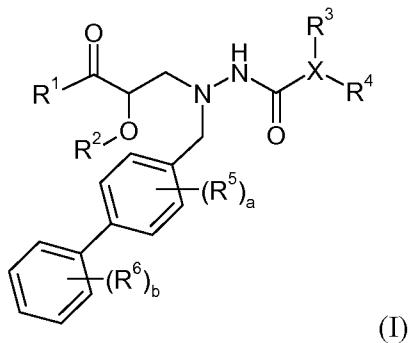
Neprilysin (neutral endopeptidase, EC 3.4.24.11) (NEP), is an endothelial membrane bound Zn^{2+} metallopeptidase found in many organs and tissues, including the 15 brain, kidneys, lungs, gastrointestinal tract, heart, and the peripheral vasculature. NEP degrades and inactivates a number of endogenous 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 20 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 25 et al. (1999) *Exp. Opin. Ther. Patents* 9(12): 1665-1677.

SUMMARY OF THE INVENTION

The present invention provides novel compounds that have been found to possess neprilysin (NEP) enzyme inhibition activity. Accordingly, compounds of the invention are expected to be useful and advantageous as therapeutic agents for treating conditions such 30 as hypertension and heart failure.

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



where:

R¹ is selected from -OR⁷ and -NR⁸R⁹;

R² is H or -P(O)(OH)₂ or R² is taken together with R⁷ to form -CR¹⁸R¹⁹- or is taken 5 together with R⁸ to form -C(O)-;

X is a -C₁₋₉heteroaryl;

R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -NH₂; -C₁₋₆alkyl; -CF₃; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹;

-C(O)NR²²R²³; -NHC(O)R²⁴; =O; -NO₂; -C(CH₃)=N(OH); phenyl optionally substituted

10 with one or two groups independently selected from halo, -OH, -CF₃, -OCH₃, -NHC(O)CH₃, and phenyl; naphthalenyl; pyridinyl; pyrazinyl; pyrazolyl optionally substituted with methyl; thiophenyl optionally substituted with methyl or halo; furanyl; and -CH₂-morpholinyl; and R³, when present, is attached to a carbon atom;

R⁴ is absent or is selected from H; -OH; -C₁₋₆alkyl; -C₁₋₂alkylene-COOR³⁵;

15 -CH₂OC(O)CH(R³⁶)NH₂; -OCH₂OC(O)CH(R³⁶)NH₂; -OCH₂OC(O)CH₃; -CH₂OP(O)(OH)₂; -CH₂CH(OH)CH₂OH; -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo, -COOR³⁵, -OCH₃, -OCF₃, and -SCF₃; and R⁴, when present, is attached to a carbon or nitrogen atom;

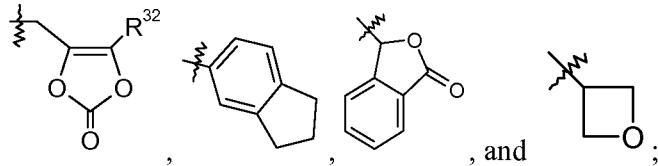
20 or R³ and R⁴ are taken together to form -phenylene-O-(CH₂)₁₋₃- or -phenylene-O-CH₂-CHOH-CH₂;

a is 0 or 1; R⁵ is selected from halo, -CH₃, -CF₃, and -CN;

b is 0 or an integer from 1 to 3; each R⁶ is independently selected from halo, -OH, -CH₃, -OCH₃, and -CF₃;

25 R⁷ is selected from H, -C₁₋₈alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R¹⁰, -C₁₋₆alkylene-NR¹²R¹³, -C₁₋₆alkylene-C(O)R³¹, -C₀₋₆alkylenemorpholinyl; -C₁₋₆alkylene-

SO₂-C₁₋₆alkyl;



R¹⁰ is selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₇cycloalkyl, -O-C₃₋₇cycloalkyl, phenyl, -O-phenyl, -NR¹²R¹³, -CH[CH(CH₃)₂]-NH₂, -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, and -CH(NH₂)CH₂COOCH₃; and R¹² and R¹³ are independently selected from H, -C₁₋₆alkyl, and benzyl; or R¹² and R¹³ are taken together as -(CH₂)₃₋₆-, -C(O)-(CH₂)₃-, or -(CH₂)₂O(CH₂)₂-; and R³¹ is selected from -O-C₁₋₆alkyl, -O-benzyl, and -NR¹²R¹³; R³² is -C₁₋₆alkyl or -C₀₋₆alkylene-C₆₋₁₀aryl;

R⁸ is selected from H, -OH, -OC(O)R¹⁴, -CH₂COOH, -O-benzyl, pyridyl, and -OC(S)NR¹⁵R¹⁶; R¹⁴ is selected from H, -C₁₋₆alkyl, -C₆₋₁₀aryl, -OCH₂-C₆₋₁₀aryl, -CH₂O-C₆₋₁₀aryl, and -NR¹⁵R¹⁶; and R¹⁵ and R¹⁶ are independently selected from H and -C₁₋₄alkyl;

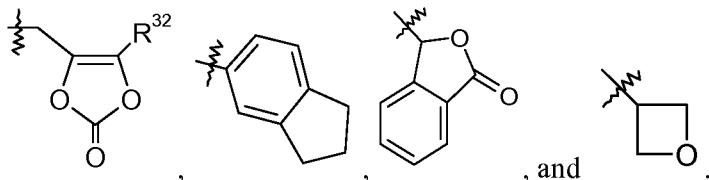
R⁹ is selected from H, -C₁₋₆alkyl, and -C(O)R¹⁷; and R¹⁷ is selected from H, -C₁₋₆alkyl, -C₃₋₇cycloalkyl, -C₆₋₁₀aryl, and -C₁₋₉heteroaryl;

R¹⁸ and R¹⁹ are independently selected from H, -C₁₋₆alkyl, and -O-C₃₋₇cycloalkyl, or R¹⁸ and R¹⁹ are taken together to form =O;

R²⁰ is selected from H and -C₁₋₆alkyl;

R²¹ and R³⁵ are independently selected from H, -C₁₋₆alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R²⁵, -C₁₋₆alkylene-NR²⁷R²⁸, -C₁₋₆alkylene-C(O)R³³, -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-

20 SO₂-C₁₋₆alkyl,



R²⁵ is selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₇cycloalkyl, -O-C₃₋₇cycloalkyl, phenyl, -O-phenyl, -NR²⁷R²⁸, -CH[CH(CH₃)₂]-NH₂, -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, and -CH(NH₂)CH₂COOCH₃; R²⁷ and R²⁸ are independently selected from H, -C₁₋₆alkyl, and benzyl; or R²⁷ and R²⁸ are taken together as -(CH₂)₃₋₆-, -C(O)-(CH₂)₃-, or -(CH₂)₂O(CH₂)₂-;

R³³ is selected from -O-C₁₋₆alkyl, -O-benzyl, and -NR²⁷R²⁸; and R³⁴ is -C₁₋₆alkyl or -C₀₋₆alkylene-C₆₋₁₀aryl;

R²² and R²³ are independently selected from H, -C₁₋₆alkyl, -CH₂COOH, -(CH₂)₂OH; -(CH₂)₂OCH₃, -(CH₂)₂SO₂NH₂, -(CH₂)₂N(CH₃)₂, -C₀₋₁alkylene-C₃₋₇cycloalkyl, and -(CH₂)₂-imidazolyl; or R²² and R²³ are taken together to form a saturated or partially unsaturated -C₃₋₅heterocycle optionally substituted with halo, -OH, -COOH, or -CONH₂;

5 and optionally containing an oxygen atom in the ring;

R²⁴ is selected from -C₁₋₆alkyl; -C₀₋₁alkylene-O-C₁₋₆alkyl; phenyl optionally substituted with halo or -OCH₃; and -C₁₋₉heteroaryl; and

R³⁶ is selected from H, -CH(CH₃)₂, phenyl, and benzyl;

where each alkyl group in R¹, R³, and R⁴ is optionally substituted with 1 to 8 fluoro atoms; and;

where the methylene linker on the biphenyl is optionally substituted with one or two -C₁₋₆alkyl groups or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

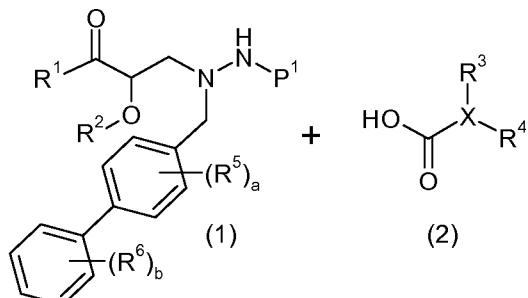
Another aspect of the invention relates to pharmaceutical compositions comprising 15 a pharmaceutically acceptable carrier and a compound of the invention. Such compositions may optionally contain other therapeutic agents. Accordingly, in yet another aspect of the invention, a pharmaceutical composition comprises a compound of the invention as the first therapeutic agent, one or more secondary therapeutic agent, and a pharmaceutically acceptable carrier. Another aspect of the invention relates to a 20 combination of active agents, comprising a compound of the invention and a second therapeutic agent. The compound of the 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 of the invention relates to a combination of pharmaceutical compositions, the combination 25 comprising: a first pharmaceutical composition comprising a compound of the 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, the invention relates to a kit containing such pharmaceutical compositions, for example where the first and second pharmaceutical compositions are 30 separate pharmaceutical compositions.

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 of the 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 of the invention relates to a method of treating hypertension, 5 heart failure, or renal disease, comprising administering to a patient a therapeutically effective amount of a compound of the invention. Still another aspect of the 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 10 useful as research tools. Accordingly, one aspect of the 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 of the invention relates to a method of evaluating a test compound in a biological assay, comprising: (a) 15 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 20 aspect of the 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 of the invention relates to processes and intermediates useful for 25 preparing compounds of the invention. Accordingly, another aspect of the 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 *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises deprotecting the compound of formula I when P^1 is an amino protecting group; and where

5 R¹-R⁶, a, b, and X are as defined for formula I. Another aspect of the 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, the invention relates to products prepared by any of the processes described herein, as well as novel intermediates

10 used in such process. In one aspect of the invention novel intermediates have formulas 1, 6, 7, 8, 9, or a salt thereof, as defined herein.

Yet another aspect of the 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

15 disease. Another aspect of the invention relates to use of a compound of the invention for inhibiting a NEP enzyme in a mammal. Still another aspect of the invention relates to the use of a compound of the invention as a research tool. Other aspects and embodiments of the invention are disclosed herein.

DETAILED DESCRIPTION OF THE INVENTION

20

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

25 "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

30 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.

The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms and include, for example, -C₁₋₄alkyl, -C₁₋₅alkyl, -C₂₋₅alkyl, -C₁₋₆alkyl, -C₁₋₈alkyl, and -C₁₋₁₀alkyl. Representative alkyl groups include, by way of example, 5 methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, *n*-hexyl, *n*-heptyl, *n*-octyl, *n*-nonyl, *n*-decyl and the like.

When a specific number of carbon atoms is intended for a particular term used herein, the number of carbon atoms is shown preceding the term as subscript. For example, the term "-C₁₋₆alkyl" means an alkyl group having from 1 to 6 carbon atoms, and 10 the term "-C₃₋₇cycloalkyl" means a cycloalkyl group having from 3 to 7 carbon atoms, respectively, where the carbon atoms are in any acceptable configuration.

The term "alkylene" means a divalent saturated hydrocarbon group that may be linear or branched. Unless otherwise defined, such alkylene groups typically contain from 0 to 10 carbon atoms and include, for example, -C₀₋₁alkylene-, -C₀₋₆alkylene-, 15 -C₁₋₃alkylene-, and -C₁₋₆alkylene-. Representative alkylene groups include, by way of example, methylene, ethane-1,2-diyl ("ethylene"), propane-1,2-diyl, propane-1,3-diyl, butane-1,4-diyl, pentane-1,5-diyl and the like. It is understood that when the alkylene term include zero carbons such as -C₀₋₁alkylene-, such terms are intended to include the absence of carbon atoms, that is, the alkylene group is not present except for a covalent bond 20 attaching the groups separated by the alkylene term.

The term "aryl" means a monovalent aromatic hydrocarbon having a single ring (i.e., phenyl) or one or more fused rings. Fused ring systems include those that are fully 25 unsaturated (e.g., naphthalene) as well as those that are partially unsaturated (e.g., 1,2,3,4-tetrahydronaphthalene). Unless otherwise defined, such aryl groups typically contain from 6 to 10 carbon ring atoms and include, for example, -C₆₋₁₀aryl. Representative aryl groups include, by way of example, phenyl and naphthalene-1-yl, naphthalene-2-yl, and the like.

The term "cycloalkyl" means a monovalent saturated carbocyclic hydrocarbon group. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms and include, for example, -C₃₋₅cycloalkyl, -C₃₋₆cycloalkyl and 30 -C₃₋₇cycloalkyl. Representative cycloalkyl groups include, by way of example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like.

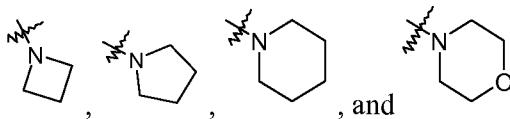
The term "halo" means fluoro, chloro, bromo and iodo.

The term "heterocycle" is intended to include monovalent unsaturated (aromatic)

heterocycles having a single ring or two fused rings as well as monovalent saturated and partially unsaturated groups having a single ring or multiple condensed rings. The heterocycle ring can contain from 3 to 15 total ring atoms, of which 1 to 14 are ring carbon atoms, and 1 to 4 are ring heteroatoms selected from nitrogen, oxygen or sulfur. Typically, 5 however, the heterocycle ring contains from 3 to 10 total ring atoms, of which 1 to 9 are ring carbon atoms, and 1 to 4 are ring heteroatoms. The point of attachment is at any available carbon or nitrogen ring atom. Exemplary heterocycles include, for example, -C₁₋₇heterocycle, -C₃₋₅heterocycle, -C₂₋₆heterocycle, -C₃₋₁₂heterocycle, -C₅₋₉heterocycle, -C₁₋₉heterocycle, -C₁₋₁₁heterocycle, and -C₁₋₁₄heterocycle.

10 Monovalent unsaturated heterocycles are also commonly referred to as "heteroaryl" groups. Unless otherwise defined, heteroaryl groups typically contain from 5 to 10 total ring atoms, of which 1 to 9 are ring carbon atoms, and 1 to 4 are ring heteroatoms, and include, for example, -C₁₋₉heteroaryl and -C₅₋₉heteroaryl. Representative heteroaryl groups include, by way of example, pyrrole (e.g., 3-pyrrolyl and 2H-pyrrol-3-yl), imidazole (e.g., 15 2-imidazolyl), furan (e.g., 2-furyl and 3-furyl), thiophene (e.g., 2-thienyl), triazole (e.g., 1,2,3-triazolyl and 1,2,4-triazolyl), pyrazole (e.g., 1H-pyrazol-3-yl), oxazole (e.g., 2-oxazolyl), isoxazole (e.g., 3-isoxazolyl), thiazole (e.g., 2-thiazolyl and 4-thiazolyl), and isothiazole (e.g., 3-isothiazolyl), pyridine (e.g., 2-pyridyl, 3-pyridyl, and 4-pyridyl), pyridylimidazole, pyridyltriazole, pyrazine, pyridazine (e.g., 3-pyridazinyl), pyrimidine 20 (e.g., 2-pyrimidinyl), tetrazole, triazine (e.g., 1,3,5-triazinyl), indolyle (e.g., 1H-indol-2-yl, 1H-indol-4-yl and 1H-indol-5-yl), benzofuran (e.g., benzofuran-5-yl), benzothiophene (e.g., benzo/b]thien-2-yl and benzo/b]thien-5-yl), benzimidazole, benzoxazole, benzothiazole, benzotriazole, quinoline (e.g., 2-quinolyl), isoquinoline, quinazoline, quinoxaline and the like.

25 Monovalent saturated heterocycles typically contain from 3 to 10 total ring atoms, of which 2 to 9 are ring carbon atoms, and 1 to 4 are ring heteroatoms, and include, for example -C₃₋₅heterocycle. Representative monovalent saturated heterocycles include, by way of example, monovalent species of pyrrolidine, imidazolidine, pyrazolidine, piperidine, 1,4-dioxane, morpholine, thiomorpholine, piperazine, 3-pyrroline and the like. 30 In some instances, moieties may be described as being taken together to form a saturated -C₃₋₅heterocycle optionally containing an oxygen atom in the ring. Such groups include:



Monovalent partially unsaturated heterocycles typically contain from 3 to 10 total ring atoms, of which 2 to 11 are ring carbon atoms, and 1 to 3 are ring heteroatoms, and include, for example -C₃₋₅heterocycle and -C₂₋₁₂heterocycle. Representative monovalent 5 partially unsaturated heterocycles include, by way of example, pyran, benzopyran, benzodioxole (e.g., benzo[1,3]dioxol-5-yl), tetrahydropyridazine, 2,5-dihydro-1H-pyrrole, dihydroimidazole, dihydrotriazole, dihydrooxazole, dihydroisoxazole, dihydrothiazole, dihydroisothiazole, dihydrooxadiazole, dihydrothiadiazole, tetrahydropyridazine, hexahydropyrroloquinoxaline, and dihydrooxadiazabenzo[e]azulene. In some instances, 10 moieties may be described as being taken together to form a partially unsaturated -C₃₋₅heterocycle. Such groups include:



The term "optionally substituted" means that group in question may be unsubstituted or it may be substituted one or several times, such as 1 to 3 times, or 1 to 5 15 times, or 1 to 8 times. For example, a phenyl group that is "optionally substituted" with halo atoms, may be unsubstituted, or it may contain 1, 2, 3, 4, or 5 halo atoms; and an alkyl group that is "optionally substituted" with fluoro atoms may be unsubstituted, or it may contain 1, 2, 3, 4, 5, 6, 7, or 8 fluoro atoms;. Similarly, a group that is "optionally substituted" with one or two -C₁₋₆alkyl groups, may be unsubstituted, or it may contain one 20 or two -C₁₋₆alkyl groups.

As used herein, the phrase "having the formula" or "having the structure" is not intended to be limiting and is used in the same way that the term "comprising" is commonly used. For example, if one structure is depicted, it is understood that all stereoisomer and tautomer forms are encompassed, unless stated otherwise.

25 The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise unacceptable when used in the invention. For example, the term "pharmaceutically acceptable carrier" refers to a material that can be incorporated into a composition and administered to a patient without causing unacceptable biological effects or interacting in an unacceptable manner with other components of the composition. Such 30 pharmaceutically acceptable materials typically have met the required standards of

toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug administration.

The term "pharmaceutically acceptable salt" means a salt prepared from a base or an acid which is acceptable for administration to a patient, such as a mammal (for example, 5 salts having acceptable mammalian safety for a given dosage regime). However, it is understood that the salts covered by the invention are not required to be pharmaceutically acceptable salts, such as salts of intermediate compounds that are not intended for administration to a patient. Pharmaceutically acceptable salts can be derived from pharmaceutically acceptable inorganic or organic bases and from pharmaceutically acceptable inorganic or organic acids. In addition, when a compound of formula I contains both a basic moiety, such as an amine, pyridine or imidazole, and an acidic moiety such as a carboxylic acid or tetrazole, zwitterions may be formed and are included within the term "salt" as used herein. Salts derived from pharmaceutically acceptable inorganic bases include ammonium, calcium, copper, ferric, ferrous, lithium, magnesium, manganic, 10 manganous, potassium, sodium, and zinc salts, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary amines, including substituted amines, cyclic amines, naturally-occurring amines and the like, such as arginine, betaine, caffeine, choline, *N,N'*-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, 15 ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine, piperadine, polyamine resins, procaine, purines, theobromine, triethylamine, trimethylamine, tripropylamine, tromethamine and the like. Salts derived from pharmaceutically acceptable inorganic acids include salts of boric, carbonic, hydrohalic 20 (hydrobromic, hydrochloric, hydrofluoric or hydroiodic), nitric, phosphoric, sulfamic and sulfuric acids. Salts derived from pharmaceutically acceptable organic acids include salts of aliphatic hydroxyl acids (for example, citric, gluconic, glycolic, lactic, lactobionic, malic, and tartaric acids), aliphatic monocarboxylic acids (for example, acetic, butyric, formic, propionic and trifluoroacetic acids), amino acids (for example, aspartic and 25 glutamic acids), aromatic carboxylic acids (for example, benzoic, p-chlorobenzoic, diphenylacetic, gentisic, hippuric, and triphenylacetic acids), aromatic hydroxyl acids (for example, o-hydroxybenzoic, p-hydroxybenzoic, 1-hydroxynaphthalene-2-carboxylic and 3-hydroxynaphthalene-2-carboxylic acids), ascorbic, dicarboxylic acids (for example, 30

fumaric, maleic, oxalic and succinic acids), glucoronic, mandelic, mucic, nicotinic, orotic, pamoic, pantothenic, sulfonic acids (for example, benzenesulfonic, camphosulfonic, edisyllic, ethanesulfonic, isethionic, methanesulfonic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic and p-toluenesulfonic acids), xinafoic acid, and
5 the like.

As used herein, the term "prodrug" is intended to mean an inactive (or significantly less active) precursor of a drug that is converted into its active form in the body under physiological conditions, for example, by normal metabolic processes. Such compounds may not possess pharmacological activity at NEP, but may be administered orally or
10 parenterally and thereafter metabolized in the body to form compounds that are pharmacologically active at NEP. Exemplary prodrugs include esters such as C₁-6alkylesters and aryl-C₁-6alkylesters. In one embodiment, the active compound has a free carboxyl and the prodrug is an ester derivative thereof, i.e., the prodrug is an ester such as -C(O)OCH₂CH₃. Such ester prodrugs are then converted by solvolysis or under
15 physiological conditions to be the free carboxyl compound. The term is also intended to include certain protected derivatives of compounds of formula I that may be made prior to a final deprotection stage. Thus, all protected derivatives and prodrugs of compounds formula I are included within the scope of the invention.

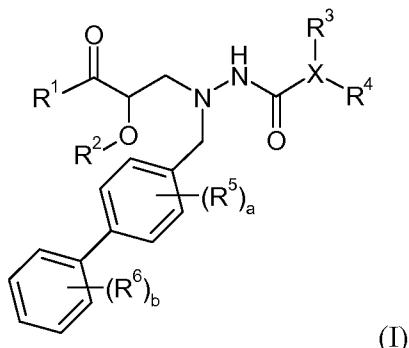
The term "therapeutically effective amount" means an amount sufficient to effect
20 treatment when administered to a patient in need thereof, that is, the amount of drug needed to obtain the desired therapeutic effect. For example, a therapeutically effective amount for treating hypertension is an amount of compound needed to, for example, reduce, suppress, eliminate, or prevent the symptoms of hypertension, or to treat the underlying cause of hypertension. In one embodiment, a therapeutically effective amount
25 is that amount of drug needed to reduce blood pressure or the amount of drug needed to maintain normal blood pressure. On the other hand, the term "effective amount" means an amount sufficient to obtain a desired result, which may not necessarily be a therapeutic result. For example, when studying a system comprising a NEP enzyme, an "effective amount" may be the amount needed to inhibit the enzyme.

30 The term "treating" or "treatment" as used herein means the treating or treatment of a disease or medical condition (such as hypertension) in a patient, such as a mammal (particularly a human) that includes one or more of the following: (a) preventing the disease or medical condition from occurring, i.e., preventing the reoccurrence of the

disease or medical condition or prophylactic treatment of a patient that is pre-disposed to the disease or medical condition; (b) ameliorating the disease or medical condition, i.e., eliminating or causing regression of the disease or medical condition in a patient; (c) suppressing the disease or medical condition, i.e., slowing or arresting the development of the disease or medical condition in a patient; or (d) alleviating the symptoms of the disease or medical condition in a patient. For example, the term "treating hypertension" would include preventing hypertension from occurring, ameliorating hypertension, suppressing hypertension, and alleviating the symptoms of hypertension (for example, lowering blood pressure). The term "patient" is intended to include those mammals, such as humans, that are in need of treatment or disease prevention or that are presently being treated for disease prevention or treatment of a specific disease or medical condition, as well as test subjects in which compounds of the invention are being evaluated or being used in an assay, for example an animal model.

All other terms used herein are intended to have their ordinary meaning as understood by those of ordinary skill in the art to which they pertain.

In one aspect, the invention relates to compounds of formula I:



or a pharmaceutically acceptable salt thereof.

As used herein, the term "compound of the invention" includes all compounds encompassed by formula I such as the species embodied in formulas Ia and Ib, as well as the compounds encompassed by formulas II and III, and species thereof. 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 acid, or in various salt forms. All such salt forms are included within the scope of the invention. Furthermore, the compounds of the invention may also exist as prodrugs. Accordingly, those skilled in the art will recognize that reference to a compound herein, for example, reference to a "compound of the invention" or a "compound of formula I"

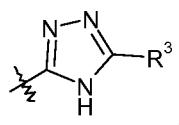
includes a compound of formula I as well as pharmaceutically acceptable salts and prodrugs of that compound unless otherwise indicated. Further, the term "or a pharmaceutically acceptable salt and/or prodrug thereof" is intended to include all permutations of salts and prodrugs, such as a pharmaceutically acceptable salt of a prodrug.

5 Furthermore, solvates of compounds of formula I are included within the scope of this invention.

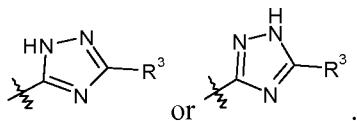
The compounds of formula I may contain one or more chiral centers and therefore, these compounds may be prepared and used in various stereoisomeric forms. Accordingly, the invention also relates to racemic mixtures, pure stereoisomers (e.g., enantiomers and 10 diastereoisomers), stereoisomer-enriched mixtures, and the like unless otherwise indicated. When a chemical structure is depicted herein without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Thus, for example, the terms "compound of formula I," "compounds of formula II," and so forth, are intended to include all possible stereoisomers of the compound. Similarly, when a particular

15 stereoisomer is shown or named herein, it will be understood by those skilled in the art that minor amounts of other stereoisomers may be present in the compositions of the invention unless otherwise indicated, provided that the utility of the composition as a whole is not eliminated by the presence of such other isomers. Individual stereoisomers may be obtained by numerous methods that are well known in the art, including chiral 20 chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereoisomers, separating the diastereoisomers by conventional means such as chromatography or recrystallization, then regenerating the original stereoisomer.

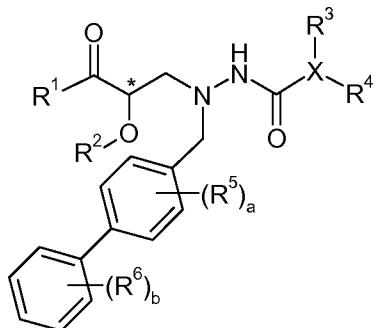
25 Additionally, where applicable, all *cis-trans* or *E/Z* isomers (geometric isomers), tautomeric forms and topoisomeric forms of the compounds of the invention are included within the scope of the invention unless otherwise specified. For example, if X is depicted as (R⁴ being hydrogen):



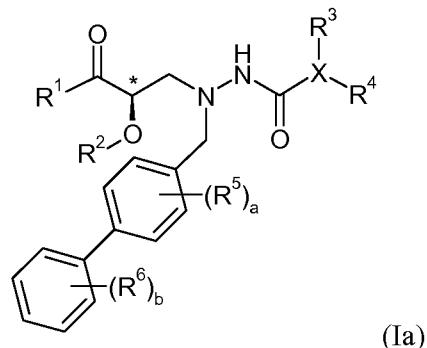
it is understood that the compound may also exist in a tautomeric form such as:



More specifically, compounds of formula I can contain at least one chiral center indicated by the symbol * in the following formula:

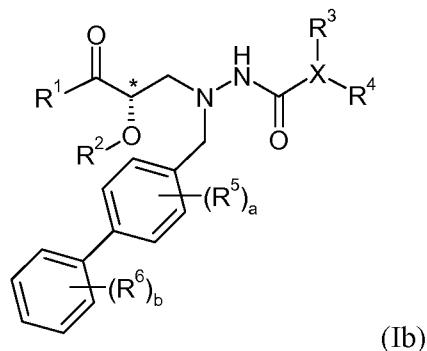


In one embodiment of the invention, the carbon atom identified by the symbol * has 5 the (R) configuration. This embodiment of the invention is shown in formula Ia:



In this embodiment, compounds have the (R) configuration at the * carbon atom or are enriched in a stereoisomeric form having the (R) configuration at this carbon atom.

In another embodiment, the carbon atom identified by the symbol * has the (S) 10 configuration. This embodiment of the invention is shown in formula Ib:



In this embodiment, compounds have the (S) configuration at the * carbon atom or are enriched in a stereoisomeric form having the (S) configuration at this carbon atom.

In some embodiments, in order to optimize the therapeutic activity of the 15 compounds of the invention, e.g., to treat hypertension, it may be desirable that the carbon

atom identified by the * symbol has a particular (R) or (S) configuration or is enriched in a stereoisomeric form having such configuration. For example, in one embodiment, the compounds of the invention have the (R) configuration of formula Ia are enriched in a stereoisomeric form having the (R) configuration, and in another embodiment, the 5 compounds of the invention have the (S) configuration of formula Ib, or are enriched in a stereoisomeric form having the (S) configuration. In other embodiments, the compounds of the invention are present as a racemic mixture, for example as a mixture of enantiomers of formula Ia and Ib.

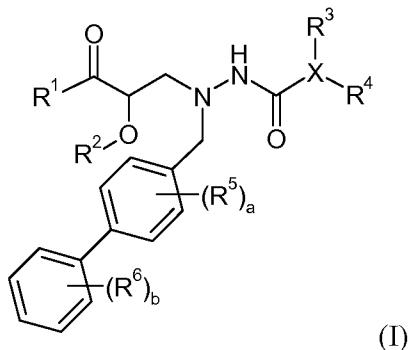
The compounds of the invention, as well as those compounds used in their 10 synthesis, may also include isotopically-labeled compounds, that is, where one or more atoms have been enriched with atoms having an atomic mass different from the atomic mass predominately found in nature. Examples of isotopes that may be incorporated into the compounds of formula I, for example, include, but are not limited to, ²H, ³H, ¹³C, ¹⁴C, ¹⁵N, ¹⁸O, ¹⁷O, ³⁵S, ³⁶Cl, and ¹⁸F. Of particular interest are compounds of formula I enriched 15 in tritium or carbon-14 which can be used, for example, in tissue distribution studies; compounds of formula I enriched in deuterium especially at a site of metabolism resulting, for example, in compounds having greater metabolic stability; and compounds of formula I enriched in a positron emitting isotope, such as ¹¹C, ¹⁸F, ¹⁵O and ¹³N, which can be used, for example, in Positron Emission Topography (PET) studies.

20 The nomenclature used herein to name the compounds of the invention is illustrated in the Examples herein. This nomenclature has been derived using the commercially available AutoNom software (MDL, San Leandro, California).

REPRESENTATIVE EMBODIMENTS

The following substituents and values are intended to provide representative 25 examples of various aspects and embodiments of the invention. These representative values are intended to further define and illustrate such aspects and embodiments and are not intended to exclude other embodiments or to limit the scope of the invention. In this regard, the representation that a particular value or substituent is preferred is not intended in any way to exclude other values or substituents from the invention unless specifically 30 indicated.

In one aspect, this invention relates to compounds of formula I:



R^1 is selected from $-OR^7$ and $-NR^8R^9$. The R^7 moiety is selected from:

H ;

$-C_{1-8}$ alkyl, e.g., $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-CH_2CH(CH_3)_2$,

5 $-(CH_2)_3CH_3$, $-(CH_2)_4CH_3$, $-(CH_2)_2CH(CH_3)_2$, $-(CH_2)_5CH_3$, and $-(CH_2)_6CH_3$;

$-C_{1-3}$ alkylene- C_{6-10} aryl, e.g., benzyl;

$-C_{1-3}$ alkylene- C_{1-9} heteroaryl, e.g., $-CH_2$ -pyridinyl and $-(CH_2)_2$ -pyridinyl;

$-C_{3-7}$ cycloalkyl, e.g., cyclopentyl;

$-[(CH_2)_2O]_{1-3}CH_3$, e.g., $-(CH_2)_2OCH_3$ and $-[(CH_2)_2O]_2CH_3$;

10 $-C_{1-6}$ alkylene- $OC(O)R^{10}$, e.g., $-CH_2OC(O)CH_3$, $-CH_2OC(O)CH_2CH_3$,

$-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2CH(CH_3)OC(O)CH_2CH_3$, $-CH_2OC(O)OCH_3$,

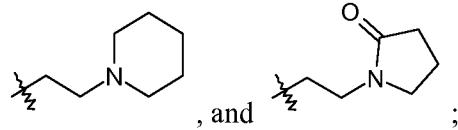
$-CH_2OC(O)OCH_2CH_3$, $-CH(CH_3)OC(O)OCH_2CH_3$, $-CH(CH_3)OC(O)O-CH(CH_3)_2$,

$-CH_2CH(CH_3)OC(O)$ -cyclopentyl, $-CH_2OC(O)O$ -cyclopropyl, $-CH(CH_3)OC(O)O$ - O -cyclohexyl, $-CH_2OC(O)O$ -cyclopentyl, $-CH_2CH(CH_3)OC(O)$ -phenyl, $-CH_2OC(O)O$ -

15 phenyl, $-CH_2OC(O)-CH[CH(CH_3)_2]-NH_2$, $-CH_2OC(O)-CH[CH(CH_3)_2]-NHC(O)OCH_3$,

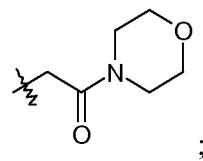
and $-CH(CH_3)OC(O)-CH(NH_2)CH_2COOCH_3$;

$-C_{1-6}$ alkylene- $NR^{12}R^{13}$, e.g., $-(CH_2)_2-N(CH_3)_2$,

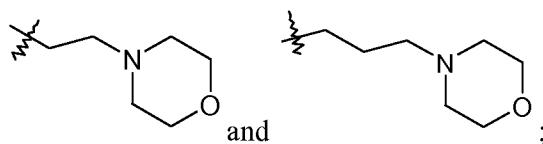


$-C_{1-6}$ alkylene- $C(O)R^{31}$, e.g., $-CH_2C(O)OCH_3$, $-CH_2C(O)O$ -benzyl, $-CH_2C(O)-$

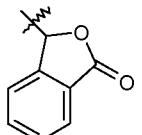
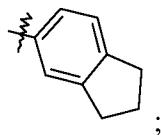
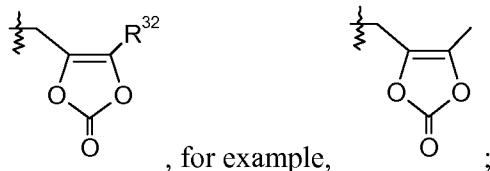
20 $N(CH_3)_2$, and



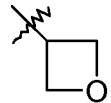
$-C_{0-6}$ alkylenemorpholinyl, e.g., $-(CH_2)_2$ -morpholinyl and $-(CH_2)_3$ -morpholinyl:



-C₁₋₆alkylene-SO₂-C₁₋₆alkyl, e.g., -(CH₂)₂SO₂CH₃;



5 ; and



The R¹⁰ moiety is selected from:

-C₁₋₆alkyl, e.g., -CH₃ and -CH₂CH₃;

-O-C₁₋₆alkyl, e.g., -OCH₃, -O-CH₂CH₃, and -O-CH(CH₃)₂;

10 -C₃₋₇cycloalkyl, e.g., cyclopentyl;

-O-C₃₋₇cycloalkyl, e.g., -O-cyclopropyl, -O-cyclohexyl, and -O-cyclopentyl; phenyl;

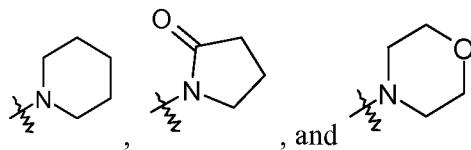
-O-phenyl;

-NR¹²R¹³;

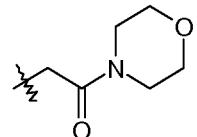
15 -CH[CH(CH₃)₂]-NH₂;

-CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, e.g., -CH[CH(CH₃)₂]-NHC(O)OCH₃; and -CH(NH₂)CH₂COOCH₃.

The R¹² and R¹³ moieties are independently selected from H, -C₁₋₆alkyl (e.g., CH₃), and benzyl. Alternately, the R¹² and R¹³ moieties can be taken together as -(CH₂)₃₋₆-, -C(O)-(CH₂)₃-, or -(CH₂)₂O(CH₂)₂-, for example to form a group such as:



The R³¹ moiety is selected from -O-C₁₋₆alkyl, e.g., -OCH₃, -O-benzyl, and -NR¹²R¹³, e.g., -N(CH₃)₂, and



5 The R³² moiety is -C₁₋₆alkyl (e.g., -CH₃ and -C(CH₃)₃) or -C₀₋₆alkylene-C₆₋₁₀aryl.

The R⁸ moiety is selected from:

H;

-OH;

-OC(O)R¹⁴, e.g., -OC(O)CH₃, -OC(O)-phenyl, -OC(O)-OCH₂-phenyl, -OC(O)-

10 CH₂O-phenyl, -OC(O)(NH₂), and -OC(O)[N(CH₃)₂];

-CH₂COOH;

-O-benzyl;

pyridyl; and

-OC(S)NR¹⁵R¹⁶, e.g., -OC(S)NH₂ and -OC(S)N(CH₃)₂.

15 The R¹⁴ moiety is selected from:

H;

-C₁₋₆alkyl, e.g., -CH₃;

-C₆₋₁₀aryl, e.g., phenyl;

-OCH₂-C₆₋₁₀aryl, e.g., -OCH₂-phenyl;

20 -CH₂O-C₆₋₁₀aryl, e.g., -CH₂O-phenyl; and

-NR¹⁵R¹⁶, e.g., -NH₂ and N(CH₃)₂.

The R¹⁵ and R¹⁶ moieties are independently selected from H and -C₁₋₄alkyl.

The R⁹ is moiety selected from H, -C₁₋₆alkyl (e.g., -CH₃), and -C(O)R¹⁷ (e.g.,

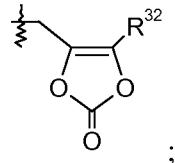
-C(O)H). The R¹⁷ moiety is selected from H, -C₁₋₆alkyl (e.g., -CH₂CH₃), -C₃₋₇cycloalkyl

25 (e.g., cyclopropyl), -C₆₋₁₀aryl (e.g., phenyl), and -C₁₋₉heteroaryl (e.g., pyridine).

In addition, each alkyl group in R¹ is optionally substituted with 1 to 8 fluoro atoms. For example, when R¹ is -OR⁷ and R⁷ is -C₁₋₈alkyl, R¹ can also be a group such as -OCH(CH₃)CF₃, -OCH₂CF₂CF₃, -OCH(CF₃)₂, -O(CH₂)₂CF₃, -OCH(CH₂F)₂,

-OC(CF₃)₂CH₃, and -OCH(CH₃)CF₂CF₃.

In one embodiment, R¹ is -OR⁷, and R⁷ is selected from H, -C₁₋₈alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₀₋₆alkylenemorpholinyl, and

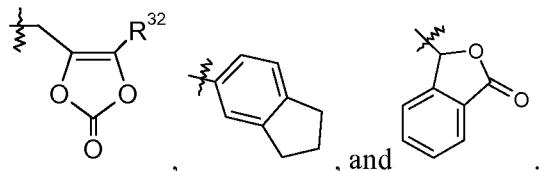


;

5 where R³² is -C₁₋₆alkyl; and where each alkyl group is optionally substituted with 1 to 8 fluoro atoms. In other embodiments these compounds have formula III.

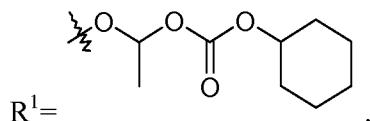
In one embodiment, R¹ is selected from -OR⁷ and -NR⁸R⁹, where R⁷ is H, R⁸ is H or -OH, and R⁹ is H. In other embodiments these compounds have formula III.

In another embodiment, R¹ is -OR⁷, where R⁷ is selected from -C₁₋₈alkyl, 10 -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R¹⁰, -C₁₋₆alkylene-NR¹²R¹³, -C₁₋₆alkylene-C(O)R³¹, -C₀₋₆alkylenemorpholinyl; -C₁₋₆alkylene-SO₂-C₁₋₆alkyl;



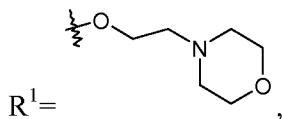
In yet another embodiment, R¹ is -NR⁸R⁹; where R⁸ is selected from -OC(O)R¹⁴,

15 -CH₂COOH, -O-benzyl, pyridyl, and -OC(S)NR¹⁵R¹⁶; and R⁹ is H. In yet another embodiment, R¹ is -NR⁸R⁹, where R⁸ is H or -OH; and R⁹ is -C₁₋₆alkyl or -C(O)R¹⁷. In yet another embodiment, R¹ is -NR⁸R⁹, where R⁸ is selected from -OC(O)R¹⁴, -CH₂COOH, -O-benzyl, pyridyl, and -OC(S)NR¹⁵R¹⁶; and R⁹ is -C₁₋₆alkyl or -C(O)R¹⁷. In another embodiment these compounds have formula III. In one aspect of the invention, these 20 compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. For example, in one embodiment, R¹ is -OR⁷ and R⁷ is -C₁₋₆alkylene-OC(O)R¹⁰, such as -O-CH(CH₃)OC(O)-O-cyclohexyl:

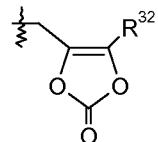


making the compound a cilexetil ester; or R¹ is -OR⁷ and R⁷ is -C₀₋₆alkylenemorpholinyl

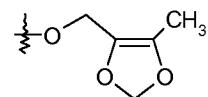
25 such as -O-(CH₂)₂-morpholinyl:



making the compound a 2-morpholinoethyl or mofetil ester; or R^1 is $-OR^7$ and R^7 is



such as $-O-CH_2-5\text{-methyl-[1,3]dioxol-2-one}$:

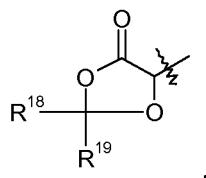


5 $R^1 = \text{[Chemical Structure: A five-membered ring with two oxygen atoms. One oxygen is part of a carbonyl group (C=O). The other oxygen is part of a wavy line representing a polymer chain. The ring is substituted with a wavy line, an R³² group, and a CH₃ group.]} ,$

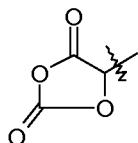
making the compound a medoxomil ester.

10 R^2 is H or $-P(O)(OH)_2$. R^2 can also be taken together with R^7 to form $-CR^{18}R^{19}-$ or taken together with R^8 to form $-C(O)-$. R^{18} and R^{19} are independently selected from H, $-C_{1-6}\text{alkyl}$, and $-O-C_{3-7}\text{cycloalkyl}$, or R^{18} and R^{19} may be taken together to form $=O$. In one embodiment, R^2 is H. In another embodiment this compound has formula III.

When R^2 is taken together with R^7 to form $-CR^{18}R^{19}-$, this embodiment can be depicted as:

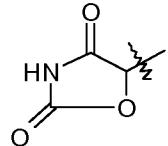


and when R^{18} and R^{19} are taken together to form $=O$, this embodiment can be depicted as:



15

When R^2 is taken together with R^8 to form $-C(O)-$, this embodiment can be depicted as:

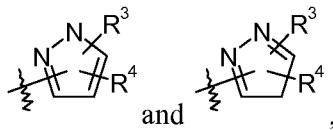


In one aspect of the invention, these compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. In another embodiment

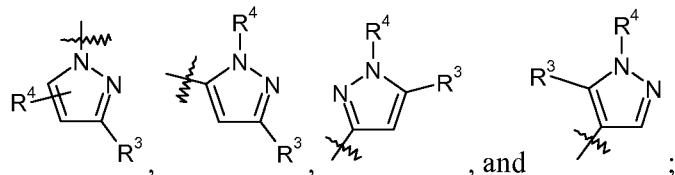
these compounds have formula III. Compounds where R² is -P(O)(OH)₂ may also find utility as prodrugs.

The "X" moiety is a -C₁₋₉heteroaryl, and the point of attachment is at any available carbon or nitrogen ring atom. Note that in some embodiments, R³ and/or R⁴ may be absent. When present, R³ is on any available carbon atom. When present, R⁴ is on any available carbon atom or nitrogen atom. Exemplary -C₁₋₉heteroaryl rings include, by way of illustration and not limitation:

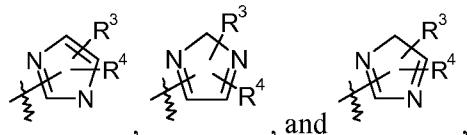
pyrazole rings such as:



10 specific examples of which include:

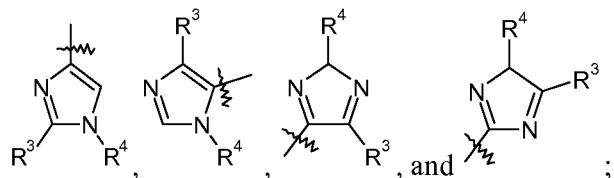


imidazole rings such as:

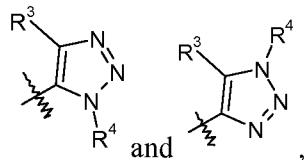


specific examples of which include:

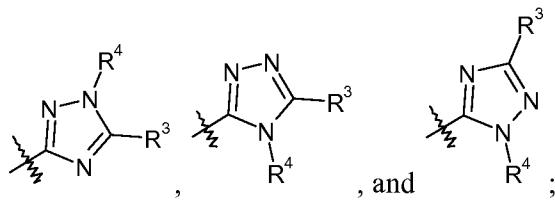
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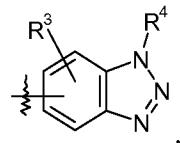
triazole rings, including 1,2,3-triazole such as:



as well as 1,2,4-triazole such as:

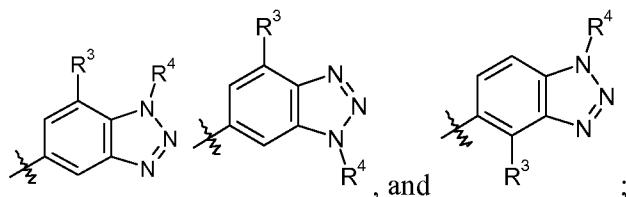


benzotriazole rings such as:

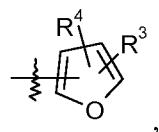


specific examples of which include:

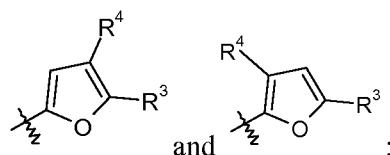
5



furan rings:

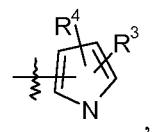


specific examples of which include:

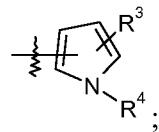


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pyrrole rings:

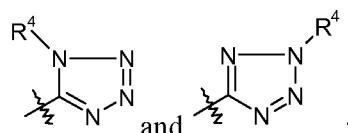


specific examples of which include:

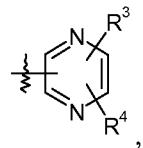


tetrazole rings such as:

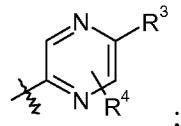
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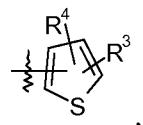
pyrazine rings:



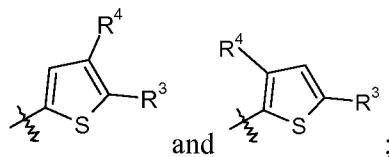
a specific example of which includes:



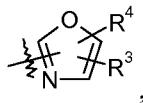
5 thiophene rings:



specific examples of which include:

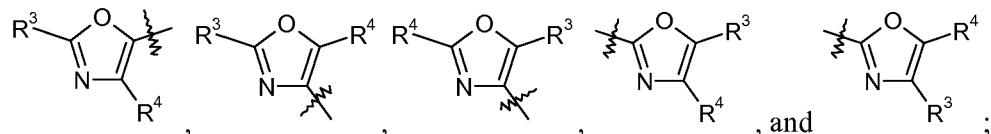


oxazole rings:

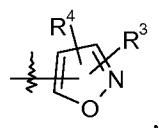


10

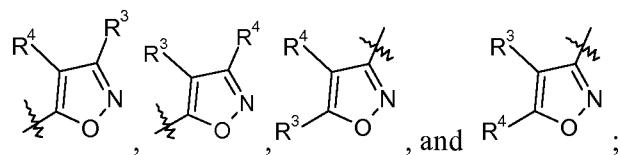
specific examples of which include:



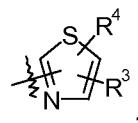
isoxazole rings:



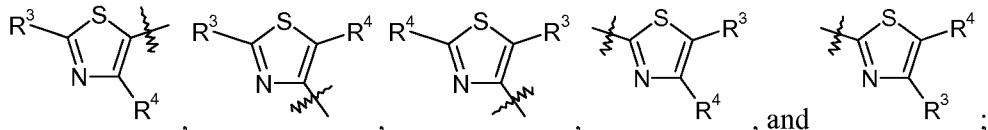
15 specific examples of which include:



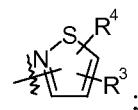
thiazole rings:



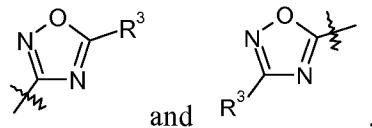
specific examples of which include:



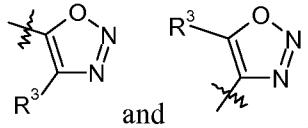
isothiazole rings:



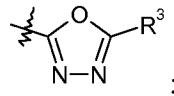
oxadiazole rings, including [1,2,4]oxadiazole such as:



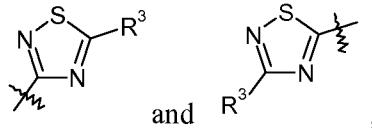
as well as [1,2,3]oxadiazole such as:



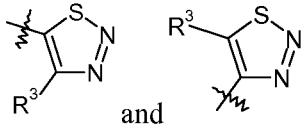
10 and [1,3,4]oxadiazole:



thiadiazole rings, including [1,2,4]thiadiazole such as:

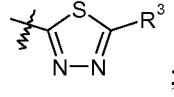


as well as [1,2,3]thiadiazole such as:

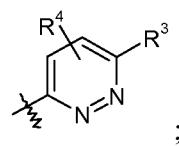


15

and [1,3,4]thiadiazole:

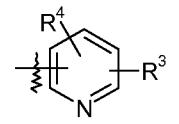


pyridazine rings:



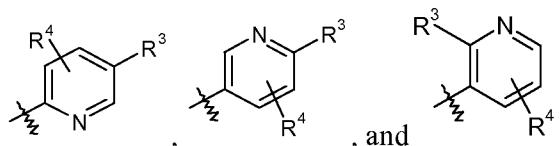
;

pyridine rings:



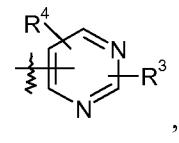
,

specific examples of which include:



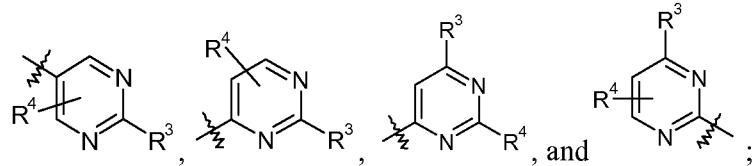
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pyrimidine rings:



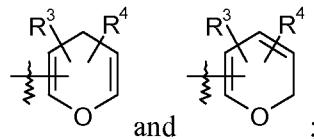
,

specific examples of which include:



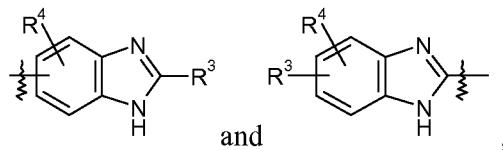
10

pyran rings such as



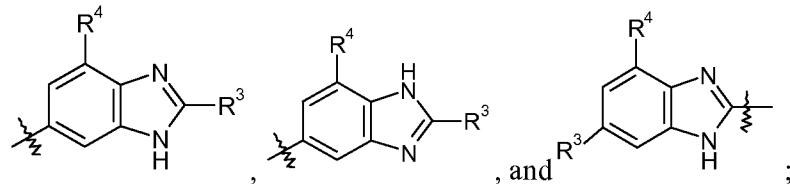
and

benzimidazole rings such as:



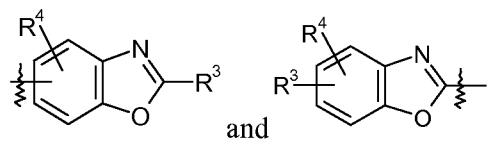
and

specific examples of which include:

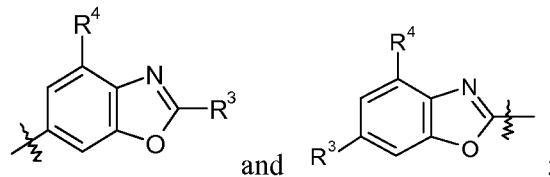


15

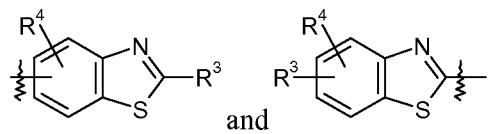
benzoxazole rings such as:



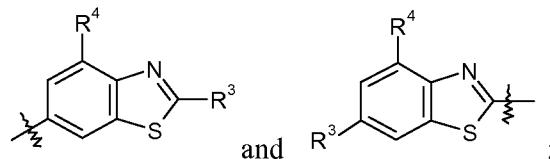
specific examples of which include:



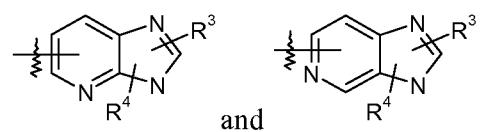
5 benzothiazole rings such as:



specific examples of which include:



pyridylimidazole rings such as :

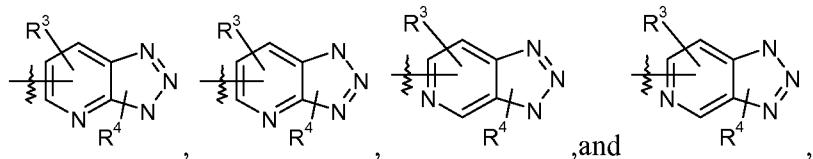


10

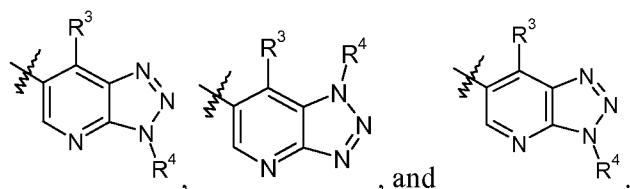
a specific example of which includes:



pyridyltriazole rings such as:



15 specific examples of which include:



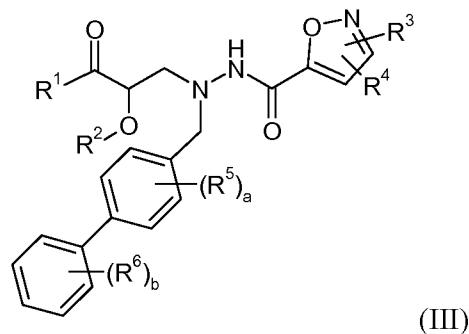
In one particular embodiment, X is selected from pyrazole, imidazole, triazole, benzotriazole, furan, pyrrole, tetrazole, pyrazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, thiadiazole, pyridazine, pyridine, pyrimidine, pyran, 5 benzimidazole, benzoxazole, benzothiazole, pyridylimidazole, and pyridyltriazole.

It is understood that some -C₁₋₉heteroaryl rings can exist in a tautomeric form, and that such tautomeric forms are part of the invention and are encompassed by the term "heteroaryl." Therefore, if a compound is depicted with a -C₁₋₉heteroaryl ring, it is understood that the compound can also exist in a tautomeric form and vice versa, and that 10 both forms are covered by the invention.

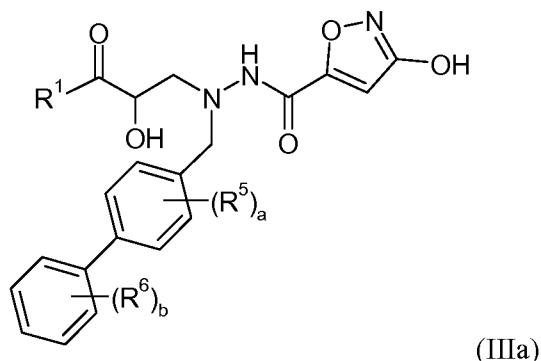
-C ₁₋₉ heteroaryl ring	exemplary ring	exemplary tautomer(s)
pyrazole		
imidazole		
triazole		
oxazole		
thiazole		
isothiazole		

$-C_{1-9}$ heteroaryl ring	exemplary ring	exemplary tautomer(s)
oxadiazole		
thiadiazole		
pyridazine		

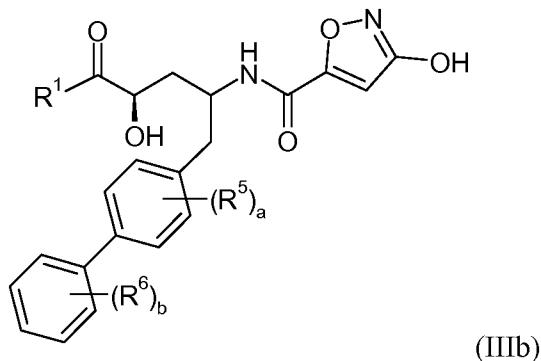
In one particular embodiment, X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, pyrimidine, and pyridyltriazole. In still another embodiment X is an isoxazole, and in one specific embodiment, have formula III:



where R¹-R⁶, a, and b are as defined for formula I. In yet another embodiment, the compounds of the invention have formula IIIa:



where R¹, R⁵, R⁶, a, and b, are as defined for formula I. In still another embodiment, the compounds of the invention have formula IIIb:



where R^1 , R^5 , R^6 , a, and b, are as defined for formula I.

The R^3 moiety can be absent. When present, R^3 is attached to a carbon atom in the "X" group, and is selected from:

5 H;
 halo, e.g., chloro and fluoro;
 $-C_{0-5}$ alkylene-OH, e.g., -OH, $-CH_2OH$, $-CH(OH)CH_3$, and $-C(CH_3)_2-OH$;
 $-NH_2$;
 $-C_{1-6}$ alkyl, e.g., $-CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, and $-(CH_2)_3-CH_3$;

10 $-CF_3$;
 $-C_{3-7}$ cycloalkyl, e.g., cyclopropyl and cyclohexyl;
 $-C_{0-2}$ alkylene-O- C_{1-6} alkyl, e.g., $-OCH_3$, $-OCH_2CH_3$, $-CH_2-OCH_3$, and $-(CH_2)_2-OCH_3$;
 $-C(O)R^{20}$, e.g., $-C(O)H$ and $-C(O)CH_3$;

15 $-C_{0-1}$ alkylene-COOR²¹, e.g., $-COOH$, $-CH_2-COOH$, $-C(O)O-CH_2CH_3$, $-C(O)O-(CH_2)_2OCH_3$, $-C(O)O-CH_2OC(O)CH_3$, $-CH_2-C(O)O-CH_2OC(O)CH_3$, $-C(O)O-CH_2OC(O)O-CH_3$, $-CH_2-C(O)O-CH_2OC(O)O-CH_3$, $-C(O)O-CH(CH_3)OC(O)O-CH_2CH_3$, $-C(O)O-CH(CH_3)OC(O)O-CH(CH_3)_2$, $-C(O)O-CH_2CH(CH_3)OC(O)-cyclopentyl$, $-C(O)O-CH_2OC(O)-cyclopropyl$, $-C(O)O-CH(CH_3)-OC(O)-O-cyclohexyl$, $-C(O)O-CH_2OC(O)O-cyclopentyl$, $-C(O)O-CH_2CH(CH_3)OC(O)-phenyl$, $-C(O)O-CH_2OC(O)O-phenyl$, $-C(O)O-CH_2-pyridine$, $-C(O)O-CH_2-pyrrolidine$, $-C(O)O-(CH_2)_2-morpholinyl$, $-C(O)O-(CH_2)_3-morpholinyl$, and $-C(O)O-(CH_2)_2-SO_2-CH_3$;
 $-C(O)NR^{22}R^{23}$, e.g., $-C(O)NH_2$, $-C(O)NHCH_3$, $-C(O)N(CH_3)_2$, $-C(O)NH-(CH_2)_2CH_3$, $-C(O)NH-CH_2COOH$, $-C(O)NH-(CH_2)_2-OH$, $-C(O)NH-(CH_2)_2-N(CH_3)_2$,

20 $-C(O)NH$ -cyclopropyl, $-C(O)NH-(CH_2)_2$ -imidazolyl, $-C(O)N(CH_3)-CH_2CH(CH_3)_2$, and $-C(O)N(CH_3)[(CH_2)_2OCH_3]$;
 $-NHC(O)R^{24}$, e.g., $-NHC(O)-CH_2CH_3$, $-NHC(O)-(CH_2)_3CH_3$, $-NHC(O)O-CH_2CH_3$,

-NHC(O)-CH₂-OCH₃, -NHC(O)-2-methoxyphenyl, -NHC(O)-2-chlorophenyl, and
-NHC(O)-2-pyridine;

=O;

-NO₂;

5 -C(CH₃)=N(OH);

phenyl optionally substituted with one or two groups independently selected from
halo, -OH, -CF₃, -OCH₃, -NHC(O)CH₃, and phenyl (e.g., phenyl, 2-chlorophenyl, 2-
fluorophenyl, 2-hydroxyphenyl, 2-trifluoromethylphenyl, 2-methoxyphenyl, 3-
chlorophenyl, 3-fluorophenyl, 3-methoxyphenyl, 3-NHC(O)CH₃-phenyl, 4-chlorophenyl,
10 4-fluorophenyl, 4-methoxyphenyl, 4-biphenyl, 2,5-dichlorophenyl, 2,5-dimethoxyphenyl,
2,4-dichlorophenyl, 2-methoxy, 5-fluorophenyl, and 3,4-dichlorophenyl);

naphthalenyl;

pyridinyl;

pyrazinyl;

15 pyrazolyl optionally substituted with methyl;

thiophenyl optionally substituted with methyl or halo (e.g., chloro);

furanyl; and

-CH₂-morpholinyl.

The R²⁰ moiety is selected from H and -C₁₋₆alkyl (e.g., -CH₃). The R²¹ moiety is selected
20 from:

H;

-C₁₋₆alkyl, e.g., -CH₃ and -CH₂CH₃;

-C₁₋₃alkylene-C₆₋₁₀aryl;

-C₁₋₃alkylene-C₁₋₉heteroaryl, e.g., -CH₂-pyridine;

25 -C₃₋₇cycloalkyl;

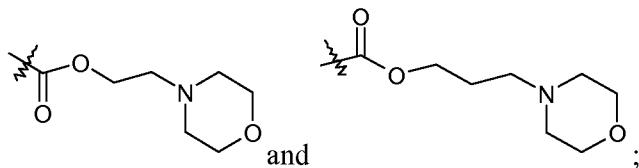
-[(CH₂)₂O]₁₋₃CH₃, e.g., -(CH₂)₂OCH₃;

-C₁₋₆alkylene-OC(O)R²⁵, e.g., -CH₂OC(O)CH₃, -CH₂OC(O)O-CH₃, -CH₂OC(O)O-
CH₃, -CH(CH₃)OC(O)O-CH₂CH₃, -CH(CH₃)OC(O)O-CH(CH₃)₂, -CH₂CH(CH₃)OC(O)-
cyclopentyl, -CH₂OC(O)O-cyclopropyl, -CH(CH₃)-OC(O)-O-cyclohexyl, -CH₂OC(O)O-
30 cyclopentyl, -CH₂CH(CH₃)OC(O)-phenyl, and -CH₂OC(O)O-phenyl;

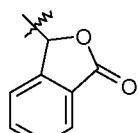
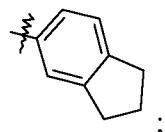
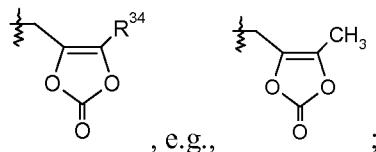
-C₁₋₆alkylene-NR²⁷R²⁸, e.g., -CH₂-pyrrolidine;

-C₁₋₆alkylene-C(O)R³³;

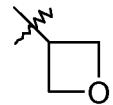
-C₀₋₆alkylenemorpholinyl, e.g., -(CH₂)₂-morpholinyl and -(CH₂)₃-morpholinyl:



-C₁₋₆alkylene-SO₂-C₁₋₆alkyl, e.g., -(CH₂)₂-SO₂-CH₃;



5 and



The R²² and R²³ moieties are independently selected from:

H;

-C₁₋₆alkyl, e.g., -CH₃ and -(CH₂)₂CH₃;

10 -CH₂COOH;

-(CH₂)₂OH;

-(CH₂)₂OCH₃;

-(CH₂)₂SO₂NH₂;

-(CH₂)₂N(CH₃)₂;

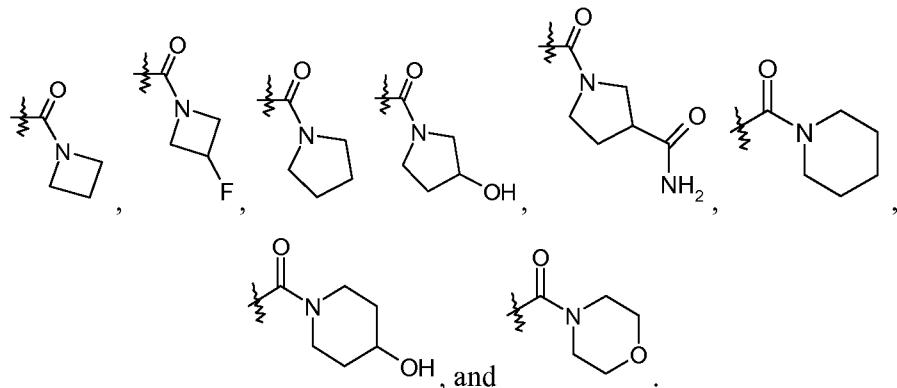
15 -C₀₋₁alkylene-C₃₋₇cycloalkyl, e.g., cyclopropyl and -CH₂-cyclopropyl; and

-(CH₂)₂-imidazolyl.

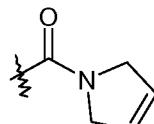
R²² and R²³ may also be taken together to form a saturated or partially unsaturated

-C₃₋₅heterocycle optionally substituted with halo, -OH, -COOH, or -CONH₂, and optionally containing an oxygen atom in the ring. Saturated -C₃₋₅heterocycles include azetidine,

20 pyrrolidine, piperidine and morpholine, such that exemplary R³ groups include:



Partially unsaturated -C₃₋₅heterocycles include 2,5-dihydro-1H-pyrrole, such that exemplary R³ groups include:



5

The R²⁴ moiety is selected from:

- C₁₋₆alkyl, e.g., -CH₂CH₃ and -(CH₂)₃CH₃;
- C₀₋₁alkylene-O-C₁₋₆alkyl, e.g., -O-CH₂CH₃ and -CH₂-OCH₃;
- phenyl optionally substituted with halo or -OCH₃, e.g., -2chlorophenyl or -2-methoxyphenyl; and
- C₁₋₉heteroaryl, e.g., 2-pyridine.

R²⁵ is selected from:

- C₁₋₆alkyl, e.g., -CH₃, -CH₂CH₃, and -(CH₂)₃CH₃;
- O-C₁₋₆alkyl, e.g., -OCH₃, -OCH₂CH₃, and -OCH(CH₃)₂;
- C₃₋₇cycloalkyl, e.g., cyclopentyl;
- O-C₃₋₇cycloalkyl, e.g., -O-cyclopropyl, -O-cyclopentyl, and -O-cyclohexyl;
- phenyl;
- O-phenyl;
- NR²⁷R²⁸;
- CH[CH(CH₃)₂]-NH₂;
- CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, e.g., -CH[CH(CH₃)₂]-NHC(O)OCH₃; and
- CH(NH₂)CH₂COOCH₃.

R²⁷ and R²⁸ are independently selected from H, -C₁₋₆alkyl, and benzyl, or R²⁷ and R²⁸ are taken together as -(CH₂)₃₋₆-, -C(O)-(CH₂)₃-, or -(CH₂)₂O(CH₂)₂-, R³³ is selected from -O-C₁₋₆alkyl, -O-benzyl, and -NR²⁷R²⁸; and R³⁴ is -C₁₋₆alkyl (e.g., -CH₃ and -C(CH₃)₃) or

-C₀₋₆alkylene-C₆₋₁₀aryl.

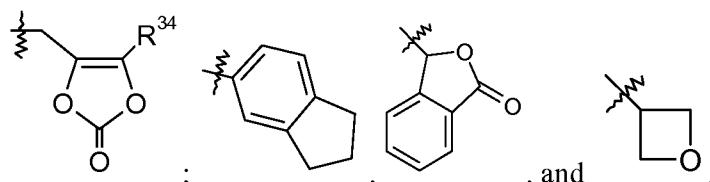
In addition, each alkyl group in R³ is optionally substituted with 1 to 8 fluoro atoms. For example, when R³ is -C₀₋₁alkylene-COOR²¹ and R²¹ is -C₁₋₆alkyl, R³ can also be a group such as -COOCH(CH₃)CF₃, -COOCH₂CF₂CF₃, -COOCH(CF₃)₂,

5 -COO(CH₂)₂CF₃, -COOCH(CH₂F)₂, -COOC(CF₃)₂CH₃, and -COOCH(CH₃)CF₂CF₃.

In one embodiment, R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -C₁₋₆alkyl; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; phenyl optionally substituted with one or two groups independently selected from halo, -OH, and -OCH₃; pyridinyl; and pyrazinyl; R²⁰ is -C₁₋₆alkyl; R²¹ is H; R²² is H or -C₁₋₆alkyl; R²³ is selected from -C₁₋₆alkyl, -(CH₂)₂OH, -(CH₂)₂OCH₃, -(CH₂)₂SO₂NH₂, and -C₀₋₁alkylene-C₃₋₇cycloalkyl; or R²² and R²³ are taken together to form a saturated or partially unsaturated -C₃₋₅heterocycle optionally substituted with halo or -OH, and optionally containing an oxygen atom in the ring; and R²⁴ is phenyl substituted with -OCH₃. In other embodiments these compounds have formula III.

15 In one embodiment, R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -NH₂; -C₁₋₆alkyl; -CF₃; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; -NO₂; -C(CH₃)=N(OH); phenyl optionally substituted with one or two groups independently selected from halo, -OH, -CF₃, -OCH₃, -NHC(O)CH₃, and phenyl; naphthalenyl; pyridinyl; pyrazinyl; pyrazolyl optionally substituted with methyl; thiophenyl optionally substituted with methyl or halo; furanyl; and -CH₂-morpholinyl; and R²¹ is H. In other embodiments these compounds have formula III.

20 In another embodiment, R³ is -C₀₋₁alkylene-COOR²¹, and R²¹ is selected from -C₁₋₆alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R²⁵; -C₁₋₆alkylene-NR²⁷R²⁸, -C₁₋₆alkylene-C(O)R³³, 25 -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-SO₂-C₁₋₆alkyl,



In one aspect of the invention, these compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. In other embodiments these compounds have formula III.

30 The R⁴ moiety can be absent. When present, R⁴ is attached to a carbon or nitrogen

atom in the "X" group, and is selected from:

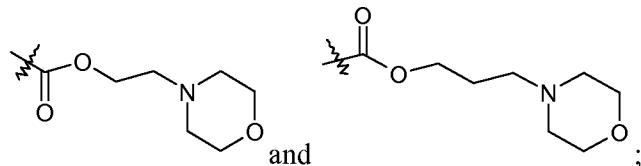
- H;
- OH;
- C₁₋₆alkyl, e.g., -CH₃;
- 5 -C₁₋₂alkylene-COOR³⁵, e.g., -CH₂COOH and -(CH₂)₂-COOH;
- CH₂OC(O)CH(R³⁶)NH₂, e.g., -CH₂OC(O)CH[CH(CH₃)₂]NH₂;
- OCH₂OC(O)CH(R³⁶)NH₂, e.g., -OCH₂OC(O)CH[CH(CH₃)₂]NH₂;
- OCH₂OC(O)CH₃;
- CH₂OP(O)(OH)₂;
- 10 -CH₂CH(OH)CH₂OH;
- CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl;
- pyridinyl; and
- phenyl or benzyl optionally substituted with one or more groups selected from halo, -COOR³⁵, -OCH₃, -OCF₃, and -SCF₃ (e.g., 4-chlorophenyl, 3-methoxyphenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2-chloro, 5-fluorophenyl, 3-trifluoromethoxy, 4-chlorophenyl, 3-trifluoromethylsulfanyl, 4-chlorophenyl, 2,6-difluoro, 4-chlorophenyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 3-carboxybenzyl, 4-carboxybenzyl, 3-methoxybenzyl, 2-chloro, 5-fluorobenzyl, 3-chloro, 5-fluorobenzyl, 2-fluoro, 4-chlorobenzyl, 3-chloro, 4-fluorobenzyl, 3-OCF₃, 4-chlorobenzyl, 3-SCF₃, 4-chlorobenzyl, 2,6-difluoro, 3-chlorobenzyl, 2,6-difluoro, 4-chlorobenzyl, and 2,3,5,6-tetrafluoro, 4-methoxy benzyl).

The R³⁵ moiety is selected from:

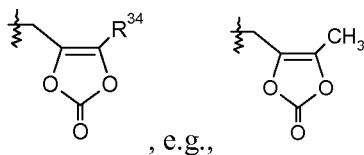
- H;
- C₁₋₆alkyl, e.g., -CH₃ and -CH₂CH₃;
- 25 -C₁₋₃alkylene-C₆₋₁₀aryl;
- C₁₋₃alkylene-C₁₋₉heteroaryl, e.g., -CH₂-pyridine;
- C₃₋₇cycloalkyl;
- [(CH₂)₂O]₁₋₃CH₃, e.g., -(CH₂)₂OCH₃;
- C₁₋₆alkylene-OC(O)R²⁵, e.g., -CH₂OC(O)CH₃, -CH₂OC(O)O-CH₃, -CH₂OC(O)O-
- 30 CH₃, -CH(CH₃)OC(O)O-CH₂CH₃, -CH(CH₃)OC(O)O-CH(CH₃)₂, -CH₂CH(CH₃)OC(O)-cyclopentyl, -CH₂OC(O)O-cyclopropyl, -CH(CH₃)OC(O)-O-cyclohexyl, -CH₂OC(O)O-cyclopentyl, -CH₂CH(CH₃)OC(O)-phenyl, and -CH₂OC(O)O-phenyl;
- C₁₋₆alkylene-NR²⁷R²⁸, e.g., -CH₂-pyrrolidine;

-C₁₋₆alkylene-C(O)R³³;

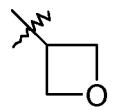
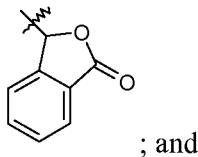
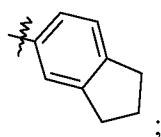
-C₀₋₆alkylenemorpholinyl, e.g., -(CH₂)₂-morpholinyl and -(CH₂)₃-morpholinyl:



-C₁₋₆alkylene-SO₂-C₁₋₆alkyl, e.g., -(CH₂)₂-SO₂-CH₃;



5

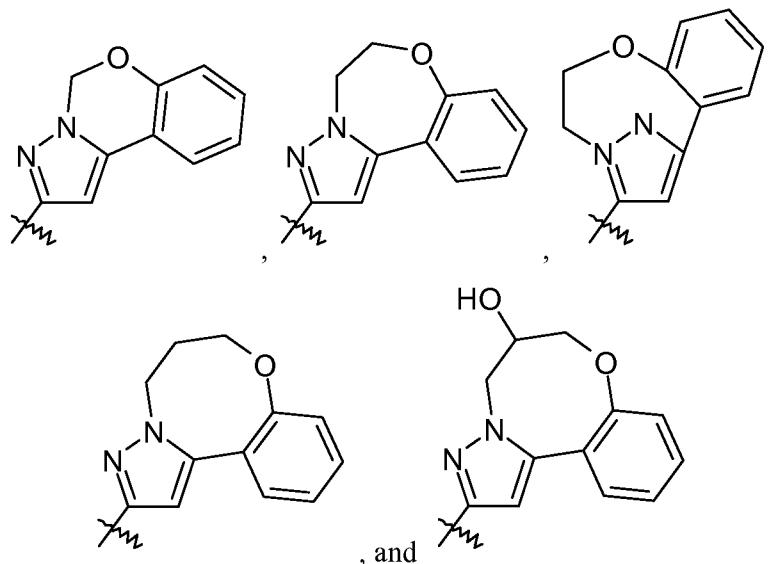


The R²⁵, R²⁷, R²⁸, R³³, and R³⁴ moieties are defined above. The R³⁶ moiety is

10 selected from H, -CH(CH₃)₂, phenyl, and benzyl.

In addition, each alkyl group in R⁴ is optionally substituted with 1 to 8 fluoro atoms. For example, when R⁴ is -C₁₋₂alkylene-COOR³⁵ and R³⁵ is -C₁₋₆alkyl, R⁴ can also be a group such as -COOCH(CH₃)CF₃, -COOCH₂CF₂CF₃, -COOCH(CF₃)₂, -COO(CH₂)₂CF₃, -COOCH(CH₂F)₂, -COOC(CF₃)₂CH₃, and -COOCH(CH₃)CF₂CF₃.

15 The R⁴ moiety can also be taken together with R³ to form -phenylene-O-(CH₂)₁₋₃- or -phenylene-O-CH₂-CHOH-CH₂- . For purposes of illustration only, these embodiments are depicted below with X being pyrazole. It is understood that other X groups can be used also.

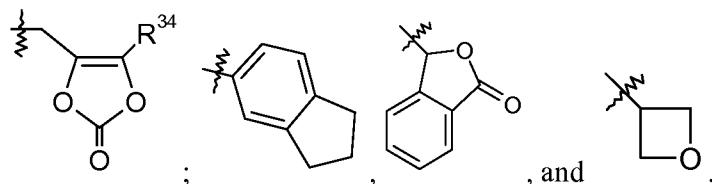


In another particular embodiment, R⁴ is selected from H; -OH; -C₁₋₂alkylene-COOR³⁵; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo and -OCH₃; and R³⁵ is H. In other embodiments these compounds have formula III.

In one embodiment, R⁴ is absent or is selected from H; -OH; -C₁₋₆alkyl; -C₁₋₂alkylene-COOR³⁵; -CH₂OC(O)CH(R³⁶)NH₂, -CH₂CH(OH)CH₂OH; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo,

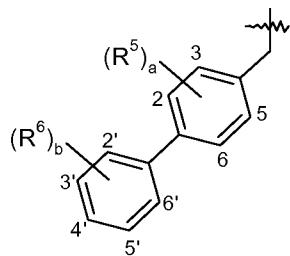
10 -COOR³⁵, -OCH₃, -OCF₃, and -SCF₃; and R³⁵ is H. In other embodiments these compounds have formula III.

In another embodiment, R⁴ is selected from -OCH₂OC(O)CH₃; -CH₂OP(O)(OH)₂; -C₁₋₂alkylene-COOR³⁵; and phenyl or benzyl substituted with at least one -COOR³⁵ group; where R³⁵ is selected from -C₁₋₆alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R²⁵; -C₁₋₆alkylene-NR²⁷R²⁸, -C₁₋₆alkylene-C(O)R³³, -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-SO₂-C₁₋₆alkyl,

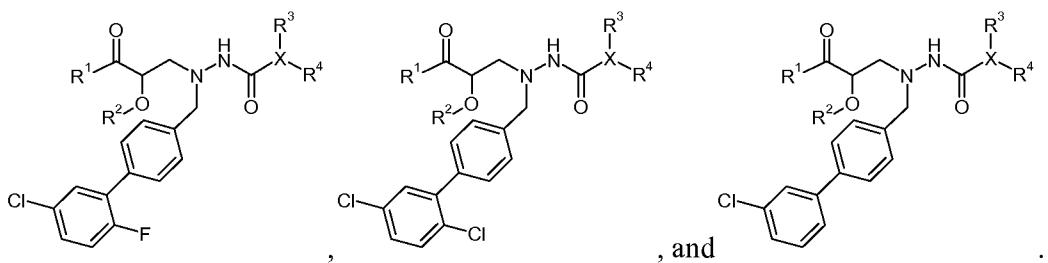


In one aspect of the invention, these compounds may find particular utility as prodrugs or as intermediates in the synthetic procedures described herein. In other embodiments these compounds have formula III.

The numbering for the R⁵ and R⁶ groups is as follows:

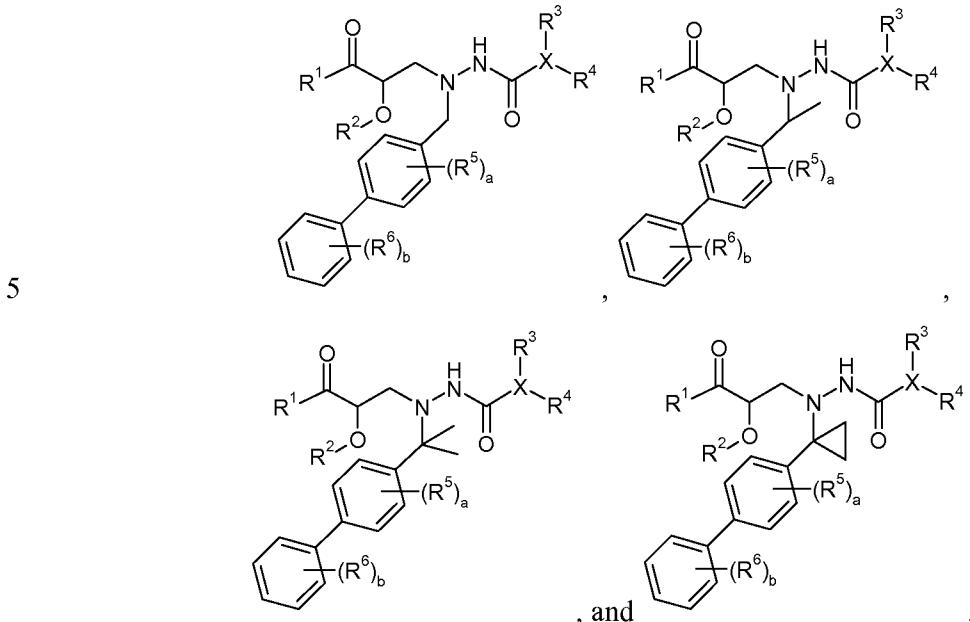


The integer "a" is 0 or 1. The R^5 moiety, when present, is selected from halo, $-CH_3$, $-CF_3$, and $-CN$. In one embodiment, a is 0. In another embodiment, a is 1, and R^5 is selected from halo and $-CN$, such as 2-chloro, 2-fluoro, 3-cyano, 3-chloro, or 3-fluoro. The integer 5 "b" is 0 or an integer from 1 to 3. The R^6 moiety, when present, is independently selected from halo, $-OH$, $-CH_3$, $-OCH_3$, and $-CF_3$. In one embodiment, b is 0. In another embodiment, b is 1 and R^6 is selected from Cl, F, $-OH$, $-CH_3$, $-OCH_3$, and $-CF_3$, such 2'-chloro, 3'-chloro, 2'-fluoro, 3'-fluoro, 2'-hydroxy, 3'-hydroxy, 3'-methyl, 2'-methoxy, or 3'-trifluoromethyl. In one embodiment, b is 2 and R^6 is 2'-fluoro-5'-chloro, 2',5'-dichloro, 10 2',5'-difluoro, 2'-methyl-5'-chloro, 3'-fluoro-5'-chloro, 3'-hydroxy-5'-chloro, 3',5'-dichloro, 3',5'-difluoro, 2'-methoxy-5'-chloro, 2'-methoxy-5'-fluoro, 2'-hydroxy-5'-fluoro, 2'-fluoro-3'-chloro, 2'-hydroxy-5'-chloro, or 2'-hydroxy-3'-chloro; and in another embodiment, b is 2 and each R^6 is independently halo, $-OH$, $-CH_3$, or $-OCH_3$, for example, 2'-fluoro-5'-chloro, 2',5'-dichloro, 2'-methyl-5'-chloro, 3'-hydroxy-5'-chloro, 3',5'-dichloro, 3',5'-difluoro, 2'-methoxy-5'-chloro, 2'-methoxy-5'-fluoro, 3'-fluoro-5'-chloro, 2'-hydroxy-5'-fluoro, 2'-fluoro-3'-chloro, 2'-hydroxy-5'-chloro, or 2'-hydroxy-3'-chloro. In another embodiment, b is 15 3 and each R^6 is independently halo or $-CH_3$, such as 2'-methyl-3', 5'-dichloro or 2'-fluoro-3'-methyl-5'-chloro. In yet another embodiment, a is 1 and b is 1 and R^5 and R^6 are independently halo, for example, 3-chloro and 3'chloro. In other embodiments these 20 compounds have formula III. Of particular interest are compounds of the formulas:



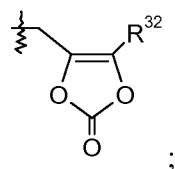
The methylene linker on the biphenyl is optionally substituted with one or two $-C_{1-6}$ alkyl groups or cyclopropyl. For example, in one embodiment, the methylene linker on the biphenyl is unsubstituted; in another embodiment, the methylene linker on the

biphenyl is substituted with one $-C_{1-6}$ alkyl group (e.g., $-CH_3$); and in yet another embodiment, the methylene linker on the biphenyl is substituted with two $-C_{1-6}$ alkyl groups (e.g., two $-CH_3$ groups); in another embodiment, the methylene linker on the biphenyl is substituted with a cyclopropyl group. These embodiments are depicted, respectively, as:



In another embodiment, R^1 is OR^7 ; R^2 is H; X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, pyrimidine, and pyridyltriazole; R^3 is absent or is selected from H; halo; $-C_{0-5}$ alkylene-OH; $-C_{1-6}$ alkyl; $-C_{3-7}$ cycloalkyl; $-C_{0-2}$ alkylene-O- C_{1-6} alkyl; $-C(O)R^{20}$; $-C_{0-1}$ alkylene-COOR²¹; $-C(O)NR^{22}R^{23}$; $-NHC(O)R^{24}$; =O; phenyl optionally substituted with one or two groups independently selected from halo, -OH, and $-OCH_3$; pyridinyl; and pyrazinyl; R^4 is selected from H; -OH; $-C_{1-2}$ alkylene-COOR³⁵; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo and $-OCH_3$; a is 0; or a is 1 and R^5 is selected from halo and -CN; b is 0; or b is 1 and R^6 is selected from Cl, F, -OH, $-CH_3$, $-OCH_3$, and $-CF_3$; or b is 2 and each R^6 is independently halo, -OH, $-CH_3$, or $-OCH_3$; or b is 3 and each R^6 is independently halo or $-CH_3$; R^7 is selected from H, $-C_{1-8}$ alkyl, $-C_{1-3}$ alkylene-C₆₋₁₀aryl, $-C_{0-6}$ alkylenemorpholinyl, and

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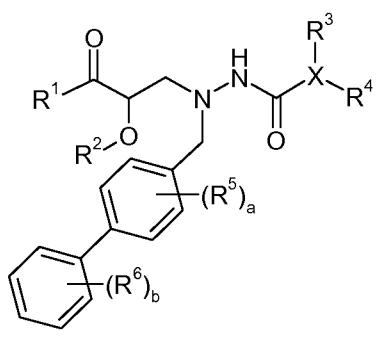
20 R^{32} is $-C_{1-6}$ alkyl; R^{20} is $-C_{1-6}$ alkyl; R^{21} is H; R^{22} is H or $-C_{1-6}$ alkyl; R^{23} is selected from

-C₁₋₆alkyl, -(CH₂)₂OH, -(CH₂)₂OCH₃, -(CH₂)₂SO₂NH₂, and -C₀₋₁alkylene-C₃₋₇cycloalkyl; or R²² and R²³ are taken together to form a saturated or partially unsaturated -C₃₋₅heterocycle optionally substituted with halo or -OH, and optionally containing an oxygen atom in the ring; R²⁴ is phenyl substituted with -OCH₃; and R³⁵ is H; and where 5 each alkyl group in R¹ is optionally substituted with 1 to 8 fluoro atoms.

In still another embodiment, R¹ is OR⁷; R² is H; X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, and pyrimidine; R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -C₁₋₆alkyl; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; 10 =O; phenyl substituted with one or two groups independently selected from halo, -OH, and -OCH₃; pyridinyl; and pyrazinyl; R⁴ is selected from H, -OH, and phenyl optionally substituted with a halo group; a is 0; or a is 1 and R⁵ is halo; b is 0; or b is 1 and R⁶ is halo or -CH₃; or b is 2 and each R⁶ is independently halo, -OH, -CH₃, or -OCH₃; R²⁰ is -C₁₋₆alkyl; R²¹ is H; R²² is -C₁₋₆alkyl; R²³ is -C₁₋₆alkyl or -C₀₋₁alkylene-C₃₋₇cycloalkyl; or 15 R²² and R²³ are taken together to form a saturated -C₃₋₅heterocycle optionally substituted with halo or -OH; R²⁴ is phenyl substituted with -OCH₃; and R⁷ is as defined for formula I.

A particular group of compounds of formula I are those disclosed in U.S.

Provisional Application No. 61/423,175, filed on December 15, 2010. This group includes compounds of formula II:

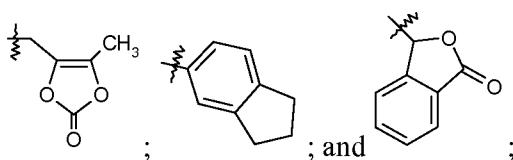


(II)

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where: R¹ is selected from -OR⁷ and -NR⁸R⁹; R⁷ is selected from H; -C₁₋₆alkyl; -C₁₋₃alkylene-C₆₋₁₀aryl; -C₁₋₃alkylene-C₁₋₉heteroaryl; -C₃₋₇cycloalkyl; -(CH₂)₂OCH₃; -C₁₋₆alkylene-OC(O)R¹⁰; -CH₂-pyridine; -CH₂-pyrrolidine; -C₀₋₆alkylenemorpholine; -C₁₋₆alkylene-SO₂-C₁₋₆alkyl;

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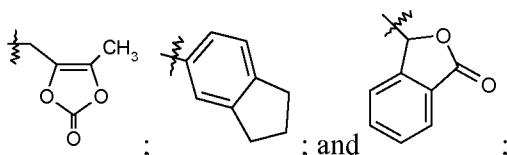
where R^{10} is selected from $-C_{1-6}\text{alkyl}$, $-O-C_{1-6}\text{alkyl}$, $-C_{3-7}\text{cycloalkyl}$, $-O-C_{3-7}\text{cycloalkyl}$, phenyl, $-O\text{-phenyl}$, $-NR^{12}R^{13}$, and $-CH(\text{NH}_2)\text{CH}_2\text{COOCH}_3$; and R^{12} and R^{13} are independently selected from H, $-C_{1-6}\text{alkyl}$, and benzyl, or R^{12} and R^{13} are taken together as $-(\text{CH}_2)_{3-6}$; R^8 is selected from H; $-\text{OH}$; $-\text{OC(O)R}^{14}$; $-\text{CH}_2\text{COOH}$; $-O\text{-benzyl}$; pyridyl; and

5 $-OC(\text{S})\text{NR}^{15}R^{16}$; where R^{14} is selected from H, $-C_{1-6}\text{alkyl}$, $-C_{6-10}\text{aryl}$, $-O\text{CH}_2-C_{6-10}\text{aryl}$, $-CH_2O-C_{6-10}\text{aryl}$, and $-NR^{15}R^{16}$; and R^{15} and R^{16} are independently selected from H and $-C_{1-4}\text{alkyl}$; R^9 is selected from H; $-C_{1-6}\text{alkyl}$; and $-C(\text{O})R^{17}$; where R^{17} is selected from H; $-C_{1-6}\text{alkyl}$; $-C_{3-7}\text{cycloalkyl}$; $-C_{6-10}\text{aryl}$; and $-C_{1-9}\text{heteroaryl}$; R^2 is H or is taken together with R^1 to form $-\text{OCHR}^{18}R^{19}$ - or $-\text{NHC(O)-}$; where R^{18} and R^{19} are independently selected from

10 H, $-C_{1-6}\text{alkyl}$, and $-O-C_{3-7}\text{cycloalkyl}$, or R^{18} and R^{19} are taken together to form $=\text{O}$; X is a $-C_{1-9}\text{heteroaryl}$ or a partially unsaturated $-C_{3-5}\text{heterocycle}$; R^3 is absent or is selected from H; halo; $-C_{0-5}\text{alkylene-OH}$; $-\text{NH}_2$; $-C_{1-6}\text{alkyl}$; $-C_{3-7}\text{cycloalkyl}$; $-C_{0-1}\text{alkylene-O-C}_{1-6}\text{alkyl}$; $-C(\text{O})R^{20}$; $-C_{0-1}\text{alkylene-C(O)OR}^{21}$; $-C(\text{O})\text{NR}^{22}R^{23}$; $-\text{NHC(O)R}^{24}$; phenyl optionally substituted with one group selected from halo, $-\text{CF}_3$, $-\text{OCH}_3$, $-\text{NHC(O)CH}_3$, and phenyl;

15 napthyl; pyridine; pyrazine; pyrazole optionally substituted with methyl; thiophene optionally substituted with methyl; and furan; and R^3 , when present, is attached to a carbon atom; R^{20} is selected from H and $-C_{1-6}\text{alkyl}$; R^{21} is selected from H; $-C_{1-6}\text{alkyl}$; $-C_{1-3}\text{alkylene-C}_{6-10}\text{aryl}$; $-C_{1-3}\text{alkylene-C}_{1-9}\text{heteroaryl}$; $-C_{3-7}\text{cycloalkyl}$; $-(\text{CH}_2)_2\text{OCH}_3$; $-C_{1-6}\text{alkylene-OC(O)R}^{25}$; $-\text{CH}_2\text{-pyridine}$; $-\text{CH}_2\text{-pyrrolidine}$; $-C_{0-6}\text{alkylenemorpholine}$;

20 $-C_{1-6}\text{alkylene-SO}_2-C_{1-6}\text{alkyl}$;



where R^{25} is selected from $-C_{1-6}\text{alkyl}$, $-O-C_{1-6}\text{alkyl}$, $-C_{3-7}\text{cycloalkyl}$, $-O-C_{3-7}\text{cycloalkyl}$, phenyl, $-O\text{-phenyl}$, $-NR^{27}R^{28}$, and $-CH(\text{NH}_2)\text{CH}_2\text{COOCH}_3$; and R^{27} and R^{28} are independently selected from H, $-C_{1-6}\text{alkyl}$, and benzyl, or R^{27} and R^{28} are taken together as

25 $-(\text{CH}_2)_{3-6}$; R^{22} and R^{23} are independently selected from H; $-C_{1-6}\text{alkyl}$; $-\text{CH}_2\text{COOH}$; $-(\text{CH}_2)_2\text{OH}$; $-(\text{CH}_2)_2\text{OCH}_3$; $-(\text{CH}_2)_2\text{SO}_2\text{NH}_2$; $-(\text{CH}_2)_2\text{N}(\text{CH}_3)_2$; $-C_{3-7}\text{cycloalkyl}$; and $-(\text{CH}_2)_2\text{-imidazole}$; or R^{22} and R^{23} are taken together to form a saturated or partially unsaturated $-C_{3-5}\text{heterocycle}$ optionally substituted with $-\text{OH}$, $-\text{COOH}$, or $-\text{CONH}_2$; and optionally containing an oxygen atom in the ring; R^{24} is selected from $-C_{1-6}\text{alkyl}$; $-O-C_{1-6}\text{alkyl}$; $-\text{CH}_2\text{-O-C}_{1-6}\text{alkyl}$; phenyl substituted with $-\text{OCH}_3$; and pyridine; R^4 is selected from H; $-C_{1-6}\text{alkyl}$; phenyl or benzyl substituted with one or more groups selected from

halo, -COOH, -OCH₃, -OCF₃, and -SCF₃; and R⁴ is attached to a carbon or nitrogen atom; a is 0 or 1; R⁵ is halo or -CF₃; and b is 0 or 1; R⁶ is halo; or a pharmaceutically acceptable salt thereof.

In addition, particular compounds of formula I that are of interest include those set forth in the Examples below, as well a pharmaceutically acceptable salt thereof.

GENERAL SYNTHETIC PROCEDURES

Compounds of the invention can be prepared from readily available starting materials using the following general methods, the procedures set forth in the Examples, or by using other methods, reagents, and starting materials that are known to those of ordinary skill in the art. Although the following procedures may illustrate a particular embodiment of the invention, it is understood that other embodiments of the invention can be similarly prepared using the same or similar methods or by using other methods, reagents and starting materials known to those of ordinary skill in the art. It will also be appreciated that where typical or preferred process conditions (for example, reaction temperatures, times, 10 mole ratios of reactants, solvents, pressures, etc.) are given, other process conditions can also be used unless otherwise stated. In some instances, reactions were conducted at room temperature and no actual temperature measurement was taken. It is understood that room temperature can be taken to mean a temperature within the range commonly associated with the ambient temperature in a laboratory environment, and will typically be in the 15 range of about 18°C to about 30°C. In other instances, reactions were conducted at room temperature and the temperature was actually measured and recorded. While optimum reaction conditions will typically vary depending on various reaction parameters such as the particular reactants, solvents and quantities used, those of ordinary skill in the art can readily determine suitable reaction conditions using routine optimization procedures.

25 Additionally, as will be apparent to those skilled in the art, conventional protecting groups may be necessary or desired to prevent certain functional groups from undergoing undesired reactions. The choice of a suitable protecting group for a particular functional group as well as suitable conditions and reagents for protection and deprotection of such functional groups are well-known in the art. Protecting groups other than those illustrated 30 in the procedures described herein may be used, if desired. For example, numerous protecting groups, and their introduction and removal, are described in T. W. Greene and G. M. Wuts, *Protecting Groups in Organic Synthesis*, Fourth Edition, Wiley, New York, 2006, and references cited therein.

Carboxy-protecting groups are suitable for preventing undesired reactions at a carboxy group, and examples include, but are not limited to, methyl, ethyl, *t*-butyl, benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), diphenylmethyl (benzhydryl, DPM) and the like. Amino-
5 protecting groups are suitable for preventing undesired reactions at an amino group, and examples include, but are not limited to, *t*-butoxycarbonyl (BOC), trityl (Tr), benzylloxycarbonyl (Cbz), 9-fluorenylmethoxycarbonyl (Fmoc), formyl, trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBDMS), and the like. Hydroxyl-protecting groups are suitable for preventing undesired reactions at a hydroxyl group, and examples include, but
10 are not limited to C₁₋₆alkyls, silyl groups including triC₁₋₆alkylsilyl groups, such as trimethylsilyl (TMS), triethylsilyl (TES), and *tert*-butyldimethylsilyl (TBDMS); esters (acyl groups) including C₁₋₆alkanoyl groups, such as formyl, acetyl, and pivaloyl, and aromatic acyl groups such as benzoyl; arylmethyl groups such as benzyl (Bn), *p*-methoxybenzyl (PMB), 9-fluorenylmethyl (Fm), and diphenylmethyl (benzhydryl, DPM);
15 and the like.

Standard deprotection techniques and reagents are used to remove the protecting groups, and may vary depending upon which group is used. For example, sodium or lithium hydroxide is commonly used when the carboxy-protecting group is methyl, an acid such as TFA or HCl is commonly used when the carboxy-protecting group is ethyl or *t*-butyl, and H₂/Pd/C may be used when the carboxy-protecting group is benzyl. A BOC amino-protecting group can be removed using an acidic reagent such as TFA in DCM or HCl in 1,4-dioxane, while a Cbz amino-protecting group can be removed by employing catalytic hydrogenation conditions such as H₂ (1 atm) and 10% Pd/C in an alcoholic solvent ("H₂/Pd/C"). H₂/Pd/C is commonly used when the hydroxyl-protecting group is benzyl, while NaOH is commonly used when the hydroxyl-protecting group is an acyl group.
20
25

Suitable bases for use in these schemes include, by way of illustration and not limitation, potassium carbonate, calcium carbonate, sodium carbonate, triethylamine, pyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), *N,N*-diisopropylethylamine (DIPEA), 4-methylmorpholine, sodium hydroxide, potassium hydroxide, potassium *t*-butoxide, and metal hydrides.
30

Suitable inert diluents or solvents for use in these schemes include, by way of illustration and not limitation, tetrahydrofuran (THF), acetonitrile (MeCN), *N,N*-

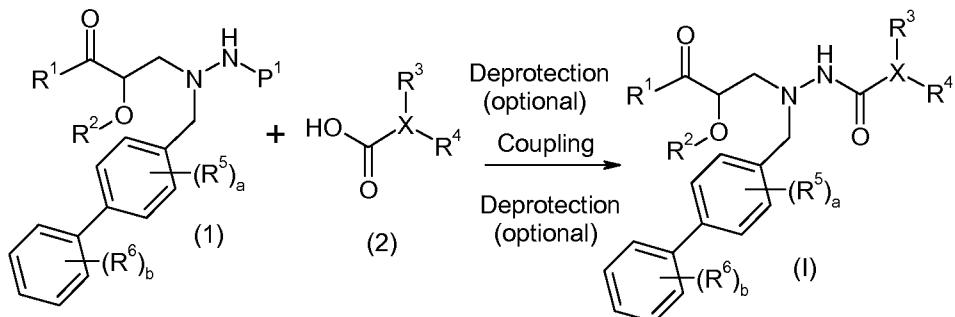
dimethylformamide (DMF), *N,N*-dimethylacetamide (DMA), dimethyl sulfoxide (DMSO), toluene, dichloromethane (DCM), chloroform (CHCl₃), carbon tetrachloride (CCl₄), 1,4-dioxane, methanol, ethanol, water, and the like.

Suitable carboxylic acid/amine coupling reagents include benzotriazol-1-
5 yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazol-1-
yloxytritypyrrolidinophosphonium hexafluorophosphate (PyBOP), *N,N,N',N'*-tetramethyl-
O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), 1,3-
dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide
(EDCI), carbonyldiimidazole (CDI), 1-hydroxybenzotriazole (HOBr), and the like.
10 Coupling reactions are conducted in an inert diluent in the presence of a base such as
DIPEA, and are performed under conventional amide bond-forming conditions.

All reactions are typically conducted at a temperature within the range of about
-78°C to 100°C, for example at room temperature. Reactions may be monitored by use of
thin layer chromatography (TLC), high performance liquid chromatography (HPLC),
15 and/or LCMS until completion. Reactions may be complete in minutes, or may take hours,
typically from 1-2 hours and up to 48 hours. Upon completion, the resulting mixture or
reaction product may be further treated in order to obtain the desired product. For
example, the resulting mixture or reaction product may be subjected to one or more of the
following procedures: concentrating or partitioning (for example, between EtOAc and
20 water or between 5% THF in EtOAc and 1M phosphoric acid); extraction (for example,
with EtOAc, CHCl₃, DCM, chloroform); washing (for example, with saturated aqueous
NaCl, saturated aqueous NaHCO₃, Na₂CO₃ (5%), CHCl₃ or 1M NaOH); drying (for
example, over MgSO₄, over Na₂SO₄, or *in vacuo*); filtering; crystallizing (for example,
from EtOAc and hexanes); being concentrated (for example, *in vacuo*); and/or purification
25 (e.g., silica gel chromatography, flash chromatography, preparative HPLC, reverse phase-
HPLC, or crystallization).

By way of illustration, Compounds of formula I, as well as their salts, can be
prepared as shown in Scheme I:

Scheme I



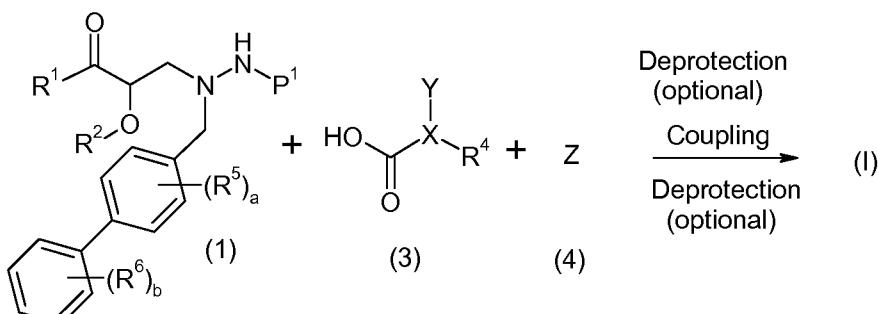
The process comprises the step of coupling compound 1 with compound 2, where R^1 - R^6 , X, a, and b are as defined for formula I, and P^1 is H or a suitable amino-protecting group, examples of which include, *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl. When P^1 is an amino protecting group, the process further comprises deprotecting the compound of formula 1, before or *in situ* with the coupling step.

In instances where R^1 is a group such as $-OCH_3$ or $-OCH_2CH_3$, the coupling step 10 may be followed by a deprotection step to provide a compound of formula I where R^1 is a group such as $-OH$. Thus, one method of preparing compounds of the invention involves coupling compounds 1 and 2, with an optional deprotection step to form a compound of formula I or a pharmaceutically acceptable salt thereof.

Methods of preparing compound 1 are described in the Examples. Compound 2 is generally commercially available or can be prepared using procedures that are known in the art.

Compounds of formula I, as well as their salts, can also be prepared as shown in Scheme II:

Scheme II



20

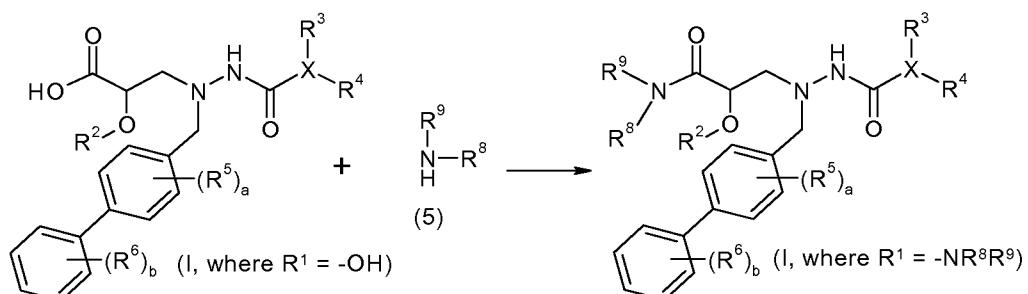
In the first step, compound 1 is coupled with compound 3 and compound 3 is coupled to compound 4, where Y and Z react *in situ* to form the R³ moiety. For example, when R³ is

-C(O)NR²²R²³, Y is -COOH and Z is HNR²²R²³. Alternately, compound 3 is first coupled to compound 4, and the resulting compound is then coupled with compound 1. As with Scheme I, in instances where R¹ is a group such as -OCH₃ or -OCH₂CH₃, the coupling step may be followed by a deprotection step to provide a compound of formula I where R¹ is a group such as -OH. Thus, one method of preparing compounds of the invention involves coupling compounds 1, 2 and 3, with an optional deprotection step to form a compound of formula I or a pharmaceutically acceptable salt thereof.

Compounds 3 and 4 are generally commercially available or can be prepared using procedures that are known in the art.

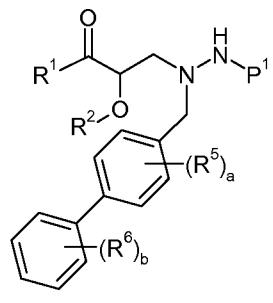
10 Compounds of formula I, as well as their salts, can also be prepared as shown in Scheme III:

Scheme III



Again, as with Schemes I and II, this is a standard coupling reaction between a compound of formula I, where R¹ is -OH and compound 5, to yield a compound of formula I, where R¹ is -NR⁸R⁹.

15 Certain intermediates described herein are believed to be novel and accordingly, such compounds are provided as further aspects of the invention including, for example, the compounds of formula 1, or a salt thereof:

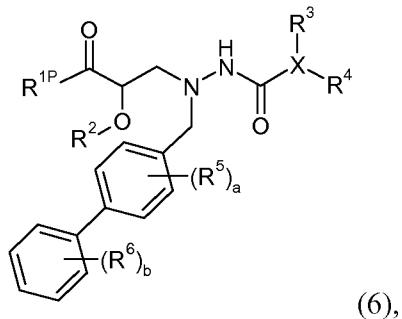


20

(1),

where P¹ is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and R¹, R², R⁵, R⁶, a and b are as defined for formula I. Another

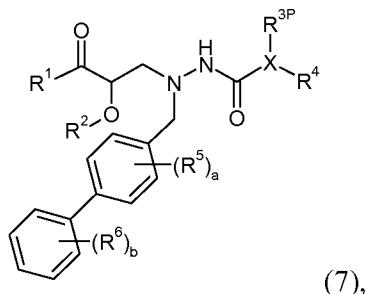
intermediate of the invention has formula 6 or a salt thereof:



where R^{1P} is selected from -O-P³, -NHP², and -NH(O-P⁴); where P² is an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-

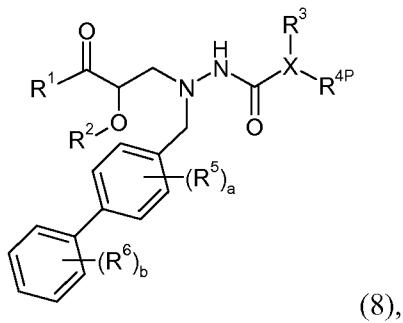
5 fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; P³ is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; P⁴ is a hydroxyl-protecting group selected from -C₁₋₆alkyl, triC₁₋₆alkylsilyl, -C₁₋₆alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl; and R², R³, R⁴, R⁵, R⁶, a, b, and

10 X are as defined for formula I. Another intermediate of the invention has formula 7 or a salt thereof:

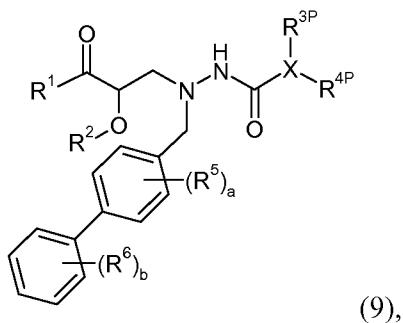


where R^{3P} is selected from -C₀₋₅alkylene-O-P⁴, -C₀₋₁alkylene-COO-P³, and phenyl substituted with -O-P⁴; P³ is a carboxy-protecting group selected from methyl, ethyl, *t*-

15 butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; P⁴ is a hydroxyl-protecting group selected from -C₁₋₆alkyl, triC₁₋₆alkylsilyl, -C₁₋₆alkanoyl, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl; and R¹, R², R⁴, R⁵, R⁶, a, b, and X are as defined for formula I. Still another intermediate of the invention has formula 8 or a salt thereof:



where 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^3 is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; 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; and R^1 , R^2 , R^3 , R^5 , R^6 , a , b , and X are as defined for formula I. Yet another intermediate of the invention has formula 9 or a salt thereof:



where 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^3 is a carboxy-protecting group selected from methyl, ethyl, *t*-butyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, trimethylsilyl, *t*-butyldimethylsilyl, and diphenylmethyl; 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; and R^1 , R^2 , R^5 , R^6 , a , b , and X are as defined for formula I. Thus, another method of preparing compounds of the invention involves deprotecting a compound of formula 1, 6, 7, 8, 9, or a salt thereof.

Further details regarding specific reaction conditions and other procedures for preparing representative compounds of the invention or intermediates thereof are described in the Examples set forth below.

UTILITY

Compounds of the invention possess neprilysin (NEP) inhibition activity, that is, the compounds are able to inhibit enzyme-catalytic activity. In another embodiment, the compounds do not exhibit significant inhibitory activity of the angiotensin-converting 5 enzyme. Compounds of formula I may be active drugs as well as prodrugs. Thus, when discussing the activity of compounds of the invention, it is understood that any such prodrugs have the expected activity once metabolized.

One measure of the ability of a compound to inhibit NEP activity is the inhibition constant (pK_i). The pK_i value is the negative logarithm to base 10 of the dissociation 10 constant (K_i), which is typically reported in molar units. Compounds of the invention of particular interest are those having a pK_i at NEP greater than or equal to 6.0, particularly those having a pK_i greater than or equal to 7.0, and even more particularly those having a pK_i greater than or equal to 8.0. In one embodiment, compounds of interest have a pK_i in the range of 6.0-6.9; in another embodiment, compounds of interest have a pK_i in the range 15 of 7.0-7.9; in yet another embodiment, compounds of interest have a pK_i in the range of 8.0-8.9; and in still another embodiment, compounds of interest have a pK_i in the range of greater than or equal to 9.0. Such values can be determined by techniques that are well known in the art, as well as in the assays described herein.

Another measure of the ability of a compound to inhibit NEP activity is the 20 apparent inhibition constant (IC_{50}), which is the molar concentration of compound that results in half-maximal inhibition of substrate conversion by the NEP enzyme. The pIC_{50} value is the negative logarithm to base 10 of the IC_{50} . Compounds of the invention that are of particular interest, include those that exhibit a pIC_{50} for NEP greater than or equal to about 5.0. Compounds of interest also include those having a pIC_{50} for NEP \geq about 6.0 or 25 a pIC_{50} for NEP \geq about 7.0. In another embodiment, compounds of interest have a pIC_{50} for NEP within the range of about 7.0-11.0; and in another embodiment, within the range of about 8.0-11.0, such as within the range of about 8.0-10.0.

It is noted that in some cases, compounds of the invention may possess weak NEP 30 inhibition activity. In such cases, those of skill in the art will recognize that these compounds still have utility as research tools.

Exemplary assays to determine properties of compounds of the invention, such as the NEP inhibiting activity, are described in the Examples and include by way of illustration and not limitation, assays that measure NEP inhibition (described in Assay 1).

Useful secondary assays include assays to measure ACE inhibition (also described in Assay 1) and aminopeptidase P (APP) inhibition (described in Sulpizio et al. (2005) *JPET* 315:1306-1313). A pharmacodynamic assay to assess the *in vivo* inhibitory potencies for ACE and NEP in anesthetized rats is described in Assay 2 (see also Seymour et al. (1985) 5 *Hypertension* 7(Suppl I):I-35-I-42 and Wigle et al. (1992) *Can. J. Physiol. Pharmacol.* 70:1525-1528), where ACE inhibition is measured as the percent inhibition of the angiotensin I pressor response and NEP inhibition is measured as increased urinary cyclic guanosine 3', 5'-monophosphate (cGMP) output.

There are many *in vivo* assays that can be used to ascertain further utilities of the 10 compounds of the invention. The conscious spontaneously hypertensive rat (SHR) model is a renin dependent hypertension model, and is described in Assay 3. See also Intengan et al. (1999) *Circulation* 100(22):2267-2275 and Badyal et al. (2003) *Indian Journal of Pharmacology* 35:349-362. The conscious desoxycorticosterone acetate-salt (DOCA-salt) rat model is a volume dependent hypertension model that is useful for measuring NEP 15 activity, and is described in Assay 4. See also Trapani et al. (1989) *J. Cardiovasc. Pharmacol.* 14:419-424, Intengan et al. (1999) *Hypertension* 34(4):907-913, and Badyal et al. (2003) *supra*). The DOCA-salt model is particularly useful for evaluating the ability of a test compound to reduce blood pressure as well as to measure a test compound's ability to prevent or delay a rise in blood pressure. The Dahl salt-sensitive (DSS) hypertensive rat 20 model is a model of hypertension that is sensitive to dietary salt (NaCl), and is described in Assay 5. See also Rapp (1982) *Hypertension* 4:753-763. The rat monocrotaline model of pulmonary arterial hypertension described, for example, in Kato et al. (2008) *J. Cardiovasc. Pharmacol.* 51(1):18-23, is a reliable predictor of clinical efficacy for the 25 treatment of pulmonary arterial hypertension. Heart failure animal models include the DSS rat model for heart failure and the aorto-caval fistula model (AV shunt), the latter of which is described, for example, in Norling et al. (1996) *J. Amer. Soc. Nephrol.* 7:1038-1044. Other animal models, such as the hot plate, tail-flick and formalin tests, can be used to 30 measure the analgesic properties of compounds of the invention, as well as the spinal nerve ligation (SNL) model of neuropathic pain. See, for example, Malmberg et al. (1999) *Current Protocols in Neuroscience* 8.9.1-8.9.15.

Compounds of the invention are expected to inhibit the NEP enzyme in any of the assays listed above, or assays of a similar nature. Thus, the aforementioned assays are useful in determining the therapeutic utility of compounds of the invention, for example,

their utility as antihypertensive agents or antidiarrheal agents. Other properties and utilities of compounds of the invention can be demonstrated using other *in vitro* and *in vivo* assays well-known to those skilled in the art. Compounds of formula I may be active drugs as well as prodrugs. Thus, when discussing the activity of compounds of the invention, it is 5 understood that any such prodrugs may not exhibit the expected activity in an assay, but are expected to exhibit the desired activity once metabolized.

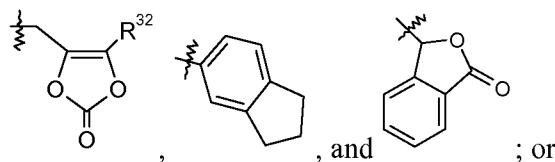
Compounds of the invention are expected to be useful for the treatment and/or prevention of medical conditions responsive to NEP inhibition. Thus it is expected that patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme 10 or by increasing the levels of its peptide substrates, can be treated by administering a therapeutically effective amount of a compound of the invention. For example, by inhibiting NEP, the compounds are expected to potentiate the biological effects of endogenous peptides that are metabolized by NEP, such as the natriuretic peptides, bombesin, bradykinins, calcitonin, endothelins, enkephalins, neuropeptides, substance P and 15 vasoactive intestinal peptide. Thus, these compounds are expected to have other physiological actions, for example, on the renal, central nervous, reproductive and gastrointestinal systems.

In one embodiment of the invention, patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme, are treated by administering a compound of 20 the invention that is in its active form, i.e., a compound of formula I where R¹ is selected from -OR⁷ and -NR⁸R⁹, R⁷ is H, R⁸ is H or -OH, R⁹ is H, and R²-R⁶, a, b, and X are as defined for formula I.

In another embodiment, patients are treated by administering a compound that is metabolized *in vitro* to form a compound of formula I where R¹ is selected from -OR⁷ and 25 -NR⁸R⁹, R⁷ is H, R⁸ is H or -OH, R⁹ is H, and R²-R⁶, a, b, and X are as defined for formula I.

In another embodiment, patients are treated by administering a compound of the invention that is in its prodrug form at the R¹ group, i.e., a compound of formula I where:

R¹ is -OR⁷; and R⁷ is selected from -C₁₋₈alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, 30 -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R¹⁰, -C₁₋₆alkylene-NR¹²R¹³, -C₁₋₆alkylene-C(O)R³¹, -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-SO₂-C₁₋₆alkyl,



R^1 is $-NR^8R^9$; R^8 is selected from $-OC(O)R^{14}$, $-CH_2COOH$, $-O\text{-benzyl}$, pyridyl, and $-OC(S)NR^{15}R^{16}$; and R^9 is H; or

R^1 is $-NR^8R^9$; R^8 is selected from $-OC(O)R^{14}$, $-CH_2COOH$, $-O\text{-benzyl}$, pyridyl, and $-OC(S)NR^{15}R^{16}$; and R^9 is $-C_{1-6}\text{alkyl}$ or $-C(O)R^{17}$;

R^1 is $-NR^8R^9$; R^8 is selected from H or $-OH$; and R^9 is selected from $-C_{1-6}\text{alkyl}$, and $-C(O)R^{17}$;

R^1 is $-OR^7$ and R^2 is taken together with R^7 to form $-CR^{18}R^{19}$; or

R^1 is $-NR^8R^9$ and R^2 is taken together with R^8 to form $-C(O)-$;

10 and R^{10} , $R^{12}-R^{17}$, R^{31} , R^{32} , R^3-R^6 , a, b, and X are as defined for formula I.

Cardiovascular Diseases

By potentiating the effects of vasoactive peptides like the natriuretic peptides and bradykinin, compounds of the invention are expected to find utility in treating and/or preventing medical conditions such as cardiovascular diseases. See, for example, Roques et al. (1993) *Pharmacol. Rev.* 45:87-146 and Dempsey et al. (2009) *Amer. J. of Pathology* 174(3):782-796. Cardiovascular diseases of particular interest include hypertension and heart failure. Hypertension includes, by way of illustration and not limitation: primary hypertension, which is also referred to as essential hypertension or idiopathic hypertension; secondary hypertension; hypertension with accompanying renal disease; severe hypertension with or without accompanying renal disease; pulmonary hypertension, including pulmonary arterial hypertension; and resistant hypertension. Heart failure includes, by way of illustration and not limitation: congestive heart failure; acute heart failure; chronic heart failure, for example with reduced left ventricular ejection fraction (also referred to as systolic heart failure) or with preserved left ventricular ejection fraction (also referred to as diastolic heart failure); and acute and chronic decompensated heart failure, with or without accompanying renal disease. Thus, one embodiment of the invention relates to a method for treating hypertension, particularly primary hypertension or pulmonary arterial hypertension, comprising administering to a patient a therapeutically effective amount of a compound of the invention.

30 For treatment of primary hypertension, the therapeutically effective amount is

typically the amount that is sufficient to lower the patient's blood pressure. This would include both mild-to-moderate hypertension and severe hypertension. When used to treat hypertension, the compound may be administered in combination with other therapeutic agents such as aldosterone antagonists, angiotensin-converting enzyme inhibitors and dual-
5 acting angiotensin-converting enzyme/neprilysin inhibitors, angiotensin-converting enzyme 2 (ACE2) activators and stimulators, angiotensin-II vaccines, anti-diabetic agents, anti-lipid agents, anti-thrombotic agents, AT₁ receptor antagonists and dual-acting AT₁ receptor antagonist/neprilysin inhibitors, β₁-adrenergic receptor antagonists, dual-acting β-adrenergic receptor antagonist/α₁-receptor antagonists, calcium channel blockers, diuretics,
10 endothelin receptor antagonists, endothelin converting enzyme inhibitors, neprilysin inhibitors, natriuretic peptides and their analogs, natriuretic peptide clearance receptor antagonists, nitric oxide donors, non-steroidal anti-inflammatory agents, phosphodiesterase inhibitors (specifically PDE-V inhibitors), prostaglandin receptor agonists, renin inhibitors, soluble guanylate cyclase stimulators and activators, and combinations thereof. In one
15 particular embodiment of the invention, a compound of the invention is combined with an AT₁ receptor antagonist, a diuretic, a calcium channel blocker, or a combination thereof, and used to treat primary hypertension. In another particular embodiment of the invention, a compound of the invention is combined with an AT₁ receptor antagonist, and used to treat hypertension with accompanying renal disease.

20 For treatment of pulmonary arterial hypertension, the therapeutically effective amount is typically the amount that is sufficient to lower the pulmonary vascular resistance. Other goals of therapy are to improve a patient's exercise capacity. For example, in a clinical setting, the therapeutically effective amount can be the amount that improves a patient's ability to walk comfortably for a period of 6 minutes (covering a
25 distance of approximately 20-40 meters). When used to treat pulmonary arterial hypertension the compound may be administered in combination with other therapeutic agents such as α-adrenergic antagonists, β₁-adrenergic receptor antagonists, β₂-adrenergic receptor agonists, angiotensin-converting enzyme inhibitors, anticoagulants, calcium channel blockers, diuretics, endothelin receptor antagonists, PDE-V inhibitors,
30 prostaglandin analogs, selective serotonin reuptake inhibitors, and combinations thereof. In one particular embodiment of the invention, a compound of the invention is combined with a PDE-V inhibitor or a selective serotonin reuptake inhibitor and used to treat pulmonary arterial hypertension.

Another embodiment of the invention relates to a method for treating heart failure, in particular congestive heart failure (including both systolic and diastolic congestive heart failure), comprising administering to a patient a therapeutically effective amount of a compound of the invention. Typically, the therapeutically effective amount is the amount 5 that is sufficient to lower blood pressure and/or improve renal functions. In a clinical setting, the therapeutically effective amount can be the amount that is sufficient to improve cardiac hemodynamics, like for instance reduction in wedge pressure, right atrial pressure, filling pressure, and vascular resistance. In one embodiment, the compound is administered as an intravenous dosage form. When used to treat heart failure, the 10 compound may be administered in combination with other therapeutic agents such as adenosine receptor antagonists, advanced glycation end product breakers, aldosterone antagonists, AT₁ receptor antagonists, β₁-adrenergic receptor antagonists, dual-acting β-adrenergic receptor antagonist/α₁-receptor antagonists, chymase inhibitors, digoxin, diuretics, endothelin converting enzyme (ECE) inhibitors, endothelin receptor antagonists, 15 natriuretic peptides and their analogs, natriuretic peptide clearance receptor antagonists, nitric oxide donors, prostaglandin analogs, PDE-V inhibitors, soluble guanylate cyclase activators and stimulators, and vasopressin receptor antagonists. In one particular embodiment of the invention, a compound of the invention is combined with an aldosterone antagonist, a β₁-adrenergic receptor antagonist, an AT₁ receptor antagonist, or 20 a diuretic, and used to treat congestive heart failure.

Diarrhea

As NEP inhibitors, compounds of the invention are expected to inhibit the degradation of endogenous enkephalins and thus such compounds may also find utility for the treatment of diarrhea, including infectious and secretory/watery diarrhea. See, for 25 example, Baumer et al. (1992) *Gut* 33:753-758; Farthing (2006) *Digestive Diseases* 24:47-58; and Marçais-Collado (1987) *Eur. J. Pharmacol.* 144(2):125-132. When used to treat diarrhea, compounds of the invention may be combined with one or more additional antidiarrheal treatments.

Renal Diseases

30 By potentiating the effects of vasoactive peptides like the natriuretic peptides and bradykinin, compounds of the invention are expected to enhance renal function (see Chen et al. (1999) *Circulation* 100:2443-2448; Lipkin et al. (1997) *Kidney Int.* 52:792-801; and Dussaule et al. (1993) *Clin. Sci.* 84:31-39) and find utility in treating and/or preventing

renal diseases. Renal diseases of particular interest include diabetic nephropathy, chronic kidney disease, proteinuria, and particularly acute kidney injury or acute renal failure (see Sharkovska et al. (2011) *Clin. Lab.* 57:507-515 and Newaz et al. (2010) *Renal Failure* 32:384-390). When used to treat renal disease, the compound may be administered in 5 combination with other therapeutic agents such as angiotensin-converting enzyme inhibitors, AT₁ receptor antagonists, and diuretics.

Preventative Therapy

By potentiating the effects of the natriuretic peptides, compounds of the invention are also expected to be useful in preventative therapy, due to the antihypertrophic and 10 antifibrotic effects of the natriuretic peptides (see Potter et al. (2009) *Handbook of Experimental Pharmacology* 191:341-366), for example in preventing the progression of cardiac insufficiency after myocardial infarction, preventing arterial restenosis after angioplasty, preventing thickening of blood vessel walls after vascular operations, preventing atherosclerosis, and preventing diabetic angiopathy.

15 *Glaucoma*

By potentiating the effects of the natriuretic peptides, compounds of the invention are expected to be useful to treat glaucoma. See, for example, Diestelhorst et al. (1989) *International Ophthalmology* 12:99-101. When used to treat glaucoma, compounds of the invention may be combined with one or more additional anti-glaucoma agents.

20 *Pain Relief*

As NEP inhibitors, compounds of the invention are expected to inhibit the degradation of endogenous enkephalins and thus such compounds may also find utility as analgesics. See, for example, Roques et al. (1980) *Nature* 288:286-288 and Thanawala et al. (2008) *Current Drug Targets* 9:887-894. When used to treat pain, compounds of the 25 invention may be combined with one or more additional antinociceptive drugs such as aminopeptidase N or dipeptidyl peptidase III inhibitors, non-steroidal anti-inflammatory agents, monoamine reuptake inhibitors, muscle relaxants, NMDA receptor antagonists, opioid receptor agonists, 5-HT_{1D} serotonin receptor agonists, and tricyclic antidepressants.

Other Utilities

30 Due to their NEP inhibition properties, compounds of the invention are also expected to be useful as antitussive agents, as well as find utility in the treatment of portal hypertension associated with liver cirrhosis (see Sansoe et al. (2005) *J. Hepatol.* 43:791-798), cancer (see Vesely (2005) *J. Investigative Med.* 53:360-365), depression (see Noble

et al. (2007) *Exp. Opin. Ther. Targets* 11:145-159), menstrual disorders, preterm labor, pre-eclampsia, endometriosis, reproductive disorders (for example, male and female infertility, polycystic ovarian syndrome, implantation failure), and male and female sexual dysfunction, including male erectile dysfunction and female sexual arousal disorder. More 5 specifically, the compounds of the invention are expected to be useful in treating female sexual dysfunction (see Pryde et al. (2006) *J. Med. Chem.* 49:4409-4424), which is often defined as a female patient's difficulty or inability to find satisfaction in sexual expression. This covers a variety of diverse female sexual disorders including, by way of illustration and not limitation, hypoactive sexual desire disorder, sexual arousal disorder, orgasmic 10 disorder and sexual pain disorder. When used to treat such disorders, especially female sexual dysfunction, compounds of the invention may be combined with one or more of the following secondary agents: PDE-V inhibitors, dopamine agonists, estrogen receptor agonists and/or antagonists, androgens, and estrogens. Due to their NEP inhibition properties, compounds of the invention are also expected to have anti-inflammatory 15 properties, and are expected to have utility as such, particularly when used in combination with statins.

Recent studies suggest that NEP plays a role in regulating nerve function in insulin-deficient diabetes and diet induced obesity. Coppey et al. (2011) *Neuropharmacology* 60:259-266. Therefore, due to their NEP inhibition properties, compounds of the invention 20 are also expected to be useful in providing protection from nerve impairment caused by diabetes or diet induced obesity.

The amount of the compound of the invention administered per dose or the total amount administered per day may be predetermined or it may be determined on an individual patient basis by taking into consideration numerous factors, including the nature 25 and severity of the patient's condition, the condition being treated, the age, weight, and general health of the patient, the tolerance of the patient to the active agent, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetics and toxicology profiles of the compound and any secondary agents being administered, and the like. Treatment of a patient suffering from a disease or medical 30 condition (such as hypertension) can begin with a predetermined dosage or a dosage determined by the treating physician, and will continue for a period of time necessary to prevent, ameliorate, suppress, or alleviate the symptoms of the disease or medical condition. Patients undergoing such treatment will typically be monitored on a routine

basis to determine the effectiveness of therapy. For example, in treating hypertension, blood pressure measurements may be used to determine the effectiveness of treatment. Similar indicators for other diseases and conditions described herein, are well known and are readily available to the treating physician. Continuous monitoring by the physician will

5 insure that the optimal amount of the compound of the invention will be administered at any given time, as well as facilitating the determination of the duration of treatment. This is of particular value when secondary agents are also being administered, as their selection, dosage, and duration of therapy may also require adjustment. In this way, the treatment regimen and dosing schedule can be adjusted over the course of therapy so that the lowest

10 amount of active agent that exhibits the desired effectiveness is administered and, further, that administration is continued only so long as is necessary to successfully treat the disease or medical condition.

Research Tools

Since compounds of the invention possess NEP enzyme inhibition activity, such

15 compounds are also useful as research tools for investigating or studying biological systems or samples having a NEP enzyme, for example to study diseases where the NEP enzyme or its peptide substrates plays a role. Any suitable biological system or sample having a NEP enzyme may be employed in such studies which may be conducted either *in vitro* or *in vivo*. Representative biological systems or samples suitable for such studies

20 include, but are not limited to, cells, cellular extracts, plasma membranes, tissue samples, isolated organs, mammals (such as mice, rats, guinea pigs, rabbits, dogs, pigs, humans, and so forth), and the like, with mammals being of particular interest. In one particular embodiment of the invention, NEP enzyme activity in a mammal is inhibited by administering a NEP-inhibiting amount of a compound of the invention. Compounds of

25 the invention can also be used as research tools by conducting biological assays using such compounds.

When used as a research tool, a biological system or sample comprising a NEP enzyme is typically contacted with a NEP enzyme-inhibiting amount of a compound of the invention. After the biological system or sample is exposed to the compound, the effects

30 of inhibiting the NEP enzyme are determined using conventional procedures and equipment, such as by measuring receptor binding in a binding assay or measuring ligand-mediated changes in a functional assay. Exposure encompasses contacting cells or tissue with the compound, administering the compound to a mammal, for example by *i.p.*, *p.o.*,

i.v., *s.c.*, or inhaled administration, and so forth. This determining step can involve measuring a response (a quantitative analysis) or can involve making an observation (a qualitative analysis). Measuring a response involves, for example, determining the effects of the compound on the biological system or sample using conventional procedures and 5 equipment, such as enzyme activity assays and measuring enzyme substrate or product mediated changes in functional assays. The assay results can be used to determine the activity level as well as the amount of compound necessary to achieve the desired result, that is, a NEP enzyme-inhibiting amount. Typically, the determining step will involve determining the effects of inhibiting the NEP enzyme.

10 Additionally, compounds of the invention can be used as research tools for evaluating other chemical compounds, and thus are also useful in screening assays to discover, for example, new compounds having NEP-inhibiting activity. In this manner, a compound of the invention is used as a standard in an assay to allow comparison of the results obtained with a test compound and with compounds of the invention to identify 15 those test compounds that have about equal or superior activity, if any. For example, pK_i data for a test compound or a group of test compounds is compared to the pK_i data for a compound of the invention to identify those test compounds that have the desired properties, for example, test compounds having a pK_i value about equal or superior to a compound of the invention, if any. This aspect of the invention includes, as separate 20 embodiments, both the generation of comparison data (using the appropriate assays) and the analysis of test data to identify test compounds of interest. Thus, a test compound can be evaluated in a biological assay, by a method comprising the steps of: (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; 25 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.

PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

Compounds of the invention are typically administered to a patient in the form of a 30 pharmaceutical composition or formulation. Such pharmaceutical compositions may be administered to the patient by any acceptable route of administration including, but not limited to, oral, rectal, vaginal, nasal, inhaled, topical (including transdermal), ocular, and parenteral modes of administration. Further, the compounds of the invention may be

administered, for example orally, in multiple doses per day (for example, two, three, or four times daily), in a single daily dose or a single weekly dose. It will be understood that any form of the compounds of the invention, (that is, free base, free acid, pharmaceutically acceptable salt, solvate, etc.) that is suitable for the particular mode of administration can 5 be used in the pharmaceutical compositions discussed herein.

Accordingly, in one embodiment, the invention relates to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the invention. The compositions may contain other therapeutic and/or formulating agents if desired. When discussing compositions, the "compound of the invention" may also be 10 referred to herein as the "active agent," to distinguish it from other components of the formulation, such as the carrier. Thus, it is understood that the term "active agent" includes compounds of formula I as well as pharmaceutically acceptable salts, solvates and prodrugs of that compound.

The pharmaceutical compositions of the invention typically contain a 15 therapeutically effective amount of a compound of the invention. Those skilled in the art will recognize, however, that a pharmaceutical composition may contain more than a therapeutically effective amount, such as in bulk compositions, or less than a therapeutically effective amount, that is, individual unit doses designed for multiple administration to achieve a therapeutically effective amount. Typically, the composition 20 will contain from about 0.01-95 wt% of active agent, including, from about 0.01-30 wt%, such as from about 0.01-10 wt%, with the actual amount depending upon the formulation itself, the route of administration, the frequency of dosing, and so forth. In one embodiment, a composition suitable for an oral dosage form, for example, may contain about 5-70 wt%, or from about 10-60 wt% of active agent.

25 Any conventional carrier or excipient may be used in the pharmaceutical compositions of the invention. The choice of a particular carrier or excipient, or combinations of carriers or excipients, will depend on the mode of administration being used to treat a particular patient or type of medical condition or disease state. In this regard, the preparation of a suitable composition for a particular mode of administration is 30 well within the scope of those skilled in the pharmaceutical arts. Additionally, carriers or excipients used in such compositions are commercially available. By way of further illustration, conventional formulation techniques are described in *Remington: The Science and Practice of Pharmacy*, 20th Edition, Lippincott Williams & White, Baltimore,

Maryland (2000); and H. C. Ansel et al., *Pharmaceutical Dosage Forms and Drug Delivery Systems*, 7th Edition, Lippincott Williams & White, Baltimore, Maryland (1999).

Representative examples of materials which can serve as pharmaceutically acceptable carriers include, but are not limited to, the following: sugars, such as lactose, 5 glucose and sucrose; starches, such as corn starch and potato starch; cellulose, such as microcrystalline cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene 10 glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer's solution; ethyl alcohol; phosphate buffer solutions; compressed propellant gases, such as 15 chlorofluorocarbons and hydrofluorocarbons; and other non-toxic compatible substances employed in pharmaceutical compositions.

Pharmaceutical compositions are typically prepared by thoroughly and intimately mixing or blending the active agent with a pharmaceutically acceptable carrier and one or more optional ingredients. The resulting uniformly blended mixture may then be shaped or loaded into tablets, capsules, pills, canisters, cartridges, dispensers and the like using 20 conventional procedures and equipment.

In one embodiment, the pharmaceutical compositions are suitable for oral administration. Suitable compositions for oral administration may be in the form of capsules, tablets, pills, lozenges, cachets, dragees, powders, granules; solutions or suspensions in an aqueous or non-aqueous liquid; oil-in-water or water-in-oil liquid 25 emulsions; elixirs or syrups; and the like; each containing a predetermined amount of the active agent.

When intended for oral administration in a solid dosage form (capsules, tablets, pills and the like), the composition will typically comprise the active agent and one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate. Solid 30 dosage forms may also comprise: fillers or extenders, such as starches, microcrystalline cellulose, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate,

potato or tapioca starch, alginic acid, certain silicates, and/or sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as cetyl alcohol and/or glycerol monostearate; absorbents, such as kaolin and/or bentonite clay; lubricants, such as talc, calcium stearate, 5 magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and/or mixtures thereof; coloring agents; and buffering agents.

Release agents, wetting agents, coating agents, sweetening, flavoring and perfuming agents, preservatives and antioxidants may also be present in the pharmaceutical compositions. Exemplary coating agents for tablets, capsules, pills and like, include those 10 used for enteric coatings, such as cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate, methacrylic acid-methacrylic acid ester copolymers, cellulose acetate trimellitate, carboxymethyl ethyl cellulose, hydroxypropyl methyl cellulose acetate succinate, and the like. Examples of pharmaceutically acceptable antioxidants include: water-soluble antioxidants, such as ascorbic acid, cysteine 15 hydrochloride, sodium bisulfate, sodium metabisulfate sodium sulfite and the like; oil-soluble antioxidants, such as ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, lecithin, propyl gallate, alpha-tocopherol, and the like; and metal-chelating agents, such as citric acid, ethylenediamine tetraacetic acid, sorbitol, tartaric acid, phosphoric acid, and the like.

20 Compositions may also be formulated to provide slow or controlled release of the active agent using, by way of example, hydroxypropyl methyl cellulose in varying proportions or other polymer matrices, liposomes and/or microspheres. In addition, the pharmaceutical compositions of the invention may contain opacifying agents and may be formulated so that they release the active agent only, or preferentially, in a certain portion 25 of the gastrointestinal tract, optionally, in a delayed manner. Examples of embedding compositions which can be used include polymeric substances and waxes. The active agent can also be in micro-encapsulated form, optionally with one or more of the above-described excipients.

30 Suitable liquid dosage forms for oral administration include, by way of illustration, pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. Liquid dosage forms typically comprise the active agent and an inert diluent, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl

benzoate, propylene glycol, 1,3-butylene glycol, oils (for example, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof. Suspensions may contain suspending agents such as, for example, ethoxylated isostearyl alcohols, polyoxyethylene 5 sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

When intended for oral administration, the pharmaceutical compositions of the invention may be packaged in a unit dosage form. The term "unit dosage form" refers to a physically discrete unit suitable for dosing a patient, that is, each unit containing a 10 predetermined quantity of the active agent calculated to produce the desired therapeutic effect either alone or in combination with one or more additional units. For example, such unit dosage forms may be capsules, tablets, pills, and the like.

In another embodiment, the compositions of the invention are suitable for inhaled administration, and will typically be in the form of an aerosol or a powder. Such 15 compositions are generally administered using well-known delivery devices, such as a nebulizer, dry powder, or metered-dose inhaler. Nebulizer devices produce a stream of high velocity air that causes the composition to spray as a mist that is carried into a patient's respiratory tract. An exemplary nebulizer formulation comprises the active agent dissolved in a carrier to form a solution, or micronized and combined with a carrier to form 20 a suspension of micronized particles of respirable size. Dry powder inhalers administer the active agent as a free-flowing powder that is dispersed in a patient's air-stream during inspiration. An exemplary dry powder formulation comprises the active agent dry-blended with an excipient such as lactose, starch, mannitol, dextrose, polylactic acid, polylactide-co-glycolide, and combinations thereof. Metered-dose inhalers discharge a measured 25 amount of the active agent using compressed propellant gas. An exemplary metered-dose formulation comprises a solution or suspension of the active agent in a liquefied propellant, such as a chlorofluorocarbon or hydrofluoroalkane. Optional components of such formulations include co-solvents, such as ethanol or pentane, and surfactants, such as sorbitan trioleate, oleic acid, lecithin, glycerin, and sodium lauryl sulfate. Such 30 compositions are typically prepared by adding chilled or pressurized hydrofluoroalkane to a suitable container containing the active agent, ethanol (if present) and the surfactant (if present). To prepare a suspension, the active agent is micronized and then combined with the propellant. Alternatively, a suspension formulation can be prepared by spray drying a

coating of surfactant on micronized particles of the active agent. The formulation is then loaded into an aerosol canister, which forms a portion of the inhaler.

Compounds of the invention can also be administered parenterally (for example, by subcutaneous, intravenous, intramuscular, or intraperitoneal injection). For such administration, the active agent is provided in a sterile solution, suspension, or emulsion. Exemplary solvents for preparing such formulations include water, saline, low molecular weight alcohols such as propylene glycol, polyethylene glycol, oils, gelatin, fatty acid esters such as ethyl oleate, and the like. Parenteral formulations may also contain one or more anti-oxidants, solubilizers, stabilizers, preservatives, wetting agents, emulsifiers, and dispersing agents. Surfactants, additional stabilizing agents or pH-adjusting agents (acids, bases or buffers) and anti-oxidants are particularly useful to provide stability to the formulation, for example, to minimize or avoid hydrolysis of ester and amide linkages, or dimerization of thiols that may be present in the compound. These formulations may be rendered sterile by use of a sterile injectable medium, a sterilizing agent, filtration, irradiation, or heat. In one particular embodiment, the parenteral formulation comprises an aqueous cyclodextrin solution as the pharmaceutically acceptable carrier. Suitable cyclodextrins include cyclic molecules containing six or more α -D-glucopyranose units linked at the 1,4 positions by a linkages as in amylose, β -cyclodextrin or cycloheptaamyllose. Exemplary cyclodextrins include cyclodextrin derivatives such as hydroxypropyl and sulfobutyl ether cyclodextrins such as hydroxypropyl- β -cyclodextrin and sulfobutyl ether β -cyclodextrin. Exemplary buffers for such formulations include carboxylic acid-based buffers such as citrate, lactate and maleate buffer solutions.

Compounds of the invention can also be administered transdermally using known transdermal delivery systems and excipients. For example, the compound can be admixed with permeation enhancers, such as propylene glycol, polyethylene glycol monolaurate, azacycloalkan-2-ones and the like, and incorporated into a patch or similar delivery system. Additional excipients including gelling agents, emulsifiers and buffers, may be used in such transdermal compositions if desired.

Secondary Agents

The compounds of the invention may be useful as the sole treatment of a disease or may be combined with one or more other therapeutic agents in order to obtain the desired therapeutic effect. Thus, in one embodiment, pharmaceutical compositions of the invention contain other drugs that are co-administered with a compound of the invention.

For example, the composition may further comprise one or more drugs (also referred to as "secondary agents(s)"). Such therapeutic agents are well known in the art, and include adenosine receptor antagonists, α -adrenergic receptor antagonists, β_1 -adrenergic receptor antagonists, β_2 -adrenergic receptor agonists, dual-acting β -adrenergic receptor antagonist/ α_1 -receptor antagonists, advanced glycation end product breakers, aldosterone antagonists, aldosterone synthase inhibitors, aminopeptidase N inhibitors, androgens, angiotensin-converting enzyme inhibitors and dual-acting angiotensin-converting enzyme/neprilysin inhibitors, angiotensin-converting enzyme 2 activators and stimulators, angiotensin-II vaccines, anticoagulants, anti-diabetic agents, antidiarrheal agents, anti-10 glaucoma agents, anti-lipid agents, antinociceptive agents, anti-thrombotic agents, AT₁ receptor antagonists and dual-acting AT₁ receptor antagonist/neprilysin inhibitors and multifunctional angiotensin receptor blockers, bradykinin receptor antagonists, calcium channel blockers, chymase inhibitors, digoxin, diuretics, dopamine agonists, endothelin converting enzyme inhibitors, endothelin receptor antagonists, HMG-CoA reductase 15 inhibitors, estrogens, estrogen receptor agonists and/or antagonists, monoamine reuptake inhibitors, muscle relaxants, natriuretic peptides and their analogs, natriuretic peptide clearance receptor antagonists, neprilysin inhibitors, nitric oxide donors, non-steroidal anti-inflammatory agents, N-methyl D-aspartate receptor antagonists, opioid receptor agonists, phosphodiesterase inhibitors, prostaglandin analogs, prostaglandin receptor agonists, renin 20 inhibitors, selective serotonin reuptake inhibitors, sodium channel blocker, soluble guanylate cyclase stimulators and activators, tricyclic antidepressants, vasopressin receptor antagonists, and combinations thereof. Specific examples of these agents are detailed herein.

Accordingly, in yet another aspect of the invention, a pharmaceutical composition 25 comprises a compound of the invention, a second active agent, and a pharmaceutically acceptable carrier. Third, fourth etc. active agents may also be included in the composition. In combination therapy, the amount of compound of the invention that is administered, as well as the amount of secondary agents, may be less than the amount typically administered in monotherapy.

30 Compounds of the invention may be physically mixed with the second active agent to form a composition containing both agents; or each agent may be present in separate and distinct compositions which are administered to the patient simultaneously or at separate times. For example, a compound of the invention can be combined with a second active

agent using conventional procedures and equipment to form a combination of active agents comprising a compound of the invention and a second active agent. Additionally, the active agents may be combined with a pharmaceutically acceptable carrier to form a pharmaceutical composition comprising a compound of the invention, a second active 5 agent and a pharmaceutically acceptable carrier. In this embodiment, the components of the composition are typically mixed or blended to create a physical mixture. The physical mixture is then administered in a therapeutically effective amount using any of the routes described herein.

Alternatively, the active agents may remain separate and distinct before 10 administration to the patient. In this embodiment, the agents are not physically mixed together before administration but are administered simultaneously or at separate times as separate compositions. Such compositions can be packaged separately or may be packaged together in a kit. When administered at separate times, the secondary agent will typically be administered less than 24 hours after administration of the compound of the invention, 15 ranging anywhere from concurrent with administration of the compound of the invention to about 24 hours post-dose. This is also referred to as sequential administration. Thus, a compound of the invention can be orally administered simultaneously or sequentially with another active agent using two tablets, with one tablet for each active agent, where sequential may mean being administered immediately after administration of the 20 compound of the invention or at some predetermined time later (for example, one hour later or three hours later). It is also contemplated that the secondary agent may be administered more than 24 hours after administration of the compound of the invention. Alternatively, the combination may be administered by different routes of administration, that is, one orally and the other by inhalation.

25 In one embodiment, the kit comprises a first dosage form comprising a compound of the invention and at least one additional dosage form comprising one or more of the secondary agents set forth herein, in quantities sufficient to carry out the methods of the invention. The first dosage form and the second (or third, etc.) dosage form together comprise a therapeutically effective amount of active agents for the treatment or prevention 30 of a disease or medical condition in a patient.

Secondary agent(s), when included, are present in a therapeutically effective amount such that they are typically administered in an amount that produces a therapeutically beneficial effect when co-administered with a compound of the invention.

The secondary agent can be in the form of a pharmaceutically acceptable salt, solvate, optically pure stereoisomer, and so forth. The secondary agent may also be in the form of a prodrug, for example, a compound having a carboxylic acid group that has been esterified. Thus, secondary agents listed herein are intended to include all such forms, and 5 are commercially available or can be prepared using conventional procedures and reagents.

In one embodiment, compounds of the invention are administered in combination with an adenosine receptor antagonist, representative examples of which include, but are not limited to, naxifylline, rolofylline, SLV-320, theophylline, and tonapofylline.

10 In one embodiment, compounds of the invention are administered in combination with an α -adrenergic receptor antagonist, representative examples of which include, but are not limited to, doxazosin, prazosin, tamsulosin, and terazosin.

Compounds of the invention may also be administered in combination with a β_1 -adrenergic receptor antagonist (" β_1 -blockers"). Representative β_1 -blockers include, but are not limited to, acebutolol, alprenolol, amosulalol, arotinolol, atenolol, befunolol, betaxolol, 15 bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol, bupranolol, bubridine, butofilolol, carazolol, carteolol, carvedilol, celiprolol, cetamolol, cloranolol, dilevalol, epanolol, esmolol, indenolol, labetolol, levobunolol, mepindolol, metipranolol, metoprolol such as metoprolol succinate and metoprolol tartrate, moprolol, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, penbutolol, perbutolol, pindolol, 20 practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilsolol, timolol, toliprolol, xibenolol, and combinations thereof. In one particular embodiment, the β_1 -antagonist is selected from atenolol, bisoprolol, metoprolol, propranolol, sotalol, and combinations thereof. Typically, the β_1 -blocker will be administered in an amount sufficient to provide from about 2-900 mg per dose.

25 In one embodiment, compounds of the invention are administered in combination with a β_2 -adrenergic receptor agonist, representative examples of which include, but are not limited to, albuterol, bitolterol, fenoterol, formoterol, indacaterol, isoetharine, levalbuterol, metaproterenol, pirbuterol, salbutamol, salmefamol, salmeterol, terbutaline, vilanterol, and the like. Typically, the β_2 -adrenergic receptor agonist will be administered in an amount 30 sufficient to provide from about 0.05-500 μ g per dose.

In one embodiment, compounds of the invention are administered in combination with an advanced glycation end product (AGE) breaker, examples of which include, by way of illustration and not limitation, alagebrium (or ALT-711), and TRC4149.

In another embodiment, compounds of the invention are administered in combination with an aldosterone antagonist, representative examples of which include, but are not limited to, eplerenone, spironolactone, and combinations thereof. Typically, the aldosterone antagonist will be administered in an amount sufficient to provide from about 5 5-300 mg per day.

In one embodiment, compounds of the invention are administered in combination with an aminopeptidase N or dipeptidyl peptidase III inhibitor, examples of which include, by way of illustration and not limitation, bestatin and PC18 (2-amino-4-methylsulfonyl butane thiol, methionine thiol).

10 Compounds of the invention can also be administered in combination with an angiotensin-converting enzyme (ACE) inhibitor. Representative ACE inhibitors include, but are not limited to, accupril, alacepril, benazepril, benazeprilat, captopril, ceranapril, cilazapril, delapril, enalapril, enalaprilat, fosinopril, fosinoprilat, imidapril, lisinopril, moexipril, monopril, moveltopril, pentopril, perindopril, quinapril, quinaprilat, ramipril, 15 ramiprilat, saralasin acetate, spirapril, temocapril, trandolapril, zofenopril, and combinations thereof. In a particular embodiment, the ACE inhibitor is selected from: benazepril, captopril, enalapril, lisinopril, ramipril, and combinations thereof. Typically, the ACE inhibitor will be administered in an amount sufficient to provide from about 1-150 mg per day.

20 In one embodiment, compounds of the invention are administered in combination with a dual-acting agent, such as an angiotensin-converting enzyme/neprilysin (ACE/NEP) inhibitor, examples of which include, but are not limited to: AVE-0848 ((4S,7S,12bR)-7-[3-methyl-2(S)-sulfanylbutyramido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]-benzazepine-4-carboxylic acid); AVE-7688 (ilepatril) and its parent compound; BMS- 25 182657 (2-[2-oxo-3(S)-[3-phenyl-2(S)-sulfanylpropionamido]-2,3,4,5-tetrahydro-1H-1-benzazepin-1-yl]acetic acid); CGS-26303 ([N-[2-(biphenyl-4-yl)-1(S)-(1H-tetrazol-5-yl)ethyl]amino]methylphosphonic acid); CGS-35601 (N-[1-[4-methyl-2(S)-sulfanylpentanamido]cyclopentylcarbonyl]-L-tryptophan); fasidotril; fasidotrilate; enalaprilat; ER-32935 ((3R,6S,9aR)-6-[3(S)-methyl-2(S)-sulfanylpentanamido]-5-oxoperhydrothiazolo[3,2-a]azepine-3-carboxylic acid); gempatriлат; MDL-101264 ((4S,7S,12bR)-7-[2(S)-(2-morpholinoacetylthio)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid); MDL-101287 ([4S-[4a,7a(R*)],12bβ]-7-[2-(carboxymethyl)-3-phenylpropionamido]-6-oxo-

1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid); omapatrilat; RB-105 (N-[2(S)-(mercaptopethyl)-3(R)-phenylbutyl]-L-alanine); sampatrilat; SA-898 ((2R,4R)-N-[2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)thiazolidin-4-ylcarbonyl]-L-phenylalanine); Sch-50690 (N-[1(S)-carboxy-2-[N2-(methanesulfonyl)-L-
5 lysylamino]ethyl]-L-valyl-L-tyrosine); and combinations thereof, may also be included. In one particular embodiment, the ACE/NEP inhibitor is selected from: AVE-7688, enalaprilat, fasidotril, fasidotrilate, omapatrilat, sampatrilat, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an angiotensin-converting enzyme 2 (ACE2) activator or stimulator.

10 In one embodiment, compounds of the invention are administered in combination with an angiotensin-II vaccine, examples of which include, but are not limited to ATR12181 and CYT006-AngQb.

In one embodiment, compounds of the invention are administered in combination with an anticoagulant, representative examples of which include, but are not limited to:

15 coumarins such as warfarin; heparin; and direct thrombin inhibitors such as argatroban, bivalirudin, dabigatran, and lepirudin.

In yet another embodiment, compounds of the invention are administered in combination with an anti-diabetic agent. Representative anti-diabetic agents include injectable drugs as well as orally effective drugs, and combinations thereof. Examples of 20 injectable drugs include, but are not limited to, insulin and insulin derivatives. Examples of orally effective drugs include, but are not limited to: biguanides such as metformin; glucagon antagonists; α -glucosidase inhibitors such as acarbose and miglitol; dipeptidyl peptidase IV inhibitors (DPP-IV inhibitors) such as alogliptin, denagliptin, linagliptin, saxagliptin, sitagliptin, and vildagliptin; meglitinides such as repaglinide; 25 oxadiazolidinediones; sulfonylureas such as chlorpropamide, glimepiride, glipizide, glyburide, and tolazamide; thiazolidinediones such as pioglitazone and rosiglitazone; and combinations thereof.

In another embodiment, compounds of the invention are administered in combination with antidiarrheal treatments. Representative treatment options include, but 30 are not limited to, oral rehydration solutions (ORS), loperamide, diphenoxylate, and bismuth subsalicylate.

In yet another embodiment, a compound of the invention is administered in combination with an anti-glaucoma agent. Representative anti-glaucoma agents include,

but are not limited to: α -adrenergic agonists such as brimonidine; β_1 -adrenergic receptor antagonists; topical β_1 -blockers such as betaxolol, levobunolol, and timolol; carbonic anhydrase inhibitors such as acetazolamide, brinzolamide, or dorzolamide; cholinergic agonists such as cevimeline and DMXB-anabaseine; epinephrine compounds; miotics such 5 as pilocarpine; and prostaglandin analogs.

In yet another embodiment, compounds of the invention are administered in combination with an anti-lipid agent. Representative anti-lipid agents include, but are not limited to: cholesteryl ester transfer protein inhibitors (CETPs) such as anacetrapib, 10 dalcetrapib, and torcetrapib; statins such as atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin; and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an anti-thrombotic agent. Representative anti-thrombotic agents include, but are not limited to: aspirin; anti-platelet agents such as clopidogrel, prasugrel, and ticlopidine; heparin, and combinations thereof.

15 In one embodiment, compounds of the invention are administered in combination with an AT₁ receptor antagonist, also known as angiotensin II type 1 receptor blockers (ARBs). Representative ARBs include, but are not limited to, abitesartan, azilsartan (e.g., azilsartan medoxomil), benzyllosartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, EXP3174, fonsartan, forasartan, glycyllosartan, 20 irbesartan, isoteoline, losartan, medoximil, milfasartan, olmesartan (e.g., olmesartan medoxomil), opomisartan, pratosartan, ripisartan, saprisartan, saralasin, sarmesin, TAK-591, tasosartan, telmisartan, valsartan, zolasartan, and combinations thereof. In a particular embodiment, the ARB is selected from azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, irbesartan, saprisartan, tasosartan, 25 telmisartan, valsartan, and combinations thereof. Exemplary salts and/or prodrugs include candesartan cilexetil, eprosartan mesylate, losartan potassium salt, and olmesartan medoxomil. Typically, the ARB will be administered in an amount sufficient to provide from about 4-600 mg per dose, with exemplary daily dosages ranging from 20-320 mg per day.

30 Compounds of the invention may also be administered in combination with a dual-acting agent, such as an AT₁ receptor antagonist/neprilysin inhibitor (ARB/NEP) inhibitor, examples of which include, but are not limited to, compounds described in U.S.

Publication Nos. 2008/0269305 and 2009/0023228, both to Allegretti et al. filed on April

23, 2008, such as the compound, 4'-{2-ethoxy-4-ethyl-5-[(*S*)-2-mercaptop-4-methylpentanoylamino)-methyl]imidazol-1-ylmethyl}-3'-fluorobiphenyl-2-carboxylic acid.

Compounds of the invention may also be administered in combination with multifunctional angiotensin receptor blockers as described in Kurtz & Klein (2009)

5 *Hypertension Research* 32:826-834.

In one embodiment, compounds of the invention are administered in combination with a bradykinin receptor antagonist, for example, icatibant (HOE-140). It is expected that this combination therapy may present the advantage of preventing angioedema or other unwanted consequences of elevated bradykinin levels.

10 In one embodiment, compounds of the invention are administered in combination with a calcium channel blocker. Representative calcium channel blockers include, but are not limited to, amlodipine, anipamil, aranipine, barnidipine, bencyclane, benidipine, bepridil, clentiazem, cilnidipine, cinnarizine, diltiazem, efondipine, elgodipine, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lercanidipine, 15 lidoflazine, lomerizine, manidipine, mibepradil, nicardipine, nifedipine, niguldipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, perhexiline, prenylamine, ryosidine, semotiadil, terodiline, tiapamil, verapamil, and combinations thereof. In a particular embodiment, the calcium channel blocker is selected from amlodipine, bepridil, diltiazem, felodipine, isradipine, lacidipine, nicardipine, nifedipine, 20 niguldipine, niludipine, nimodipine, nisoldipine, ryosidine, verapamil, and combinations thereof. Typically, the calcium channel blocker will be administered in an amount sufficient to provide from about 2-500 mg per dose.

In one embodiment, compounds of the invention are administered in combination with a chymase inhibitor, such as TPC-806 and 2-(5-formylamino-6-oxo-2-phenyl-1,6-25 dihydropyrimidine-1-yl)-N-[{3,4-dioxo-1-phenyl-7-(2-pyridyloxy)}-2-heptyl]acetamide (NK3201).

In one embodiment, compounds of the invention are administered in combination with a diuretic. Representative diuretics include, but are not limited to: carbonic anhydrase inhibitors such as acetazolamide and dichlorphenamide; loop diuretics, which include 30 sulfonamide derivatives such as acetazolamide, ambuside, azosernide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ethoxolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, triamidine, and xipamide, as well as non-sulfonamide diuretics such as ethacrynic acid and other

phenoxyacetic acid compounds such as tienilic acid, indacrinone and quincarbamate; osmotic diuretics such as mannitol; potassium-sparing diuretics, which include aldosterone antagonists such as spironolactone, and Na^+ channel inhibitors such as amiloride and triamterene; thiazide and thiazide-like diuretics such as althiazide, bendroflumethiazide, 5 benzylhydrochlorothiazide, benzthiazide, buthiazide, chlorthalidone, chlorothiazide, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, fenquizone, flumethiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, meticrane, metolazone, paraflutiazide, polythiazide, quinethazone, teclothiazide, and trichloromethiazide; and combinations thereof. In a particular embodiment, the diuretic is 10 selected from amiloride, bumetanide, chlorothiazide, chlorthalidone, dichlorphenamide, ethacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, metolazone, torsemide, triamterene, and combinations thereof. The diuretic will be administered in an amount sufficient to provide from about 5-50 mg per day, more typically 6-25 mg per day, with common dosages being 6.25 mg, 12.5 mg or 25 15 mg per day.

Compounds of the invention may also be administered in combination with an endothelin converting enzyme (ECE) inhibitor, examples of which include, but are not limited to, phosphoramidon, CGS 26303, and combinations thereof.

In a particular embodiment, compounds of the invention are administered in 20 combination with an endothelin receptor antagonist. Representative endothelin receptor antagonists include, but are not limited to: selective endothelin receptor antagonists that affect endothelin A receptors, such as avosentan, ambrisentan, atrasentan, BQ-123, clazosentan, darusentan, sitaxentan, and zibotentan; and dual endothelin receptor antagonists that affect both endothelin A and B receptors, such as bosentan, macitentan, 25 tezosentan).

In yet another embodiment, a compound of the invention is administered in combination with one or more HMG-CoA reductase inhibitors, which are also known as statins. Representative statins include, but are not limited to, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

30 In one embodiment, compounds of the invention are administered in combination with a monoamine reuptake inhibitor, examples of which include, by way of illustration and not limitation, norepinephrine reuptake inhibitors such as atomoxetine, bupropion and the bupropion metabolite hydroxybupropion, maprotiline, reboxetine, and viloxazine;

selective serotonin reuptake inhibitors (SSRIs) such as citalopram and the citalopram metabolite desmethylcitalopram, dapoxetine, escitalopram (e.g., escitalopram oxalate), fluoxetine and the fluoxetine desmethyl metabolite norfluoxetine, fluvoxamine (e.g., fluvoxamine maleate), paroxetine, sertraline and the sertraline metabolite
5 demethylsertraline; dual serotonin-norepinephrine reuptake inhibitors (SNRIs) such as bicalutamide, duloxetine, milnacipran, nefazodone, and venlafaxine; and combinations thereof.

In another embodiment, compounds of the invention are administered in combination with a muscle relaxant, examples of which include, but are not limited to:
10 carisoprodol, chlorzoxazone, cyclobenzaprine, diflunisal, metaxalone, methocarbamol, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a natriuretic peptide or analog, examples of which include but are not limited to: carperitide, CD-NP (Nile Therapeutics), CU-NP, nesiritide, PL-3994 (Palatin
15 Technologies, Inc.), ularitide, cenderitide, and compounds described in Ogawa et al (2004) *J.Biol.Chem.* 279:28625-31. These compounds are also referred to as natriuretic peptide receptor-A (NPR-A) agonists. In another embodiment, compounds of the invention are administered in combination with a natriuretic peptide clearance receptor (NPR-C) antagonist such as SC-46542, cANF (4-23), and AP-811 (Veale (2000) *Bioorg Med Chem Lett* 10:1949-52). For example, AP-811 has shown synergy when combined with the NEP
20 inhibitor, thiophan (Wegner (1995) *Clin.Exper.Hypert.* 17:861-876).

In another embodiment, compounds of the invention are administered in combination with a neprilysin (NEP) inhibitor. Representative NEP inhibitors include, but are not limited to: AHU-377; candoxatril; candoxatrilat; dexecadotril ((+)-N-[2(R)-
25 (acetylthiomethyl)-3-phenylpropionyl]glycine benzyl ester); CGS-24128 (3-[3-(biphenyl-4-yl)-2-(phosphonomethylamino)propionamido]propionic acid); CGS-24592 ((S)-3-[3-(biphenyl-4-yl)-2-(phosphonomethylamino)propionamido]propionic acid); CGS-25155 (N-[9(R)-(acetylthiomethyl)-10-oxo-1-azacyclodecan-2(S)-ylcarbonyl]-4(R)-hydroxy-L-
30 proline benzyl ester); 3-(l-carbamoylcyclohexyl)propionic acid derivatives described in WO 2006/027680 to Hepworth et al. (Pfizer Inc.); JMV-390-1 (2(R)-benzyl-3-(N-hydroxycarbamoyl)propionyl-L-isoleucyl-L-leucine); ecadotril; phosphoramidon; retrothiophan; RU-42827 (2-(mercaptopethyl)-N-(4-pyridinyl)benzenepropionamide); RU-44004 (N-(4-morpholinyl)-3-phenyl-2-(sulfanyl methyl)propionamide); SCH-32615

((*S*)-N-[N-(1-carboxy-2-phenylethyl)-L-phenylalanyl]- β -alanine) and its prodrug SCH-34826 ((*S*)-N-[N-[1-[(2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]carbonyl]-2-phenylethyl]-L-phenylalanyl]- β -alanine); sialorphin; SCH-42495 (N-[2(*S*)-(acetylsulfanyl methyl)-3-(2-methylphenyl)propionyl]-L-methionine ethyl ester); spinorphin; SQ-28132 (N-[2-5 (mercaptomethyl)-1-oxo-3-phenylpropyl]leucine); SQ-28603 (N-[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]- β -alanine); SQ-29072 (7-[[2-(mercaptomethyl)-1-oxo-3-phenylpropyl]amino]heptanoic acid); thiorphin and its prodrug racecadotril; UK-69578 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]cyclopentyl]carbonyl]amino]cyclohexanecarboxylic acid); UK-447,841 (2-{1-[3-(4-chlorophenyl)propylcarbamoyl]-10 cyclopentylmethyl}-4-methoxybutyric acid); UK-505,749 ((*R*)-2-methyl-3-{1-[3-(2-methylbenzothiazol-6-yl)propylcarbamoyl]cyclopentyl}propionic acid); 5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid and 5-biphenyl-4-yl-4-(3-carboxypropionylamino)-2-methylpentanoic acid ethyl ester (WO 2007/056546); daglutril [(3*S*,2*R*)-3-{1-[2'-(ethoxycarbonyl)-4'-phenylbutyl]-cyclopentan-1-carbonylamino}-15 2,3,4,5-tetrahydro-2-oxo-1H-1-benzazepine-1-acetic acid] described in WO 2007/106708 to Khder et al. (Novartis AG); and combinations thereof. In a particular embodiment, the NEP inhibitor is selected from AHU-377, candoxatril, candoxatrilat, CGS-24128, phosphoramidon, SCH-32615, SCH-34826, SQ-28603, thiorphin, and combinations thereof. In a particular embodiment, the NEP inhibitor is a compound such 20 as daglutril, which also has activity both as an inhibitor of the endothelin converting enzyme (ECE) and of NEP. Other dual acting ECE/NEP compounds can also be used. The NEP inhibitor will be administered in an amount sufficient to provide from about 20-800 mg per day, with typical daily dosages ranging from 50-700 mg per day, more commonly 100-600 or 100-300 mg per day.

25 In one embodiment, compounds of the invention are administered in combination with a nitric oxide donor, examples of which include, but are not limited to nicorandil; organic nitrates such as pentaerythritol tetranitrate; and sydnonimines such as linsidomine and molsidomine.

30 In yet another embodiment, compounds of the invention are administered in combination with a non-steroidal anti-inflammatory agent (NSAID). Representative NSAIDs include, but are not limited to: acemetacin, acetyl salicylic acid, alclofenac, alminoprofen, amfenac, amiprilose, amoxiprin, anirolac, apazone, azapropazone, benorilate, benoxaprofen, bezpiperylon, broperamole, bucloxic acid, carprofen, clidanac,

diclofenac, diflunisal, diftalone, enolicam, etodolac, etoricoxib, fenbufen, fenclofenac, fencloxic acid, fenoprofen, fentiazac, feprazole, flufenamic acid, flufenisal, fluprofen, flurbiprofen, furofenac, ibufenac, ibuprofen, indomethacin, indoprofen, isoxepac, isoxicam, ketoprofen, ketorolac, lofemizole, lornoxicam, meclofenamate, meclofenamic acid, mefenamic acid, meloxicam, mesalamine, miroprofen, mofebutazone, nabumetone, naproxen, niflumic acid, oxaprozin, oxpinac, oxyphenbutazone, phenylbutazone, piroxicam, pirprofen, pranoprofen, salsalate, sudoxicam, sulfasalazine, sulindac, suprofen, tenoxicam, tiopinac, tiaprofenic acid, tioxaprofen, tolfenamic acid, tolmetin, triflumidate, zidometacin, zomepirac, and combinations thereof. In a particular embodiment, the 5 NSAID is selected from etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, oxaprozin, piroxicam, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with an N-methyl d-aspartate (NMDA) receptor antagonist, examples of which include, by way of illustration and not limitation, including amantadine, dextromethorphan, 10 dextropropoxyphene, ketamine, ketobemidone, memantine, methadone, and so forth.

In still another embodiment, compounds of the invention are administered in combination with an opioid receptor agonist (also referred to as opioid analgesics). Representative opioid receptor agonists include, but are not limited to: buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, 15 levallorphan, levorphanol, meperidine, methadone, morphine, nalbuphine, nalnefene, nalorphine, naloxone, naltrexone, nalorphine, oxycodone, oxymorphone, pentazocine, propoxyphene, tramadol, and combinations thereof. In certain embodiments, the opioid receptor agonist is selected from codeine, dihydrocodeine, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, and combinations thereof.

20 In a particular embodiment, compounds of the invention are administered in combination with a phosphodiesterase (PDE) inhibitor, particularly a PDE-V inhibitor. Representative PDE-V inhibitors include, but are not limited to, avanafil, lodenafil, mirodenafil, sildenafil (Revatio[®]), tadalafil (Adcirca[®]), vardenafil (Levitra[®]), and udenafil.

25 In another embodiment, compounds of the invention are administered in combination with a prostaglandin analog (also referred to as prostanoids or prostacyclin analogs). Representative prostaglandin analogs include, but are not limited to, beraprost sodium, bimatoprost, epoprostenol, iloprost, latanoprost, tafluprost, travoprost, and treprostinal, with bimatoprost, latanoprost, and tafluprost being of particular interest.

In yet another embodiment, compounds of the invention are administered in combination with a prostaglandin receptor agonist, examples of which include, but are not limited to, bimatoprost, latanoprost, travoprost, and so forth.

Compounds of the invention may also be administered in combination with a renin 5 inhibitor, examples of which include, but are not limited to, aliskiren, enalkiren, remikiren, and combinations thereof.

In another embodiment, compounds of the invention are administered in combination with a selective serotonin reuptake inhibitor (SSRI). Representative SSRIs include, but are not limited to: citalopram and the citalopram metabolite 10 desmethylcitalopram, dapoxetine, escitalopram (e.g., escitalopram oxalate), fluoxetine and the fluoxetine desmethyl metabolite norfluoxetine, fluvoxamine (e.g., fluvoxamine maleate), paroxetine, sertraline and the sertraline metabolite demethylsertraline, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination 15 with a 5-HT_{1D} serotonin receptor agonist, examples of which include, by way of illustration and not limitation, triptans such as almotriptan, avitriptan, eletriptan, frovatriptan, naratriptan rizatriptan, sumatriptan, and zolmitriptan.

In one embodiment, compounds of the invention are administered in combination with a sodium channel blocker, examples of which include, by way of illustration and not 20 limitation, carbamazepine, fosphenytoin, lamotrigine, lidocaine, mexiletine, oxcarbazepine, phenytoin, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a soluble guanylate cyclase stimulator or activator, examples of which include, but are not limited to ataciguat, riociguat, and combinations thereof.

25 In one embodiment, compounds of the invention are administered in combination with a tricyclic antidepressant (TCA), examples of which include, by way of illustration and not limitation, amitriptyline, amitriptylinoxide, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine, dosulepin, doxepin, imipramine, imipraminoxide, lofepramine, melitracen, metapramine, nitroxazepine, nortriptyline, 30 noxiptiline, pipofezine, propizepine, protriptyline, quinupramine, and combinations thereof.

In one embodiment, compounds of the invention are administered in combination with a vasopressin receptor antagonist, examples of which include, by way of illustration

and not limitation, conivaptan and tolvaptan.

Combined secondary therapeutic agents may also be helpful in further combination therapy with compounds of the invention. For example, compounds of the invention can be combined with a diuretic and an ARB, or a calcium channel blocker and an ARB, or a diuretic and an ACE inhibitor, or a calcium channel blocker and a statin. Specific examples include, a combination of the ACE inhibitor enalapril (in the maleate salt form) and the diuretic hydrochlorothiazide, which is sold under the mark Vaseretic®, or a combination of the calcium channel blocker amlodipine (in the besylate salt form) and the ARB olmesartan (in the medoxomil prodrug form), or a combination of a calcium channel blocker and a statin, all may also be used with the compounds of the invention. Other therapeutic agents such as α_2 -adrenergic receptor agonists and vasopressin receptor antagonists may also be helpful in combination therapy. Exemplary α_2 -adrenergic receptor agonists include clonidine, dexmedetomidine, and guanfacine.

The following formulations illustrate representative pharmaceutical compositions of the invention.

Exemplary Hard Gelatin Capsules For Oral Administration

A compound of the invention (50 g), 440 g spray-dried lactose and 10 g magnesium stearate are thoroughly blended. The resulting composition is then loaded into hard gelatin capsules (500 mg of composition per capsule). Alternately, a compound of the invention (20 mg) is thoroughly blended with starch (89 mg), microcrystalline cellulose (89 mg) and magnesium stearate (2 mg). The mixture is then passed through a No. 45 mesh U.S. sieve and loaded into a hard gelatin capsule (200 mg of composition per capsule).

Alternately, a compound of the invention (30 g), a secondary agent (20 g), 440 g spray-dried lactose and 10 g magnesium stearate are thoroughly blended, and processed as described above.

Exemplary Gelatin Capsule Formulation For Oral Administration

A compound of the invention (100 mg) is thoroughly blended with polyoxyethylene sorbitan monooleate (50 mg) and starch powder (250 mg). The mixture is then loaded into a gelatin capsule (400 mg of composition per capsule). Alternately, a compound of the invention (70 mg) and a secondary agent (30 mg) are thoroughly blended with polyoxyethylene sorbitan monooleate (50 mg) and starch powder (250 mg), and the resulting mixture loaded into a gelatin capsule (400 mg of composition per capsule).

Alternately, a compound of the invention (40 mg) is thoroughly blended with

microcrystalline cellulose (Avicel PH 103; 259.2 mg) and magnesium stearate (0.8 mg). The mixture is then loaded into a gelatin capsule (Size #1, White, Opaque) (300 mg of composition per capsule).

Exemplary Tablet Formulation For Oral Administration

5 A compound of the invention (10 mg), starch (45 mg) and microcrystalline cellulose (35 mg) are passed through a No. 20 mesh U.S. sieve and mixed thoroughly. The granules so produced are dried at 50-60 °C and passed through a No. 16 mesh U.S. sieve. A solution of polyvinylpyrrolidone (4 mg as a 10 % solution in sterile water) is mixed with sodium carboxymethyl starch (4.5 mg), magnesium stearate (0.5 mg), and talc (1 mg), and 10 this mixture is then passed through a No. 16 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc are then added to the granules. After mixing, the mixture is compressed on a tablet machine to afford a tablet weighing 100 mg.

15 Alternately, a compound of the invention (250 mg) is thoroughly blended with microcrystalline cellulose (400 mg), silicon dioxide fumed (10 mg), and stearic acid (5 mg). The mixture is then compressed to form tablets (665 mg of composition per tablet).

Alternately, a compound of the invention (400 mg) is thoroughly blended with cornstarch (50 mg), croscarmellose sodium (25 mg), lactose (120 mg), and magnesium stearate (5 mg). The mixture is then compressed to form a single-scored tablet (600 mg of composition per tablet).

20 Alternately, a compound of the invention (100 mg) is thoroughly blended with cornstarch (100 mg) with an aqueous solution of gelatin (20 mg). The mixture is dried and ground to a fine powder. Microcrystalline cellulose (50 mg) and magnesium stearate (5 mg) are then admixed with the gelatin formulation, granulated and the resulting mixture compressed to form tablets (100 mg of the compound of the invention per tablet).

25 *Exemplary Suspension Formulation For Oral Administration*

The following ingredients are mixed to form a suspension containing 100 mg of the compound of the invention per 10 mL of suspension:

Ingredients	Amount
Compound of the invention	1.0 g
Fumaric acid	0.5 g
Sodium chloride	2.0 g
Methyl paraben	0.15 g
Propyl paraben	0.05 g
Granulated sugar	25.5 g
Sorbitol (70% solution)	12.85 g
Veegum® K (magnesium aluminum silicate)	1.0 g

Ingredients	Amount
Flavoring	0.035 mL
Colorings	0.5 mg
Distilled water	q.s. to 100 mL

Exemplary Liquid Formulation For Oral Administration

A suitable liquid formulation is one with a carboxylic acid-based buffer such as citrate, lactate and maleate buffer solutions. For example, a compound of the invention (which may be pre-mixed with DMSO) is blended with a 100 mM ammonium citrate buffer and the pH adjusted to pH 5, or is blended with a 100 mM citric acid solution and the pH adjusted to pH 2. Such solutions may also include a solubilizing excipient such as a cyclodextrin, for example the solution may include 10 wt% hydroxypropyl- β -cyclodextrin.

Other suitable formulations include a 5% NaHCO₃ solution, with or without cyclodextrin.

Exemplary Injectable Formulation For Administration By Injection

A compound of the invention (0.2 g) is blended with 0.4 M sodium acetate buffer solution (2.0 mL). The pH of the resulting solution is adjusted to pH 4 using 0.5 N aqueous hydrochloric acid or 0.5 N aqueous sodium hydroxide, as necessary, and then sufficient water for injection is added to provide a total volume of 20 mL. The mixture is then filtered through a sterile filter (0.22 micron) to provide a sterile solution suitable for administration by injection.

Exemplary Compositions For Administration By Inhalation

A compound of the invention (0.2 mg) is micronized and then blended with lactose (25 mg). This blended mixture is then loaded into a gelatin inhalation cartridge. The contents of the cartridge are administered using a dry powder inhaler, for example.

Alternately, a micronized compound of the invention (10 g) is dispersed in a solution prepared by dissolving lecithin (0.2 g) in demineralized water (200 mL). The resulting suspension is spray dried and then micronized to form a micronized composition comprising particles having a mean diameter less than about 1.5 μ m. The micronized composition is then loaded into metered-dose inhaler cartridges containing pressurized 1,1,1,2-tetrafluoroethane in an amount sufficient to provide about 10 μ g to about 500 μ g of the compound of the invention per dose when administered by the inhaler.

Alternately, a compound of the invention (25 mg) is dissolved in citrate buffered (pH 5) isotonic saline (125 mL). The mixture is stirred and sonicated until the compound is dissolved. The pH of the solution is checked and adjusted, if necessary, to pH 5 by

slowly adding aqueous 1 N NaOH. The solution is administered using a nebulizer device that provides about 10 μ g to about 500 μ g of the compound of the invention per dose.

EXAMPLES

The following Preparations and Examples are provided to illustrate specific 5 embodiments of the invention. These specific embodiments, however, are not intended to limit the scope of the invention in any way unless specifically indicated.

The following abbreviations have the following meanings unless otherwise indicated and any other abbreviations used herein and not defined have their standard, generally accepted meaning:

10	AcOH	acetic acid
	DCM	dichloromethane or methylene chloride
	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
15	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
	Et ₃ N	triethylamine
	Et ₂ O	diethyl ether
	EtOAc	ethyl acetate
	EtOH	ethanol
20	HATU	<i>N,N,N',N'</i> -tetramethyl- <i>O</i> -(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
	HEPES	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	HOBt	1-hydroxybenzotriazole
	MeCN	acetonitrile
25	MeOH	methanol
	MeTHF	2-methyltetrahydrofuran
	SilicaCat [®] DPP-Pd	silica based diphenylphosphine palladium (II) catalyst
	SilicaCat [®] Pd(0)	silica based palladium (0) catalyst
	THF	tetrahydrofuran
30	Unless noted otherwise, all materials, such as reagents, starting materials and solvents, were purchased from commercial suppliers (such as Sigma-Aldrich, Fluka Riedel-de Haen, and the like) and were used without further purification.	

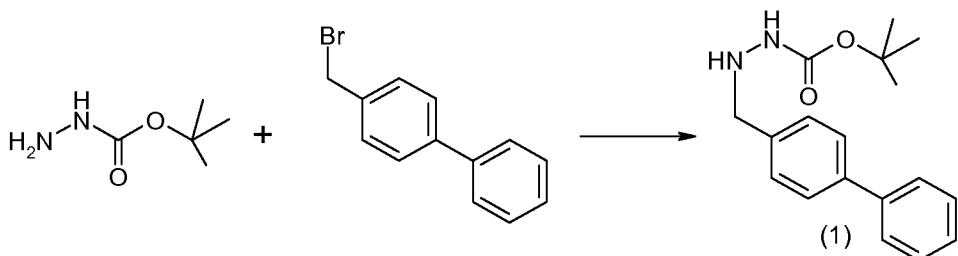
Reactions were run under nitrogen atmosphere, unless noted otherwise. The

progress of reactions were monitored by thin layer chromatography (TLC), analytical high performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of which are given in specific examples. Solvents used in analytical HPLC were as follows: solvent A was 98% H₂O/2% MeCN /1.0 mL/L TFA; solvent B was 90% MeCN/10% H₂O/1.0 mL/L TFA.

Reactions were worked up as described specifically in each preparation for example; commonly reaction mixtures were purified by extraction and other purification methods such as temperature-, and solvent-dependent crystallization, and precipitation. In addition, reaction mixtures were routinely purified by preparative HPLC, typically using Microsorb C18 and Microsorb BDS column packings and conventional eluents. Progress of reactions was typically measured by liquid chromatography mass spectrometry (LCMS). Characterization of isomers were done by Nuclear Overhauser effect spectroscopy (NOE). Characterization of reaction products was routinely carried out by mass and ¹H-NMR spectrometry. For NMR measurement, samples were dissolved in deuterated solvent (CD₃OD, CDCl₃, or DMSO-*d*₆), and ¹H-NMR spectra were acquired with a Varian Gemini 2000 instrument (400 MHz) under standard observation conditions. Mass spectrometric identification of compounds was typically conducted using an electrospray ionization method (ESMS) with an Applied Biosystems (Foster City, CA) model API 150 EX instrument or an Agilent (Palo Alto, CA) model 1200 LC/MSD instrument.

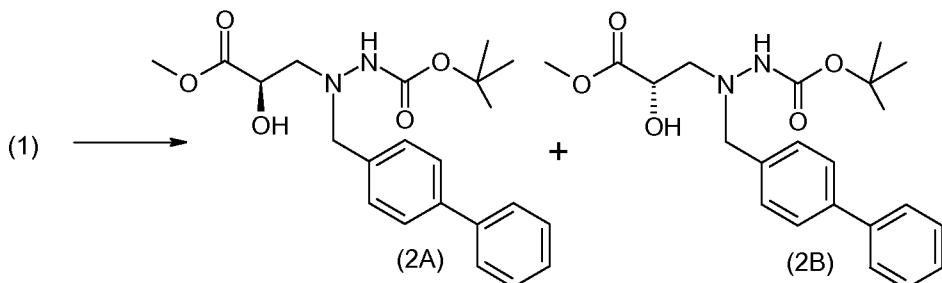
20 Preparation 1

(R)-3-(N-biphenyl-4-ylmethyl-N'-*t*-butoxycarbonylhydrazino)-2-hydroxypropionic Acid Methyl Ester (2A) and (S)-3-(N-biphenyl-4-ylmethyl-N'-*t*-butoxycarbonylhydrazino)-2-hydroxypropionic Acid Methyl Ester (2B)



25 4-(Bromomethyl)biphenyl (2.0 g, 8.1 mmol, 1.0 eq.) and DIPEA (1.4 mL, 1.0 eq.) were dissolved in DMF (40.0 mL). *t*-Butyl carbazate (2.1 g, 16.2 mmol, 2.0 eq.) was added and the mixture was stirred at room temperature overnight. The mixture was partially concentrated, and the residue was partitioned between EtOAc and a saturated

aqueous NaHCO₃ solution. The EtOAc layer was then dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography (0-60% EtOAc/hexanes with 0.5% DIPEA) to yield compound 1, N'-biphenyl-4-ylmethyl-hydrazinecarboxylic acid *t*-butyl ester (1.7 g).

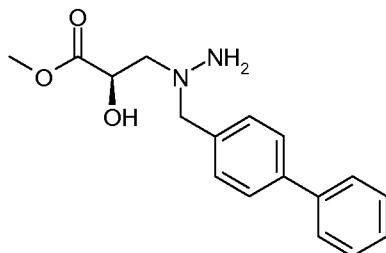


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Compound 1 (830 mg, 2.8 mmol, 1.0 eq.) was dissolved in isopropyl alcohol (20.0 mL). Methyl (2*R*)-glycidate (365 µL, 4.2 mmol, 1.5 eq.) was added and the mixture was heated at 85°C. The mixture was allowed to stir overnight and was then partitioned between EtOAc and a saturated aqueous NaHCO₃ solution. The EtOAc layer was dried over Na₂SO₄ and concentrated to yield compound 2A (803 mg), which was used without further purification. The procedure was repeated using methyl (2*S*)-glycidate (365 µL, 4.2 mmol, 1.5 eq.) to give compound 2B (717 mg), which was used without further purification.

Preparation 2

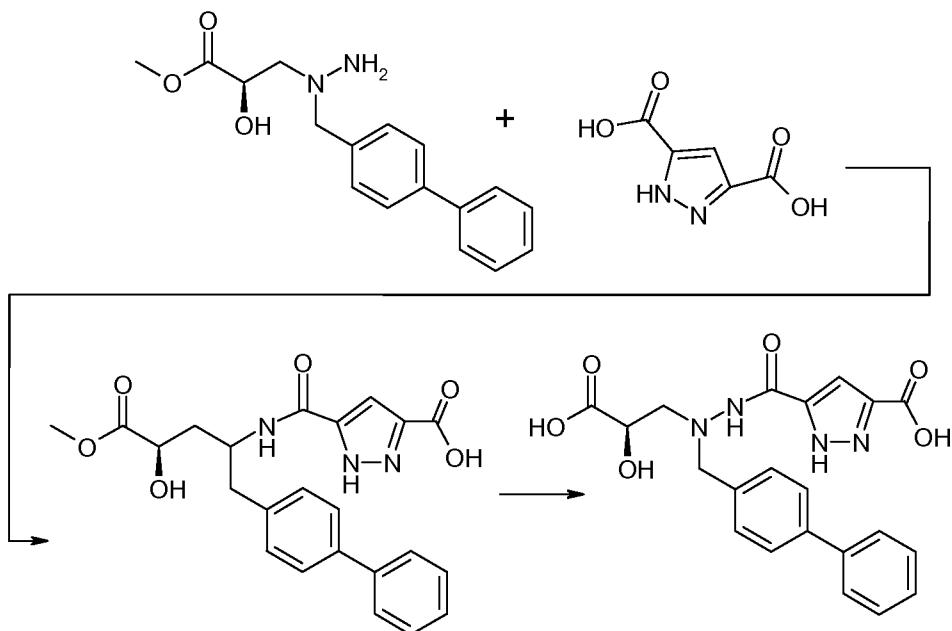
15 (R)-3-(N-Biphenyl-4-ylmethyl-hydrazino)-2-hydroxypropionic Acid Methyl Ester



(*R*)-3-(N-biphenyl-4-ylmethyl-N'-*t*-butoxycarbonylhydrazino)-2-hydroxypropionic acid methyl ester (300 mg, 749 µmol, 1.0 eq.) was dissolved in DCM (3.0 mL). TFA (3.0 mL) was added and the mixture was stirred at room temperature until the reaction was complete (approximately 1 hour). The mixture was concentrated to yield the title compound, which was used without further purification.

EXAMPLE 1

5-[N'-Biphenyl-4-ylmethyl-N'-((*R*)-2-carboxy-2-hydroxyethyl)hydrazinocarbonyl]-1H-pyrazole-3-carboxylic Acid



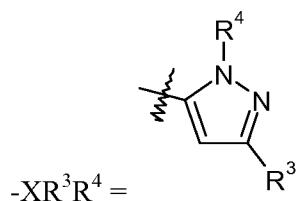
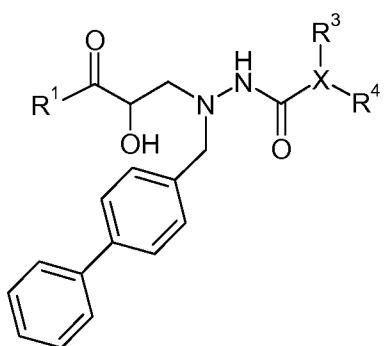
1H-pyrazole-3,5-dicarboxylic acid (58.4 mg, 374 μ mol, 1.2 eq.) was dissolved in DMF (2 mL). DIPEA (163 μ L, 3.0 eq.) was added followed by HATU (142 mg, 374 μ mol, 1.2 eq.) and the resulting solution was stirred for 30 minutes. (R)-3-(N-Biphenyl-4-ylmethyl-hydrazino)-2-hydroxy-propionic acid methyl ester (93.7 mg, 312 μ mol, 1.0 eq.) in DMF (2 mL) was then added and the mixture was stirred at room temperature overnight. The mixture was concentrated and the crude intermediate was used in the next step without further purification.

The crude intermediate was dissolved in THF (2.0 mL) and lithium hydroxide monohydrate (131 mg, 3.1 mmol) in water (2.0 mL) was added. The mixture was stirred at room temperature for approximately 2.5 hours. The reaction was quenched by the addition of AcOH (10 eq.) and the mixture was concentrated. The crude product was purified by preparative HPLC (10-70% MeCN/H₂O) to yield the title compound as a TFA salt (31.2 mg; purity 100%). MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₀N₄O₆, 425.14; found 425.2.

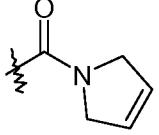
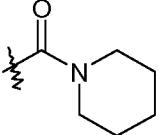
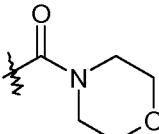
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EXAMPLE 2

Following the procedures described in the examples herein, and substituting the appropriate starting materials and reagents, compounds having the following formula were prepared as TFA salts:



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
1	-OH	-COOH	H	C ₂₁ H ₂₀ N ₄ O ₆	425.14	425.2
2	-OH	-C(O)NH(CH ₂) ₂ -OH	H	C ₂₃ H ₂₅ N ₅ O ₆	468.18	468.4
3	-OH	-C(O)NH(CH ₂) ₂ -SO ₂ NH ₂	H	C ₂₃ H ₂₆ N ₆ O ₇ S	531.16	531.4
4	-OH	-C(O)NH-cyclopropyl	H	C ₂₄ H ₂₅ N ₅ O ₅	464.19	464.4
5	-OH	-C(O)N(CH ₃)-(CH ₂) ₂ -OCH ₃	H	C ₂₅ H ₂₉ N ₅ O ₆	496.21	496.6
6	-OH	-C(O)N(CH ₃) ₂	H	C ₂₃ H ₂₅ N ₅ O ₅	452.19	452.4
7	-OH	-C(O)N(CH ₃)CH ₂ -CH(CH ₃) ₂	H	C ₂₆ H ₃₁ N ₅ O ₅	494.23	494.6
8	-OH		H	C ₂₄ H ₂₅ N ₅ O ₅	464.19	464.4
9	-OH		H	C ₂₅ H ₂₇ N ₅ O ₅	478.20	478.4
10	-OH		H	C ₂₅ H ₂₇ N ₅ O ₆	494.20	494.4
11	-OH		H	C ₂₅ H ₂₇ N ₅ O ₆	494.20	494.4
12	-OH		H	C ₂₅ H ₂₇ N ₅ O ₆	494.20	494.4

Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
13	-OH		H	C ₂₅ H ₂₅ N ₅ O ₅	476.19	476.4
14	-OH		H	C ₂₆ H ₂₉ N ₅ O ₅	492.22	492.4
15	-OH		H	C ₂₅ H ₂₇ N ₅ O ₆	494.20	494.4
16	-OH	phenyl	H	C ₂₆ H ₂₄ N ₄ O ₄	457.18	457.4

1. 5-[N'-Biphenyl-4-ylmethyl-N'-(*(S)*-2-carboxy-2-hydroxyethyl)-hydrazinocarbonyl]-1H-pyrazole-3-carboxylic acid
2. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-(2-hydroxyethylcarbamoyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid
3. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-(2-sulfamoylethylcarbamoyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid
4. (*R*)-3-[N-Biphenyl-4-ylmethyl-N'-(5-cyclopropylcarbamoyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxypropionic acid
- 10 5. (*R*)-3-(N-Biphenyl-4-ylmethyl-N'-(5-[(2-methoxyethyl)methylcarbamoyl]-2H-pyrazole-3-carbonyl)hydrazino)-2-hydroxypropionic acid
6. (*R*)-3-[N-Biphenyl-4-ylmethyl-N'-(5-dimethylcarbamoyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxypropionic acid
7. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-(5-(isobutylmethylcarbamoyl)-2H-pyrazole-3-carbonyl)hydrazino}-2-hydroxypropionic acid
- 15 8. (*R*)-3-{N'-(5-(Azetidine-1-carbonyl)-2H-pyrazole-3-carbonyl)-N-biphenyl-4-ylmethylhydrazino}-2-hydroxypropionic acid
9. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-(5-(pyrrolidine-1-carbonyl)-2H-pyrazole-3-carbonyl)hydrazino}-2-hydroxypropionic acid
- 20 10. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-(5-(3-hydroxy-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carbonyl)hydrazino}-2-hydroxypropionic acid
11. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-(5-((*R*)-3-hydroxy-pyrrolidine-1-carbonyl)-2H-

pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid

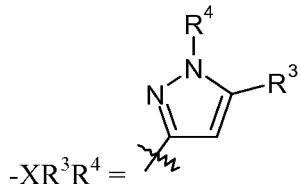
12. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-((*S*)-3-hydroxy-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid

13. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-(2,5-dihydro-pyrrole-1-carbonyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid

14. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-(piperidine-1-carbonyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid

15. (*R*)-3-{N-Biphenyl-4-ylmethyl-N'-[5-(morpholine-4-carbonyl)-2H-pyrazole-3-carbonyl]hydrazino}-2-hydroxypropionic acid

10 16. (*R*)-3-[N-Biphenyl-4-ylmethyl-N'-(5-phenyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxypropionic acid



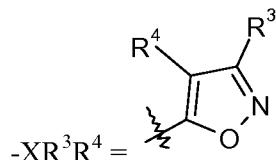
Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
17	-OH	-COOH	2,6-diF, 4-Cl-benzyl	C ₂₈ H ₂₃ ClF ₂ N ₄ O ₆	585.13	585.2
18	-OH	-COOH	2,3,5,6-tetraF, 4-methoxy benzyl	C ₂₉ H ₂₄ F ₄ N ₄ O ₇	617.16	617.4

17. 5-[N'-Biphenyl-4-ylmethyl-N'-(*R*-2-carboxy-2-hydroxyethyl)-

15 hydrazinocarbonyl]-2-(4-chloro-2,6-difluorobenzyl)-2H-pyrazole-3-carboxylic acid

18. 5-[N'-Biphenyl-4-ylmethyl-N'-(*R*-2-carboxy-2-hydroxyethyl)-

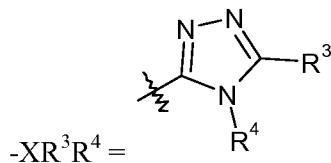
hydrazinocarbonyl]-2-(2,3,5,6-tetrafluoro-4-methoxybenzyl)-2H-pyrazole-3-carboxylic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
19	-OH	-OH	H	C ₂₀ H ₁₉ N ₃ O ₆	398.13	398.4

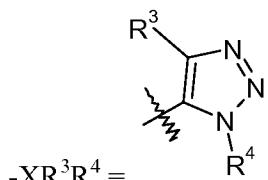
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19. (*R*)-3-[N-Biphenyl-4-ylmethyl-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
20	-OH	H	H	C ₁₉ H ₁₉ N ₅ O ₄	382.14	382.4

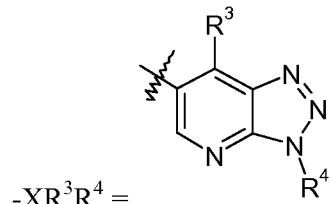
20. (S)-3-[N-Biphenyl-4-ylmethyl-N'-(4H-[1,2,4]triazole-3-carbonyl)hydrazino]-2-hydroxypropionic acid



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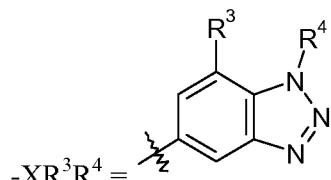
Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
21	-OH	H	H	C ₁₉ H ₁₉ N ₅ O ₄	382.14	382.2

21. (R)-3-[N-Biphenyl-4-ylmethyl-N'-(3H-[1,2,3]triazole-4-carbonyl)hydrazino]-2-hydroxypropionic acid



10

22. (S)-3-[N-Biphenyl-4-ylmethyl-N'-(3H-[1,2,3]triazolo[4,5-b]pyridine-6-carbonyl)hydrazino]-2-hydroxypropionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
23	-OH	F	H	C ₂₃ H ₂₀ FN ₅ O ₄	450.15	450.0
24	-OH	F	H	C ₂₃ H ₂₀ FN ₅ O ₄	450.15	450.0
25	-OH	Cl	H	C ₂₃ H ₂₀ ClN ₅ O ₄	466.12	466.0

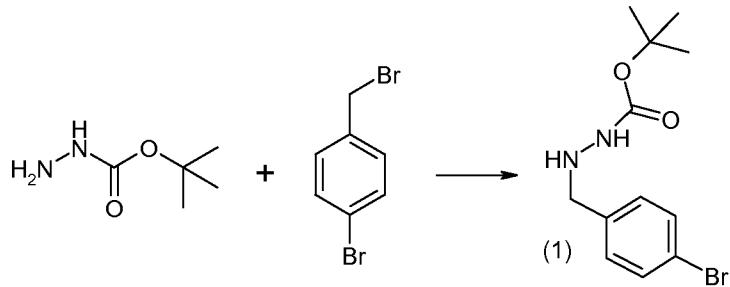
23. (R)-3-[N-Biphenyl-4-ylmethyl-N'-(7-fluoro-1H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid

24. (S)-3-[N-Biphenyl-4-ylmethyl-N'-(7-fluoro-1H-benzotriazole-5-carbonyl)-5 hydrazino]-2-hydroxypropionic acid

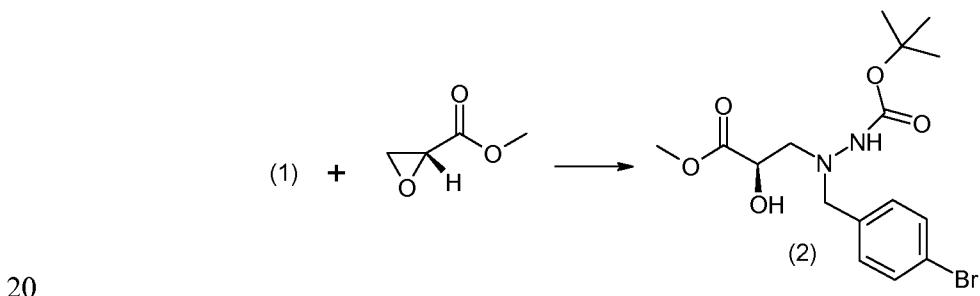
25. (S)-3-[N-Biphenyl-4-ylmethyl-N'-(7-chloro-1H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid

Preparation 3

(R)-3-[N-(4-bromobenzyl)-N'-t-butoxycarbonyl-hydrazino]-2-hydroxy-propionic Acid
 10 Methyl Ester (compound 2) and (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)hydrazino]-2-hydroxypropionic Acid Ethyl Ester (compound 3)

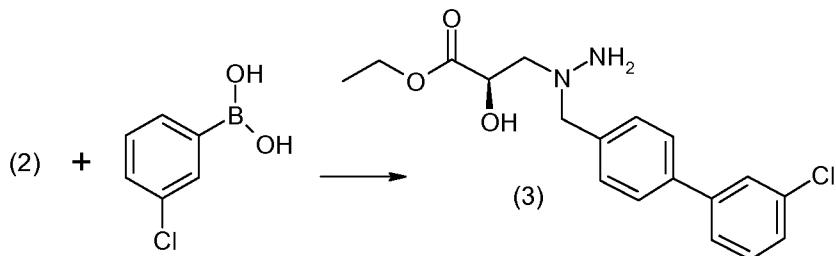


4-Bromobenzyl bromide (5.0 g, 20 mmol) and DIPEA (3.48 mL, 20.0 mmol) were dissolved in DMF (20 mL). *t*-Butyl carbazate (7.9 g, 60.0 mmol) was added and the 15 mixture was stirred at room temperature until the reaction was complete. The mixture was partially concentrated, then the residue was partitioned between EtOAc and a saturated aqueous NaHCO₃ solution. The EtOAc layer was then dried over Na₂SO₄ and concentrated. The crude product was purified by flash chromatography to yield compound 1 (3.8 g).



20 Compound 1 (1.9 g, 6.3 mmol) was dissolved in isopropyl alcohol (26.4 mL). Methyl (2*R*)-glycidate (1.1 mL, 12.6 mmol) was added and the mixture was heated at 90°C until the reaction was complete (~4 days). The mixture was cooled to room temperature

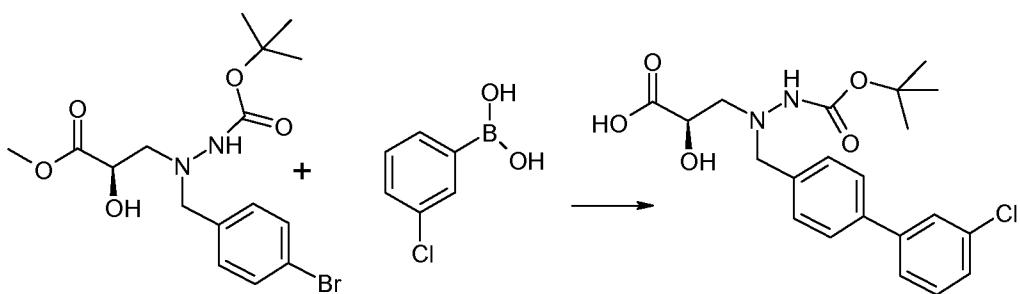
and concentrated to yield compound 2 (2.5 g) as a white solid.



Compound 2 (600 mg, 1 mmol), 3-chlorophenylboronic acid (419 mg, 2.7 mmol), and K_2CO_3 (617 mg, 4.5 mmol) were combined in EtOH (5 mL) and water (1 mL), 5 followed by the addition of SilicaCat®Pd(0) (0.09 mmol/g loading, 1160 mg, 104 μ mol). The mixture was heated at 120°C until the reaction was complete (~30 minutes). The mixture was filtered and concentrated. The residue was dissolved into MeN/AcOH and purified by reverse phase chromatography (55 g column; gradient 30-95% MeCN in water with 0.1%TFA). The clean fractions were collected, concentrated and then dissolved in 10 4M HCl in dioxane (6 mL) and EtOH (6 mL). The mixture was stirred at room temperature overnight, then concentrated to compound 3 (250 mg), which was used without further purification.

Preparation 4

15 (R)-3-[N'-t-Butoxycarbonyl-N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic Acid



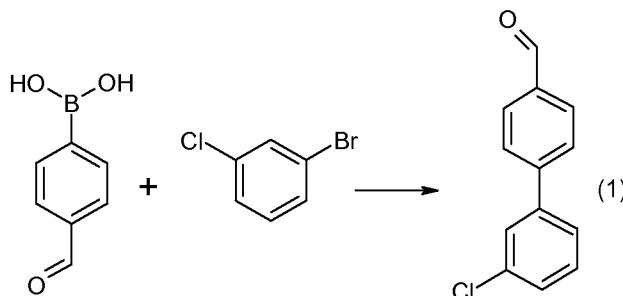
(R)-3-[N-(4-Bromobenzyl)-N'-t-butoxycarbonyl-hydrazino]-2-hydroxy-propionic acid methyl ester (1.0 g, 2.5 mmol), 3-chlorophenylboronic acid (776 mg, 5.0 mmol), and K_2CO_3 (857 mg, 6.2 mmol) were dissolved in a mixture of THF (18 mL) and water (18 mL). The reaction flask was then purged with nitrogen and tetrakis(triphenylphosphine) palladium(0) (286 mg, 248 μ mol) was added. The mixture was stirred at 90°C overnight (~18 hours). The mixture was diluted with saturated aqueous ammonium chloride and extracted with EtOAc. The organic layer was collected, dried and concentrated. The

product was purified (Interchim reverse phase chromatography column, 10-80% MeCN in water) to yield the title compound.

Preparation 5

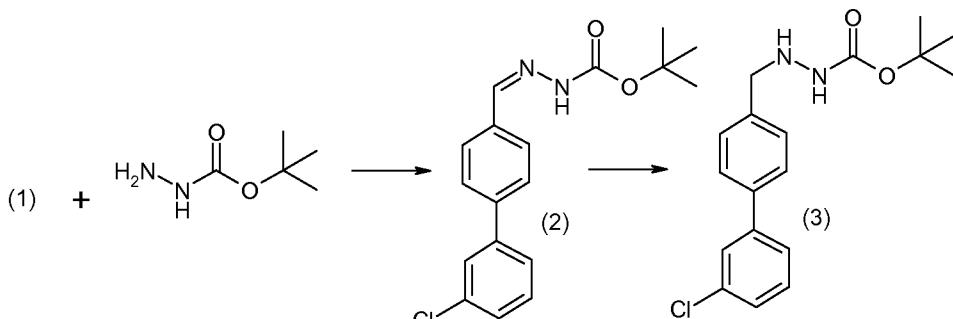
(S)-3-[N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic Acid Isopropyl Ester

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4-Formylphenylboronic acid (18 g, 120 mmol) was combined with MeTHF (300 mL), 3-chlorobromobenzene (14.1 mL, 120 mmol) and 1 M of aqueous Na₂CO₃ (120 mL). The mixture was flushed with nitrogen three times and 1,1'-bis(di-*t*-butylphosphino) 10 ferrocene palladium dichloride (540 mg, 840 µmol) was added. The mixture was again flushed with nitrogen three times, then stirred for 30 minutes while increasing the temperature to 30°C. The mixture was then heated to 50°C until the reaction was complete (~2 hours). The mixture was cooled to room temperature, 1 M aqueous Na₂CO₃ (120 mL) was added, and the mixture was stirred overnight at room temperature. The layers were 15 separated and the organic layer (dark brown color) was collected and dried over NaSO₄ and filtered. It was partially concentrated (to a 150 mL volume. To the solution was added Si-SH (mercaptan modified silica gel, ~2g). The mixture was stirred at room temperature for 2 hours the filtered through Celite®. The cake was washed with MeTHF (100 mL) to yield compound 1 (25 g), which was used without further purification.

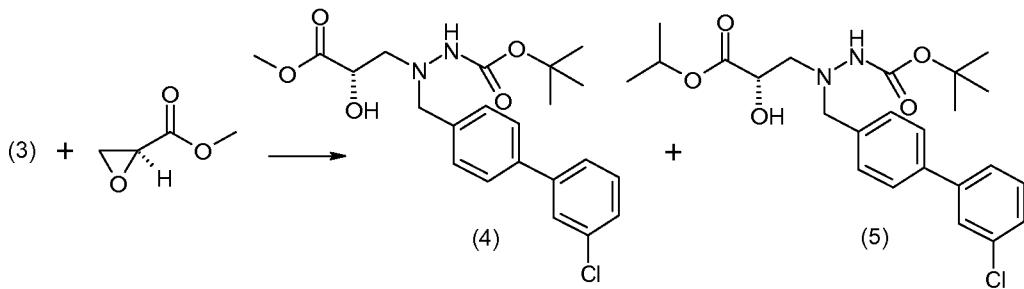
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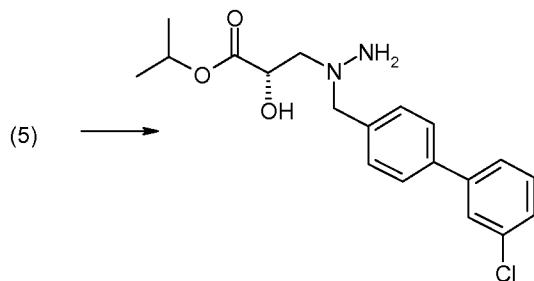
Compound 1 (25.0 g, 115.4 mmol) was combined with MeTHF (150 mL) and *t*-butyl carbazate (15.6 g, 118.0 mmol), and stirred at room temperature for one hour. AcOH

(5 mL) was added and the resulting mixture was stirred for one hour, yield compound 2, which was allowed to sit overnight.

A mixture of Compound 2 in MeTHF (250 mL) and AcOH (20.0 mL) was flushed with nitrogen and cooled with an ice bath to 0°C. After stirring for 30 minutes, sodium 5 cyanoborohydride (8.7 g, 138 mmol) was added over 5 minutes. The resulting mixture was stirred at 0°C for one hour, slowly warmed to room temperature and stirred until completion (~20 hours). The mixture was cooled with an ice bath and 1 M aqueous NaOH (346.2 mL, 346.2 mmol) was added. MeTHF (100 mL, 1.0 mol) was then added and the 10 mixture was allowed to warm to room temperature. The layers were separated and the organic layer was washed with 1 M aqueous NaOH (150 mL, 150 mmol). The layers were separated and the organic layer was dried over Na₂SO₄, filtered, and concentrated to yield an oil, which was dissolved in ether (250 mL, 2.4 mol) and stirred overnight. The mixture was concentrated to yield compound 3 (35 g), which was used without further purification.



15 Compound 3 (20.0 g, 60.1 mmol) and methyl (2*S*)-glycidate (5.8 mL, 66.1 mmol) were combined in isopropyl alcohol (170 mL) and the mixture was heated at 90°C and monitored until the reaction was complete (~several days), adding additional aliquots of methyl (2*S*)-glycidate (1.8 mL and 2 mL) as the reaction progressed. The mixture was cooled to room temperature and allowed to sit overnight. The solids were filtered off, 20 rinsed with isopropyl alcohol and dried (16 g total; 20% compound 4 and 80% compound 5).



Isopropyl alcohol (200 mL, 2 mol) was cooled in an ice bath for 15 minutes.

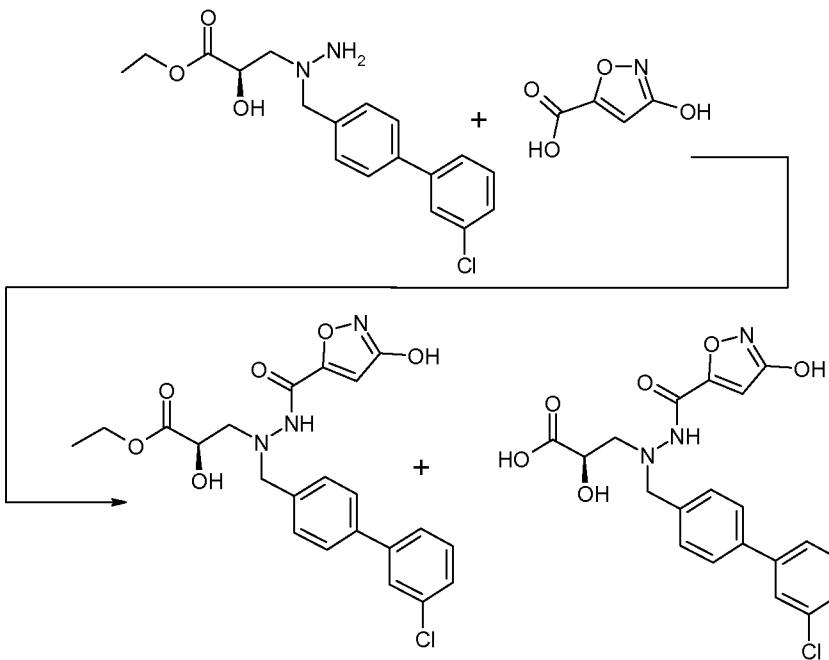
Acetyl chloride (10 mL, 200 mmol) was added, followed by Compound 5 (12.6 g, 27.2 mmol). The resulting mixture was stirred at room temperature for ~48 hours. The precipitate from crude reaction mixture was filtered, dried under vacuum, then rinsed with MeCN (40 mL) and dried under vacuum to yield the title compound (6.8 g; 98% purity).

5

EXAMPLE 3

A. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Ethyl Ester

B. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid

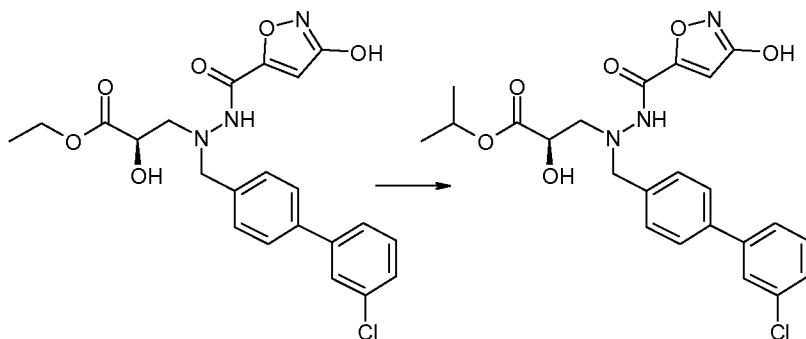


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3-Hydroxyisoxazole-5-carboxylic acid (888 mg, 6.9 mmol), HATU (2.6 g, 6.9 mmol) and DMF were combined and the resulting mixture was stirred for 5 minutes at room temperature. DIPEA (2.3 mL, 13.2 mmol) and *(R)*-3-[N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (2.0 g, 5.7 mmol) were added 15 and the resulting mixture was stirred until the reaction was complete (20 minutes). The reaction was quenched with water, the mixture was diluted with EtOAc, then washed with water and saturated aqueous NaCl. The organic layer was dried, concentrated, and purified by flash chromatography (50-90% EtOAc in hexanes with 0.1% Et₃N). The clean fractions were collected and concentrated. The organic layer, was dissolved into DCM, and the 20 precipitate was filtered and rinsed with DCM to yield the ester compound A as a TFA salt (1.3 g; purity 96%). MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₂ClN₃O₆, 460.12; found 460.4.

A portion of the ester compound A (350 mg) was dissolved in 1M LiOH (4 mL) and EtOH (10 mL). The resulting mixture was stirred at room temperature until the reaction was complete (1 hour). The mixture was concentrated, dissolved in AcOH and purified (C18 reverse phase column). The clean fractions were collected and lyophilized to yield the acid compound B as a TFA salt (280 mg; purity 99%). MS m/z [M+H]⁺ calc'd for C₂₀H₁₈ClN₃O₆, 432.09; found 432.4.

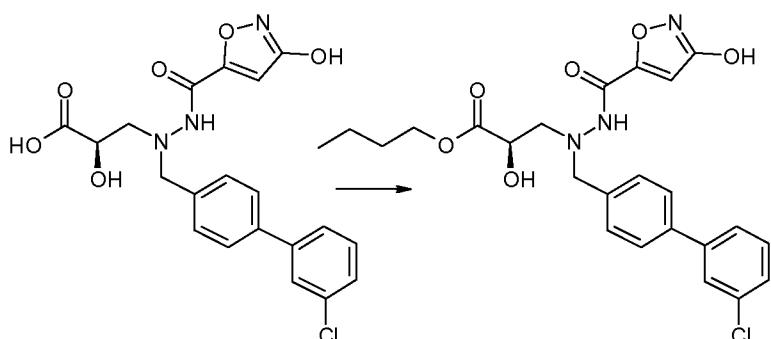
5 C. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isopropyl Ester



10 (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (1.4 g, 3.0 mmol) was dissolved in isopropyl alcohol (20 mL, 0.2 mol) and 4 M HCl in dioxane (9 mL, 40 mmol) was added. The mixture was stirred at room temperature overnight (18 hours). The mixture was warmed to 60°C for 1 hour, then cooled back to room temperature and stirred for 2 hours.

15 The mixture was concentrated and purified (Interchim C18 reverse phase chromatography column, 30-90% MeCN in water for 22 minutes). The clean fractions were combined and lyophilized to yield the title compound (110 mg; purity 98%). MS m/z [M+H]⁺ calc'd for C₂₃H₂₄ClN₃O₆, 474.14; found 474.2.

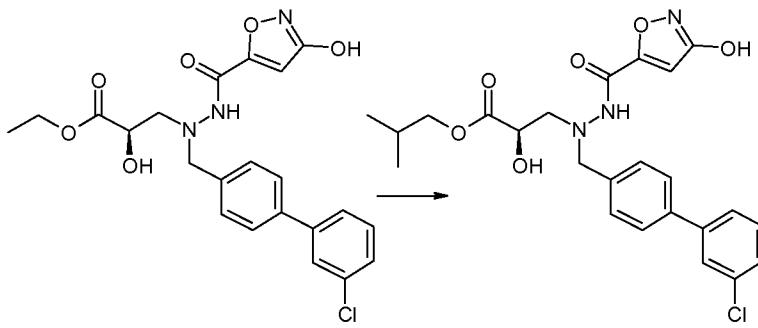
20 D. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Butyl Ester



(*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (60 mg, 0.1 mmol) was dissolved in 1-propanol (4 mL, 50 mmol) and 4 M HCl in dioxane (700 mL, 3 mmol) was added. The mixture was stirred at room temperature until the reaction was complete (~3 hours), then evaporated under reduced pressure and purified (Interchim reverse phase chromatography column, 30-95% MeCN in water with 5% TFA). The clean fractions were combined and lyophilized, then purified by preparative HPLC to yield the title compound (43 mg, purity 95%). MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₆ClN₃O₆, 488.15; found 488.4.

5 E. (*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isobutyl Ester

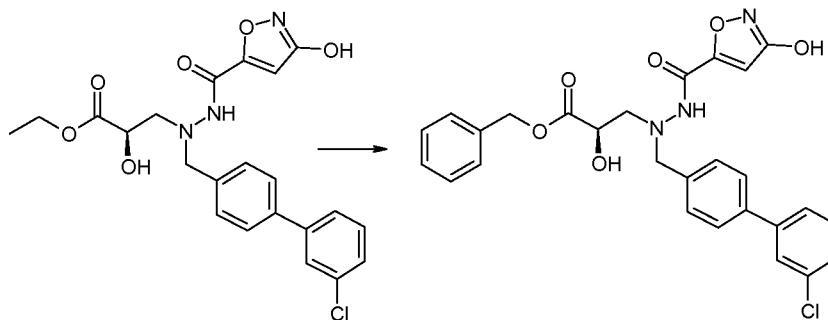
10



(*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (1.5 g, 3.3 mmol) was dissolved in isobutyl alcohol (20 mL, 200 mmol) and 4 M HCl in dioxane (10 mL, 40 mmol) was added. The mixture was stirred at room temperature for 6 hours. The mixture was concentrated, dissolved in water/MeCNe/MeOH, and purified (Interchim C18 reverse phase chromatography column, 25-75% MeCN in water for 22 minutes). The clean fractions were combined and lyophilized to yield the title compound (948 mg; purity 99%). MS *m/z* [M+H]⁺ calc'd for C₂₄H₂₆ClN₃O₆, 488.15; found 488.4.

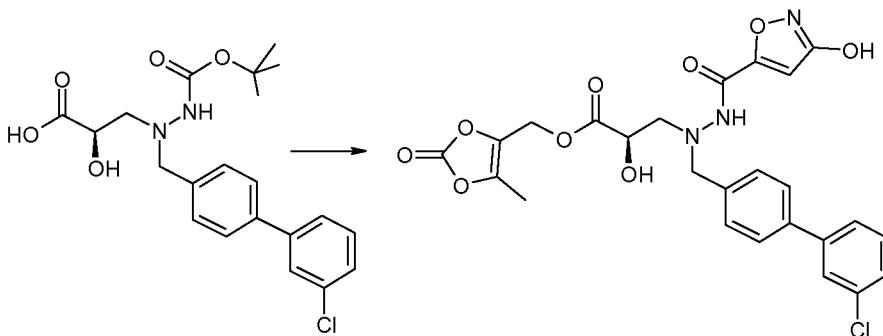
15 F. (*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Benzyl Ester

20



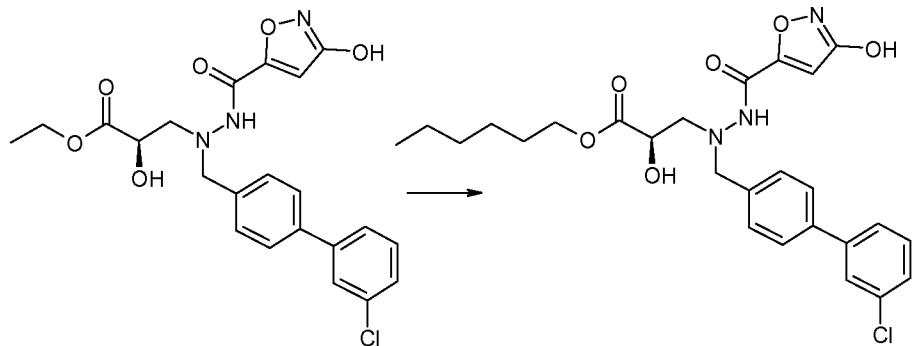
(*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (1.5 g, 3.3 mmol) was dissolved in benzyl alcohol (20 mL, 100 mmol) and 4 M HCl in dioxane (10 mL, 40 mmol) was added. The mixture was stirred at room temperature for 6 hours. The mixture was evaporated under reduced pressure and purified (Interchim C18 reverse phase chromatography column, 30-95% MeCN in water with 0.05% TFA). The clean fractions were combined, lyophilized and purified to yield the title compound (688 mg; purity 98%). MS *m/z* [M+H]⁺ calc'd for C₂₇H₂₄ClN₃O₆, 522.14; found 522.2.

5 G. (*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid 5-methyl-2-oxo-[1,3]dioxol-4-ylmethyl Ester



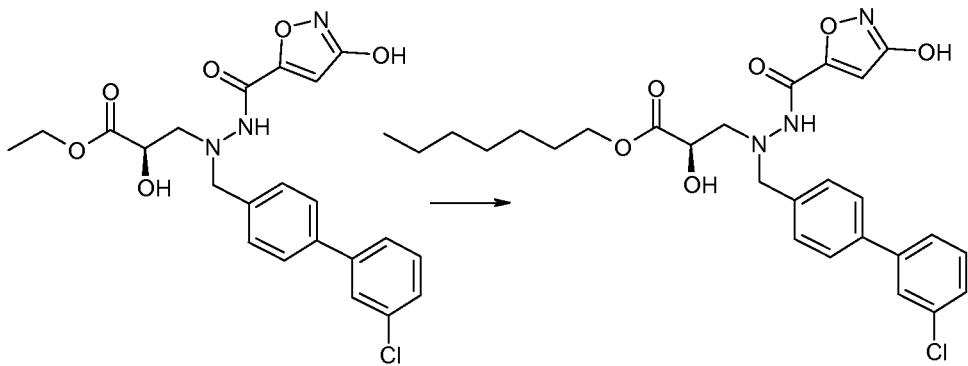
(*R*)-3-[N'-*t*-Butoxycarbonyl-N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid (150 mg, 356 μ mol), HOBT (140 mg, 1.1 mmol), EDC (0.19 mL, 1.1 mmol) were dissolved into DCM. The mixture was stirred for 10 minutes, then 4-hydroxymethyl-5-methyl-[1,3]dioxol-2-one (370 mg, 2.8 mmol) and 4-methylmorpholine (160 μ L, 1.4 mmol) were added. The mixture was stirred at room temperature for 2 hours. The mixture was concentrated and purified (combiflash, 10-95% EtOAc in hexanes with 0.01% Et₃N). The clean fractions were combined and concentrated. MeCN (10 mL, 200 mmol) and 4 M HCl in dioxane (3 mL, 10 mmol) was added and the mixture was stirred at room temperature for 3 hours. The solvent was removed to yield an intermediate HCl salt. 3-hydroxyisoxazole-5-carboxylic acid (55 mg, 430 μ mol) and HATU (160 mg, 430 μ mol) were combined in DMF (5 mL, 60 mmol). The resulting mixture was stirred for 5 minutes followed by the addition of DIPEA (120 μ L, 710 μ mol) and the intermediate HCl salt. The mixture was stirred for 30 minutes then evaporated under reduced pressure and purified by 10 preparative HPLC to yield the title compound as a TFA salt (37 mg; purity 95%). MS *m/z* [M+H]⁺ calc'd for C₂₅H₂₂ClN₃O₉, 544.10; found 544.4.

H. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Hexyl Ester



(R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid ethyl ester (50 mg, 0.1 mmol) was dissolved in 1-hexanol (4 mL, 30 mmol) and 4 M HCl in dioxane (500 μ L, 2 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (21 mg; purity 95%). MS m/z [M+H]⁺ calc'd for C₂₆H₃₀ClN₃O₆, 516.18; found 516.6.

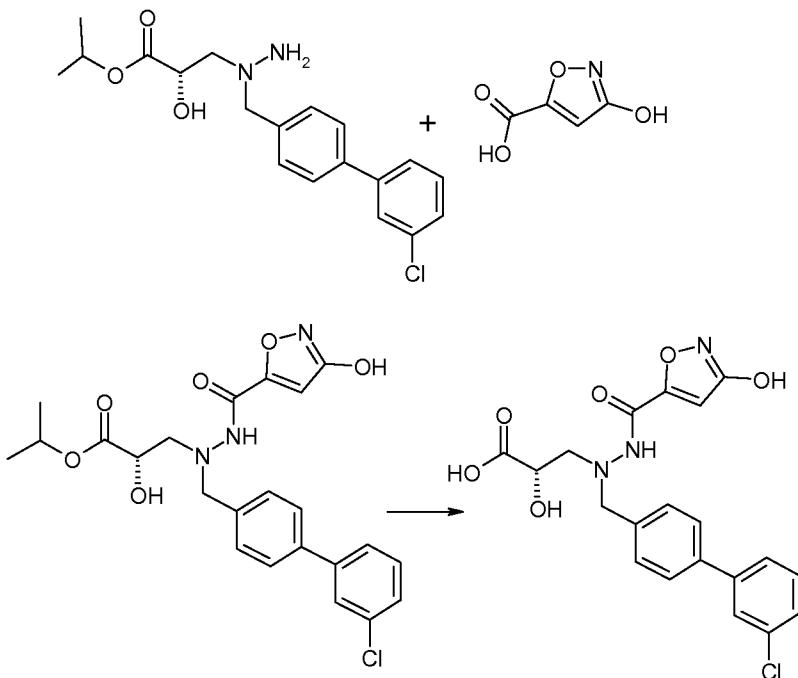
10 I. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Heptyl Ester



(R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid ethyl ester (50 mg, 0.1 mmol) was dissolved in 1-heptanol (4 mL, 30 mmol) and 4 M HCl in dioxane (500 μ L, 2 mmol) was added. The mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (39 mg; purity 95%). MS m/z [M+H]⁺ calc'd for C₂₇H₃₂ClN₃O₆, 530.20; found 530.2.

J. (S)-3-[N-(3'-Chloro-biphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isopropyl Ester

K. (S)-3-[N-(3'-Chloro-biphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydrox-propionic Acid



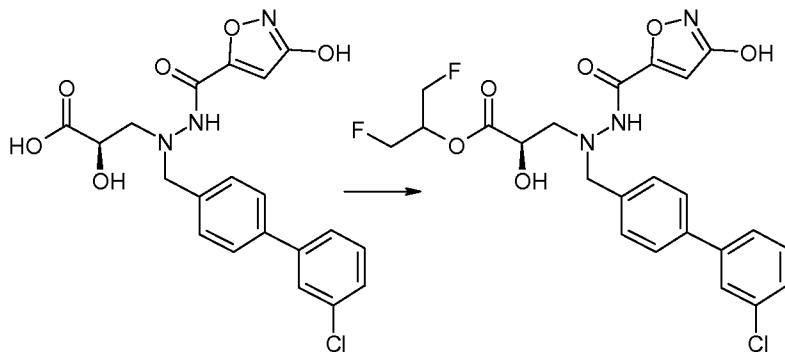
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3-Hydroxyisoxazole-5-carboxylic acid (1.6 g, 12.1 mmol), HATU (4.6 g, 12.1 mmol) and DMF (31.2 mL) were combined and the resulting mixture was stirred for 5 minutes at room temperature. DIPEA (4.0 mL, 23.1 mmol) and (S)-3-[N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester (3.7 g, 10.0 mmol) were added and the resulting mixture was stirred until the reaction was complete (20 minutes). The reaction was quenched with water, the mixture was diluted with EtOAc, then washed with water and saturated aqueous NaCl. The organic layer was dried, concentrated, and purified by flash chromatography (50-90% EtOAc in hexanes). The clean fractions were collected and concentrated. After evaporation, the ester compound J was collected as a yellow solid TFA salt (3.5 g mg). MS m/z [M+H]⁺ calc'd for $C_{23}H_{24}ClN_3O_6$, 474.14; found 474.1.

A few grams of the ester compound J (350 mg) was dissolved in EtOH (17.6 mL, 302 mmol), and 10.0 M aqueous NaOH (20.1 mL, 201 mmol) was added. The solids were filtered and the filtrate was acidified to pH=2 and extracted twice with DCM. The solution 20 was dried over MgSO₄, filtrated and concentrated to give a yellow gum. The crude was

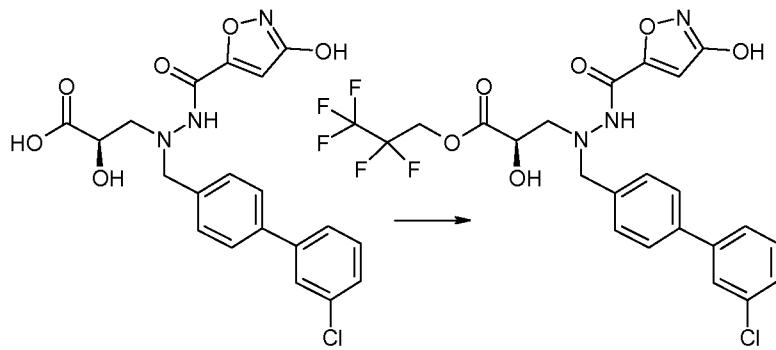
purified (C18 reverse phase column). The fractions were collected (1.4 g) and purified further to yield the acid compound K as a TFA salt (purity 100%). MS m/z [M+H]⁺ calc'd for C₂₀H₁₈ClN₃O₆, 432.09; found 432.1.

5 L. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic acid 2-fluoro-1-fluoromethyl-ethyl Ester



10 (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (8 mg, 20 μ mol) was dissolved in 1,3-difluoro-2-propanol (144 μ L, 1.9 mmol) and sonicated. A solution of 4 M HCl in dioxane (232 μ L, 0.9 mmol) was added and the resulting mixture was stirred at room temperature for 2 hours and at 50°C for 1 hour and monitored for completeness. The mixture was then stirred overnight until the reaction was complete, then evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (6.3 mg; purity 95%). MS m/z [M+H]⁺ calc'd for C₂₃H₂₂ClF₂N₃O₆, 510.12; found 510.1.

15 M. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid 2,2,3,3,3-pentafluoropropyl Ester

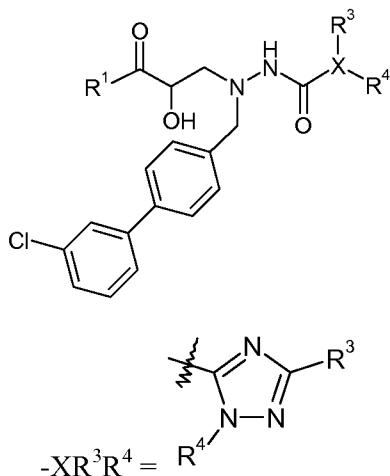


20 (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (8 mg, 20 μ mol) was dissolved in 2,2,3,3,3-pentafluoro-1-propanol (0.2 mL, 1.9 mmol) and sonicated. A solution of 4 M HCl in dioxane (232 μ L, 0.9 mmol) was added and the resulting mixture was stirred until the

reaction was complete ~48 hours), then evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (1.9 mg). MS m/z $[M+H]^+$ calc'd for $C_{23}H_{19}ClF_5N_3O_6$, 564.09; found 564.2.

EXAMPLE 4

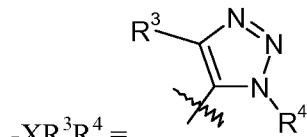
5 Following the procedures described in the examples herein, and substituting the appropriate starting materials and reagents, compounds having the following formula were prepared as TFA salts:



Ex.	R^1	R^3	R^4	Formula	MS m/z : $[M+H]^+$	
					calcd	found
1	-OH	Cl	H	$C_{19}H_{17}Cl_2N_5O_4$	450.07	450.2
2	-OH	-OH	H	$C_{19}H_{18}ClN_5O_5$	432.10	432.4

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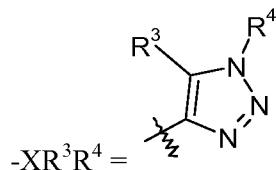
1. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-chloro-2H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid
2. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-hydroxy-2H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



15

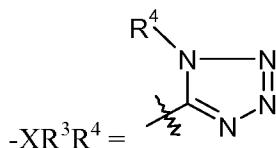
Ex.	R^1	R^3	R^4	Formula	MS m/z : $[M+H]^+$	
					calcd	found
3	-OH	H	H	$C_{19}H_{18}ClN_5O_4$	416.10	416.2

3. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
4	-OH	H	-OH	C ₁₉ H ₁₈ ClN ₅ O ₅	432.10	432.4

4. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

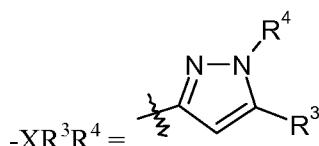


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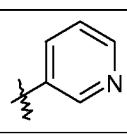
Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
5	-OH	absent	H	C ₁₈ H ₁₇ ClN ₆ O ₄	417.10	417.4
6	-OCH ₂ -CH(CH ₃) ₂	absent	H	C ₂₂ H ₂₅ ClN ₆ O ₄	473.16	473.4
7	-OCH(CH ₃) ₂	absent	H	C ₂₁ H ₂₃ ClN ₆ O ₄	459.15	459.4
8	-OCH ₂ CH ₃	absent	H	C ₂₀ H ₂₁ ClN ₆ O ₄	445.13	445.4

5. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

6. (R)-3-[N-(3'-Chloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester
 10 10. (R)-3-[N-(3'-Chloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester
 7. (R)-3-[N-(3'-Chloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

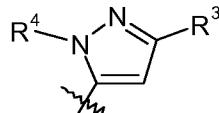


15

Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
9	-OH		H	C ₂₅ H ₂₂ ClN ₅ O ₄	492.14	492.2
10	-OH	cyclopropyl	H	C ₂₃ H ₂₃ ClN ₄ O ₄	455.14	455.2

9. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-pyridin-3-yl-1H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid (di-TFA salt)

10. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-cyclopropyl-1H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



5

-XR³R⁴ =

Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
11	-OH		H	C ₂₅ H ₂₆ ClN ₅ O ₅	512.16	512.4
12	-OH		H	C ₂₄ H ₂₄ ClN ₅ O ₅	498.15	498.6
13	-OH	-C(O)N(CH ₃) ₂	H	C ₂₃ H ₂₄ ClN ₅ O ₅	486.15	486.4
14	-OH		H	C ₂₅ H ₂₆ ClN ₅ O ₆	528.16	528.2
15	-OH	2-chlorophenyl	H	C ₂₆ H ₂₂ Cl ₂ N ₄ O ₄	525.10	525.4
16	-OH	-C(O)N(CH ₃)-[CH ₂ CH(CH ₃) ₂]	H	C ₂₆ H ₃₀ ClN ₅ O ₅	528.19	528.2
17	-OH	-C(O)N(CH ₃)-cyclopropyl	H	C ₂₆ H ₂₈ ClN ₅ O ₅	526.18	526.4
18	-OH		H	C ₂₄ H ₂₃ ClFN ₅ O ₅	516.14	516.4
19	-OH	2-hydroxyphenyl	H	C ₂₆ H ₂₃ ClN ₄ O ₅	507.14	507.2
20	-OH	2-methoxyphenyl	H	C ₂₇ H ₂₅ ClN ₄ O ₅	521.15	521.2
21	-OH		H	C ₂₅ H ₂₂ ClN ₅ O ₄	492.14	492.2
22	-OH	-(CH ₂) ₃ CH ₃	H	C ₂₄ H ₂₇ ClN ₄ O ₄	471.17	471.2
23	-OH	-COOH	H	C ₂₁ H ₁₉ ClN ₄ O ₆	459.10	459.2
24	-OH		H	C ₂₄ H ₂₁ ClN ₆ O ₄	493.13	493.2
25	-OH	-C(O)CH ₃	H	C ₂₂ H ₂₁ ClN ₄ O ₅	457.12	457.2
26	-OH	-CH ₂ OCH ₃	H	C ₂₂ H ₂₃ ClN ₄ O ₅	459.14	459.2
27	-OH	-C(CH ₃) ₂ OH	H	C ₂₃ H ₂₅ ClN ₄ O ₅	473.15	473.2

11. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(pyrrolidine-1-carbonyl)-2H-

pyrazole-3-carbonyl]-hydrazino}-2-hydroxy-propionic acid

12. (R) -3-[N'-[5-(Azetidine-1-carbonyl)-2H-pyrazole-3-carbonyl]-N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

13. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-dimethylcarbamoyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

5 14. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-[5-((R)-3-hydroxy-pyrrolidine-1-carbonyl)-2H-pyrazole-3-carbonyl]-hydrazino]-2-hydroxy-propionic acid

15. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(2-chlorophenyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10 16. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(isobutyl-methyl-carbamoyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

17. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(cyclopropylmethyl-methyl-carbamoyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

18. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(3-fluoroazetidine-1-carbonyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

15 19. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(2-hydroxy-phenyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

20. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(2-methoxy-phenyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

20 21. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-pyridin-2-yl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid (di-TFA salt)

22. (R) -3-[N'-(5-Butyl-2H-pyrazole-3-carbonyl)-N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

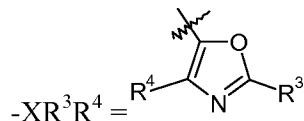
25 23. 5-[N'-((R) -2-Carboxy-2-hydroxy-ethyl)-N'-(3'-chlorobiphenyl-4-ylmethyl)-hydrazinocarbonyl]-1H-pyrazole-3-carboxylic acid

24. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-pyrazin-2-yl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid (di-TFA salt)

25 25. (R) -3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(3'-chlorobiphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

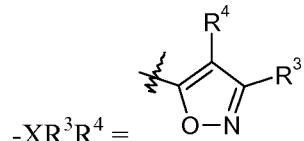
30 26. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-methoxymethyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

27. (R) -3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(5-(1-hydroxy-1-methyl-ethyl)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
28	-OH	phenyl	H	C ₂₆ H ₂₂ ClN ₃ O ₅	492.12	492.2

28. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2-phenyl-oxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



5

Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
29	-OH	2-chloro-phenyl	H	C ₂₆ H ₂₁ Cl ₂ N ₃ O ₅	526.09	526.4
30	-OH	2-methoxy-phenyl	H	C ₂₇ H ₂₄ ClN ₃ O ₆	522.14	522.2
31	-OH	2-fluoro-phenyl	H	C ₂₆ H ₂₁ ClFN ₃ O ₅	510.12	510.4
32	-OH	-OCH ₃	H	C ₂₁ H ₂₀ ClN ₃ O ₆	446.10	446.0
33	-OCH ₂ CH ₃	-OCH ₃	H	C ₂₃ H ₂₄ ClN ₃ O ₆	474.14	474.2

29. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-(2-chlorophenyl)-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

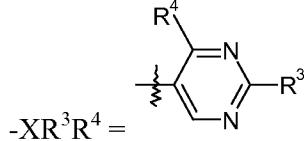
30. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-(2-methoxy-phenyl)-isoxazole-5-

10 carbonyl)-hydrazino]-2-hydroxy-propionic acid

31. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-(2-fluorophenyl)-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

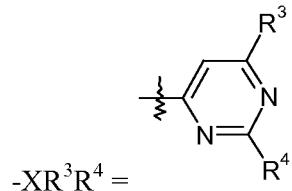
32. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

15 33. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
34	-OH	-OH	H	C ₂₁ H ₁₉ ClN ₄ O ₅	443.10	443.2

34. *(R)*-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2-hydroxy-pyrimidine-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
35	-OH	-COOH	H	C ₂₂ H ₁₉ ClN ₄ O ₆	471.10	471.4
36	-OH	-OH	-OH	C ₂₁ H ₁₉ ClN ₄ O ₆	459.10	459.4
37	-OH	H	-OH	C ₂₁ H ₁₉ ClN ₄ O ₅	443.10	443.2
38	-OH	-COOH	-OH	C ₂₂ H ₁₉ ClN ₄ O ₇	487.09	487.4

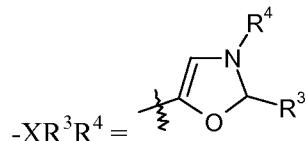
5

35. 6-[N'-(*(R)*-2-Carboxy-2-hydroxy-ethyl)-N'-(3'-chlorobiphenyl-4-ylmethyl)-hydrazinocarbonyl]-pyrimidine-4-carboxylic acid

36. *(R)*-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2,6-dihydroxy-pyrimidine-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10 37. *(R)*-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2-hydroxy-pyrimidine-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

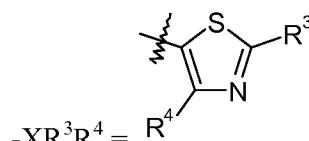
38. 6-[N'-(*(R)*-2-Carboxy-2-hydroxy-ethyl)-N'-(3'-chlorobiphenyl-4-ylmethyl)-hydrazinocarbonyl]-2-hydroxy-pyrimidine-4-carboxylic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
39	-OH	=O	H	C ₂₀ H ₁₈ ClN ₃ O ₆	432.09	432.4

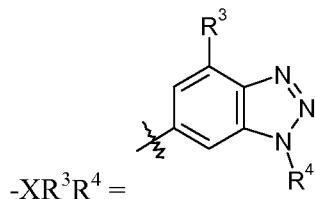
15

39. *(R)*-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2-oxo-2,3-dihydro-oxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
40	-OH	-OH	H	C ₂₀ H ₁₈ ClN ₃ O ₅ S	448.07	448.0

40. (*R*)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(2-hydroxy-thiazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



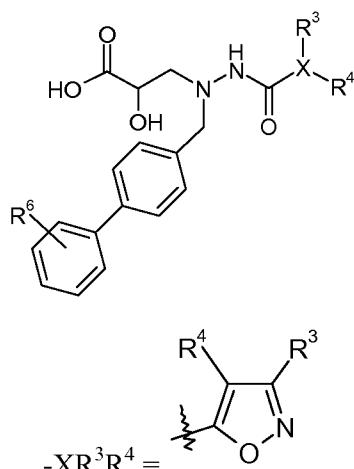
Ex.	R ¹	R ³	R ⁴	Formula	MS m/z: [M+H] ⁺	
					calcd	found
41	-OH	H	-OH	C ₂₃ H ₂₀ ClN ₅ O ₅	482.12	482.0
42	-OH	F	H	C ₂₃ H ₁₉ ClFN ₅ O ₄	484.11	484.4

5 41. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

42. (R)-3-[N-(3'-Chlorobiphenyl-4-ylmethyl)-N'-(4-fluoro-1H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

EXAMPLE 5

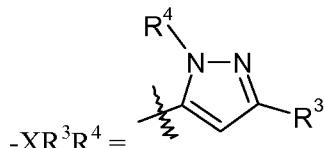
10 Following the procedures described in the examples herein, and substituting the appropriate starting materials and reagents, compounds having the following formula were prepared as TFA salts:



Ex.	R ³	R ⁴	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
					calcd	found
1	-OH	H	3'-F	C ₂₀ H ₁₈ FN ₃ O ₆	416.12	416.2
2	-OH	H	3'-CF ₃	C ₂₁ H ₁₈ F ₃ N ₃ O ₆	466.11	466.2
3	-OH	H	3'-OH	C ₂₀ H ₁₉ N ₃ O ₇	414.12	414.4
4	-OH	H	3'-CH ₃	C ₂₁ H ₂₁ N ₃ O ₆	412.14	412.2
5	-OH	H	2'-OCH ₃	C ₂₁ H ₂₁ N ₃ O ₇	428.14	428.2
6	-OH	H	2'-OH	C ₂₀ H ₁₉ N ₃ O ₇	414.12	414.2
7	-OH	H	2'-Cl	C ₂₀ H ₁₈ ClN ₃ O ₆	432.09	432.4

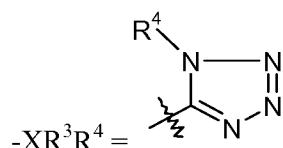
Ex.	R ³	R ⁴	R ⁶	Formula	MS m/z: [M+H] ⁺	
					calcd	found
8	-OH	H	2'-F	C ₂₀ H ₁₈ FN ₃ O ₆	416.12	416.4

1. (R)-3-[N-(3'-Fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
2. (R)-2-Hydroxy-3-[N'-(3-hydroxy-isoxazole-5-carbonyl)-N-(3'-trifluoromethyl-biphenyl-4-ylmethyl)-hydrazino]-propionic acid
- 5 3. (S)-2-Hydroxy-3-[N-(3'-hydroxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-propionic acid
4. (S)-2-Hydroxy-3-[N'-(3-hydroxy-isoxazole-5-carbonyl)-N-(3'-methyl-biphenyl-4-ylmethyl)-hydrazino]-propionic acid
- 10 5. (R)-2-Hydroxy-3-[N'-(3-hydroxy-isoxazole-5-carbonyl)-N-(2'-methoxy-biphenyl-4-ylmethyl)-hydrazino]-propionic acid
6. (R)-2-Hydroxy-3-[N-(2'-hydroxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-propionic acid
7. (R)-3-[N-(2'-Chloro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- 15 8. (R)-3-[N-(2'-Fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ³	R ⁴	R ⁶	Formula	MS m/z: [M+H] ⁺	
					calcd	found
9	-C(O)CH ₃	H	2'-OCH ₃	C ₂₃ H ₂₄ N ₄ O ₆	453.17	453.2

- 20 9. (S)-3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(2'-methoxy-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid



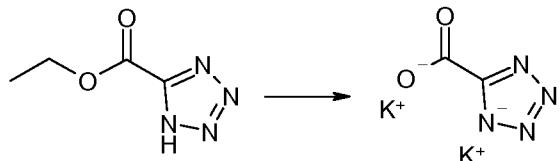
Ex.	R ³	R ⁴	R ⁶	Formula	MS m/z: [M+H] ⁺	
					calcd	found
10	absent	H	2'-OCH ₃	C ₁₉ H ₂₀ N ₆ O ₅	413.15	413.4

10. (R)-2-Hydroxy-3-[N-(2'-methoxy-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-

carbonyl)-hydrazino]-propionic acid

Preparation 6

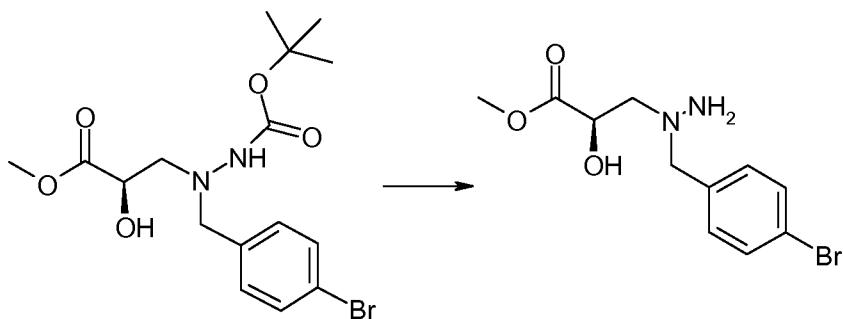
Dipotassium 1H-tetrazole-5-carboxylate



5 A solution of potassium hydroxide (1.3 g, 23.2 mmol) in water (4.2 mL, 230 mmol) was added to a solution of ethyl tetrazole-5-carboxylate (1.1 g, 7.7 mmol) in EtOH (24 mL, 410 mmol). A solid product formed immediately and was collected and washed with cold EtOH to yield the title compound (1.5 g).

Preparation 7

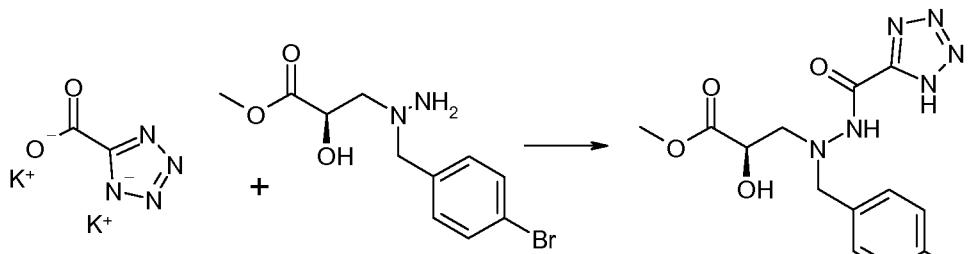
10 (R)-3-[N-(4-Bromobenzyl)-hydrazino]-2-hydroxy-propionic Acid Methyl Ester



15 (R)-3-[N-(4-Bromobenzyl)-N'-t-butoxycarbonyl-hydrazino]-2-hydroxy-propionic acid methyl ester (1.1 g, 2.8 mmol) was dissolved in MeCN (10 mL) and of 4N HCl in dioxane (6 mL, 20 mmol). The mixture was stirred at room temperature until deprotection was complete (1 hour). The precipitate was filtered and dried to yield the title compound (840 mg) as an HCl salt.

Preparation 8

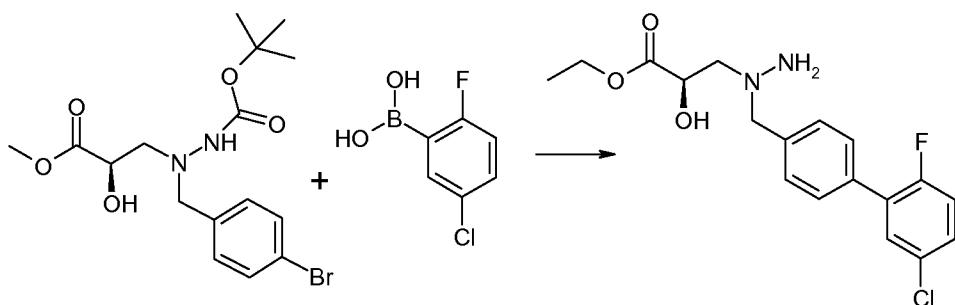
(R)-3-[N-(4-Bromobenzyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic Acid Methyl Ester



To a stirred solution of DMF (711 μ L, 9.2 mmol) in MeCN (2 mL, 40 mmol) at 0°C, was slowly added a solution of oxalyl chloride (249 μ L, 2.94 mmol) in MeCN (500 μ L, 9 mmol). After 10 minutes, dipotassium 1H-tetrazole-5-carboxylate (241 mg, 1.3 mmol) was added and after stirring for a further 15 minutes, was added to a solution of 5 compound 1 (240 mg, 0.8 mmol) in pyridine (9.6 mL, 120 mmol). The stirred reaction mixture was allowed to slowly warm to room temperature and stirred for 20 minutes. The mixture was evaporated under reduced pressure to yield the title compound.

Preparation 9

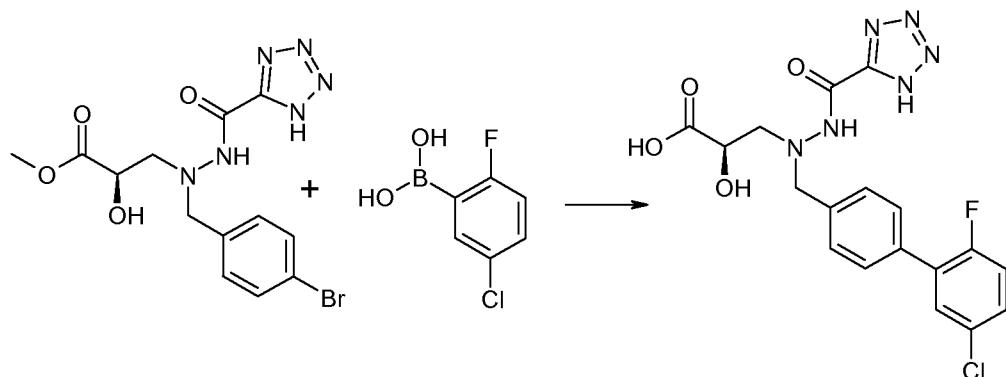
(R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-10 propionic Acid Ethyl Ester



(R)-3-[N-(4-Bromobenzyl)-N'-t-butoxycarbonyl-hydrazino]-2-hydroxy-propionic acid methyl ester (1.0 g, 2.5 mmol), 5-chloro-2-fluorophenylboronic acid (865 mg, 4.96 mmol), and K_2CO_3 (857 mg, 6.2 mmol), were combined in EtOH (30 mL, 500 mmol) and 15 water (8 mL, 400 mmol), followed by the addition of SilicaCat®DPP-Pd (0.28 mmol/g loading; 886 mg, 248 μ mol). The mixture was heated at 90°C until the reaction was complete (2 hours). The precipitate was filtered off, and the filtrate was concentrated and purified (Interchim reverse phase chromatography column; 30-95% MeCN in water with 0.5% TFA). The clean fractions were collected, lyophilized, and combined with 4 M HCl 20 in dioxane (8 mL, 30 mmol) and EtOH (10 mL, 200 mmol). The resulting mixture was stirred at room temperature until the reaction was complete (7 hours). The mixture was concentrated to yield an oil, which was stirred in ether with few drops of EtOH overnight. The precipitate was filtered off and rinsed with ether to yield the title compound (140 mg).

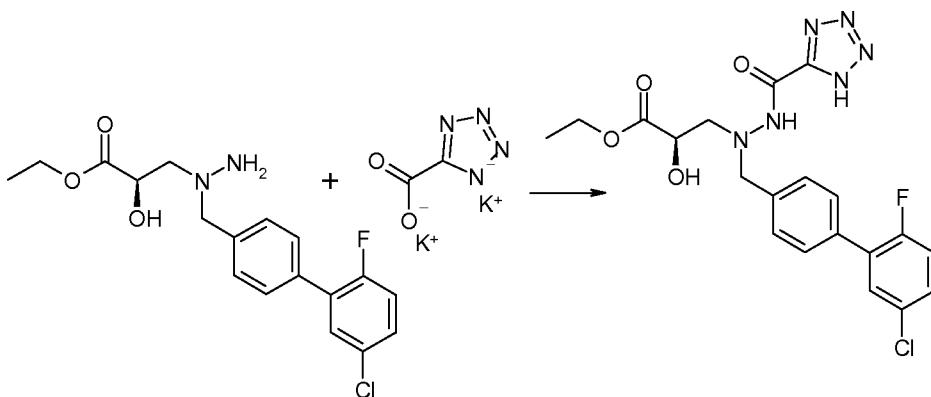
EXAMPLE 6

A. (R)-3-[N-(5'-Chloro-2'-fluorobiphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid



5 (R)-3-[N-(4-Bromobenzyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-
propionic acid methyl ester (60 mg, 0.2 mmol), 5-chloro-2-fluorophenylboronic acid (52.4
mg, 301 μ mol), and K_2CO_3 (62.3 mg, 451 μ mol) were combined in EtOH (0.8 mL) and
water (0.2 mL), followed by the addition of SilicaCat[®]DPP-Pd (0.28 mmol/g loading; 53.7
mg, 15 μ mol). The mixture was heated at 120°C until the reaction was complete (30
minutes). The precipitate was filtered off, and 1 M aqueous LiOH (1.2 mL, 1.2 mmol) was
added to the filtrate and stirred for 1 hour. The mixture was evaporated under reduced
pressure and purified by preparative HPLC to yield the title compound as a TFA salt (20
mg; purity 95%). MS m/z [M+H]⁺ calc'd for $C_{18}H_{16}ClFN_6O_4$, 435.09; found 435.4.

10 B. (R)-3-[N-(5'-Chloro-2'-fluorobiphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-
hydrazino]-2-hydroxypropionic Acid Ethyl Ester

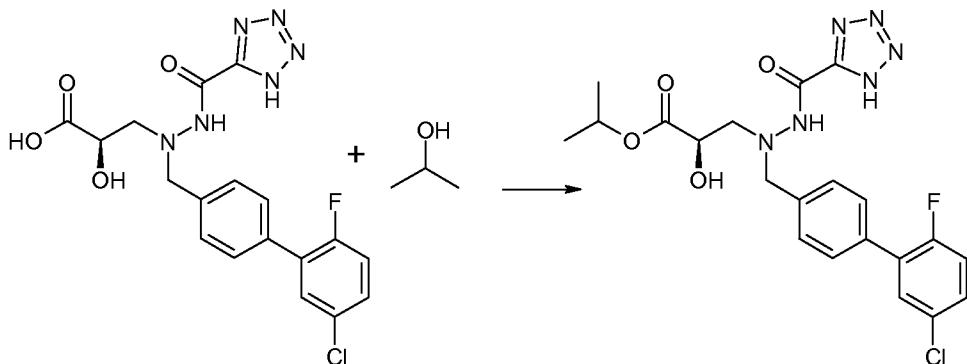


Dipotassium 1H-tetrazole-5-carboxylate was prepared as follows: A solution of potassium hydroxide (1.3 g, 23.2 mmol) in water (4.2 mL, 230 mmol) was added to a solution of ethyl tetrazole-5-carboxylate (1.1 g, 7.7 mmol) in EtOH (24 mL, 410 mmol).

The solid product that formed immediately was collected and washed with cold EtOH to yield dipotassium 1H-tetrazole-5-carboxylate (1.5 g).

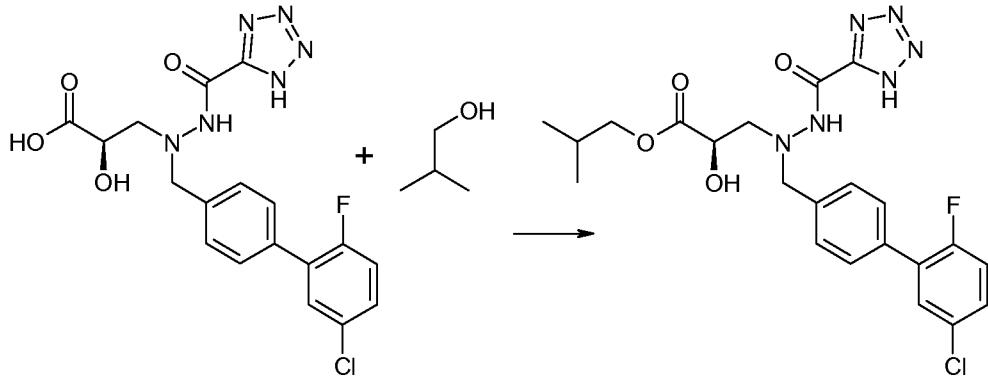
To a stirred solution of DMF (734 μ L, 9.5 mmol) in MeCN (2 mL, 50 mmol) at 0°C, was slowly added a solution of oxalyl chloride (257 μ L, 3.0 mmol) in MeCN (500 μ L, 5 mmol). After 10 minutes, dipotassium 1H-tetrazole-5-carboxylate (249 mg, 1.3 mmol) was added and after stirring for a further 15 minutes, was added to a solution of (*R*)-3-[N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (300 mg, 0.8 mmol) in MeCN (2 mL, 40 mmol) and pyridine (661 μ L, 8.2 mmol). The mixture was stirred at 0°C for 10 minutes then evaporated under reduced pressure and purified (Interchim reverse phase chromatography column; elute from 55-75 %, both peaks coeluted together) to yield the title compound (280 mg). A portion (80 mg) was further purified by preparative HPLC to yield the title compound as a TFA salt (33 mg; purity 98%). MS m/z [M+H]⁺ calc'd for C₂₀H₂₀ClFN₆O₄, 463.12; found 463.4.

C. (R)-3-[N-(5'-Chloro-2'-fluorobiphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isopropyl Ester



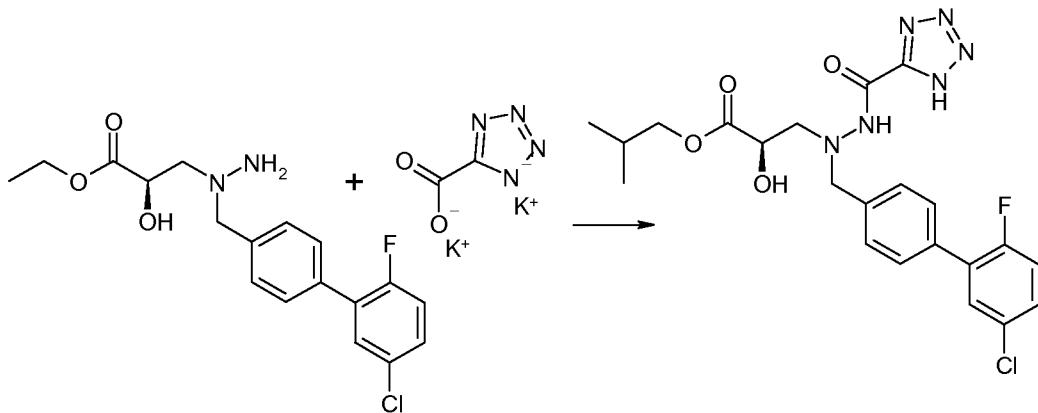
(*R*)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (50 mg, 0.1 mmol) was dissolved in isopropyl alcohol (2 mL, 30 mmol) then 4 M HCl in dioxane (0.8 mL, 3 mmol) was added. The resulting mixture was stirred at room temperature until the reaction was complete (~17 hours). The mixture was evaporated under reduced pressure and purified (Interchim C18 reverse phase column; 30-95% MeCN in water with 0.05% TFA). The clean fractions were combined and lyophilized to yield the title compound as a TFA salt (43 mg; purity 98%). MS m/z [M+H]⁺ calc'd for C₂₁H₂₂ClFN₆O₄, 477.14; found 477.2.

D. (R)-3-[N-(5'-Chloro-2'-fluorobiphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isobutyl Ester



(*R*)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1*H*-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (50 mg, 0.1 mmol) was dissolved in isobutyl alcohol (2 mL, 30 mmol) then 4 M HCl in dioxane (0.8 mL, 3 mmol) was added. The resulting mixture was stirred at room temperature until the reaction was complete (~3 hours). The mixture was evaporated under reduced pressure and purified (Interchim C18 reverse phase column; 30-95% MeCN in water with 0.05% TFA). The clean fractions were combined and lyophilized to yield the title compound as a TFA salt (34 mg; purity 98%). MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₄ClFN₆O₄, 491.15; found 491.4.

Alternate Procedure



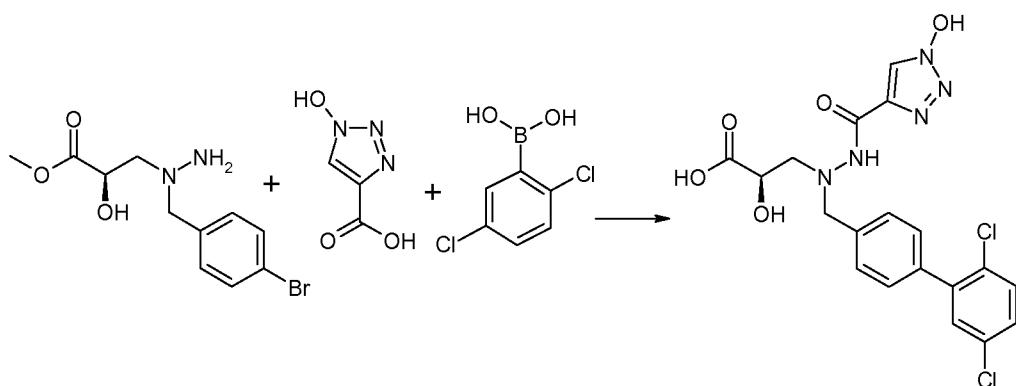
To a stirred solution of DMF (2.8 mL, 36.6 mmol) in MeCN (10 mL, 200 mmol) at 15 0°C, was slowly added a solution of oxalyl chloride (267 µL, 3.2 mmol) in MeCN (1.7 mL, 31.5 mmol). After 10 minutes, dipotassium 1*H*-tetrazole-5-carboxylate (600 mg, 3 mmol) was added and after stirring for a further 15 minutes, was added to a solution of (*R*)-3-[N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester (1000 mg, 3 mmol in pyridine (5.1 mL, 63.1 mmol). The mixture was stirred at 0°C for 10

minutes then evaporated under reduced pressure. The dried material was then dissolved into EtOH (7.4 mL, 126 mmol). A solution of 1 M aqueous LiOH (15.8 mL, 15.8 mmol) was then added and the resulting mixture was stirred at room temperature for 30 minutes. The solution was then evaporated under reduced pressure and purified (Interchim reverse 5 phase column; 10-90% MeCN in water). The purified product was dissolved in isobutyl alcohol (29.1 mL, 315 mmol). A solution of 4.0 M HCl in 1,4-dioxane (7.9 mL, 31.5 mmol) was added, and the resulting mixture was stirred at room temperature for 1 hour, then at 30°C for 1 hour. The solution was evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (186.6 mg).

10

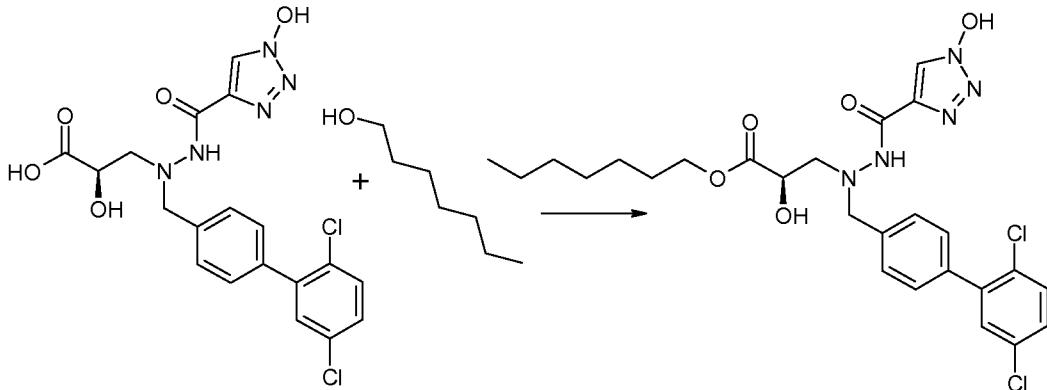
EXAMPLE 7

A. (R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxypropionic Acid



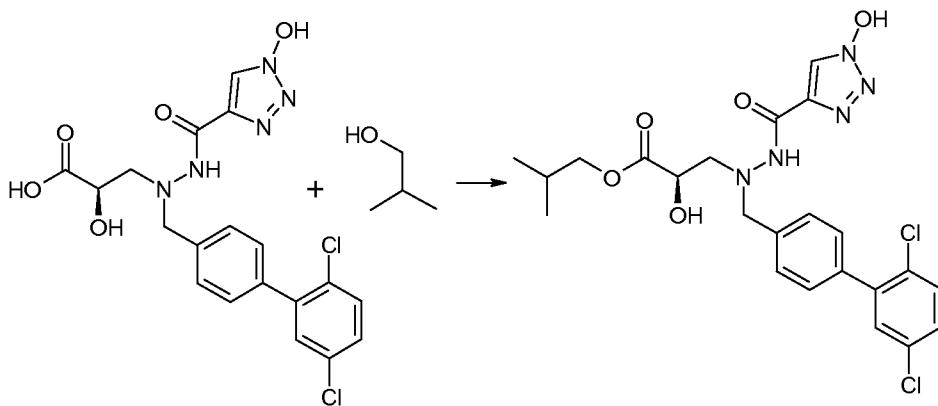
15 1-Hydroxy-1H-1,2,3-triazole-4-carboxylic acid (42.6 mg, 330 µmol) and HATU (125 mg, 330 µmol) were combined in DMF (2 mL) and stirred for 5 minutes at room temperature. DIPEA (86 µL, 495 µmol) and (R)-3-[N-(4-Bromobenzyl)-hydrazino]-2-hydroxy-propionic acid methyl ester (50 mg, 0.2 mmol) were added, and the resulting mixture was stirred for 30 minutes. The mixture was evaporated under reduced pressure and the product dissolved in EtOH (0.8 mL, 10 mmol) and water (0.2 mL, 10 mmol). 20 2,5-Dichlorophenylboronic acid (57 mg, 297 µmol), K₂CO₃ (68 mg, 495 µmol), and SilicaCat®DPP-Pd (0.28 mmol/g loading; 58.9 mg, 16.5 µmol) were added and the resulting mixture was heated at 120°C for 10 minutes. The mixture was filtered, and 1 M aqueous LiOH (1.2 mL, 1.2 mmol) was added to the filtrate. The mixture was stirred until the reaction was complete (1 hour), then vacuumed to dryness and purified by 25 preparative HPLC to yield the title compound as a TFA salt (14 mg; purity 95%). MS *m/z* [M+H]⁺ calc'd for C₁₉H₁₇Cl₂N₅O₅, 466.06; found 466.2.

B. (R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxypropionic Acid Heptyl Ester



(R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-1,2,3-triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid (150 mg, 320 μ mol) was dissolved in 1-heptanol (9.1 mL, 64.3 mmol). 4 M HCl in dioxane (3.2 mL, 12.9 mmol) was added and the resulting mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (12 mg; purity 100%). MS m/z [M+H] $^+$ calc'd for C₂₆H₃₁Cl₂N₅O₅, 10 564.17; found 564.2.

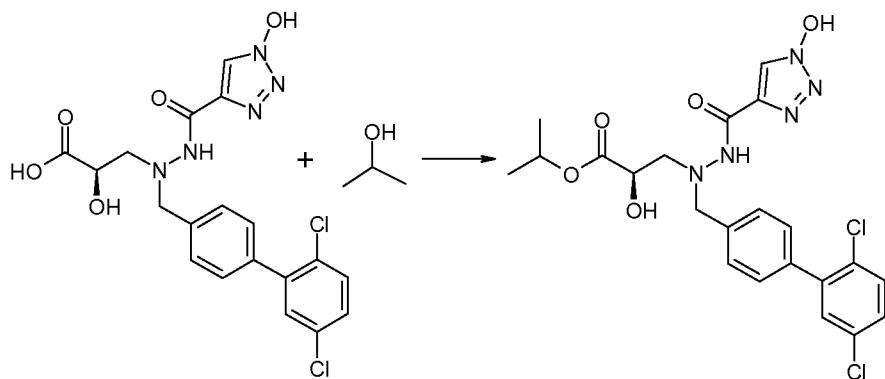
C. (R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isobutyl Ester



(R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-1,2,3-triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid (150 mg, 320 μ mol) was dissolved in isobutyl alcohol (8.9 mL, 96.5 mmol). 4 M HCl in dioxane (3.2 mL, 12.9 mmol) was added and the resulting mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (28.5mg; purity 100%). MS m/z [M+H] $^+$ calc'd for

$C_{23}H_{25}Cl_2N_5O_5$, 522.12; found 522.2.

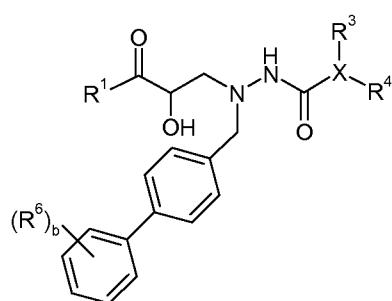
D. (R)-3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isopropyl Ester

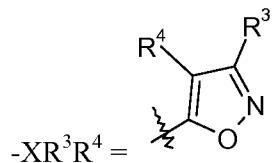


5 (R) -3-[N-(2',5'-Dichlorobiphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-1,2,3-triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid (150 mg, 320 μ mol) was dissolved in isopropyl alcohol (4.9 mL, 64.3 mmol). 4 M HCl in dioxane (3.2 mL, 12.9 mmol) was added and the resulting mixture was stirred at room temperature overnight. The mixture was evaporated under reduced pressure and purified by preparative HPLC to yield the title 10 compound as a TFA salt (4.7 mg; purity 100 %). MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}Cl_2N_5O_5$, 508.11; found 508.2.

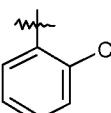
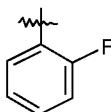
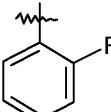
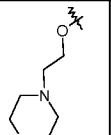
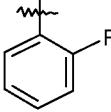
EXAMPLE 8

Following the procedures described in the examples herein, and substituting the appropriate starting materials and reagents, compounds having the following formula were 15 prepared as TFA salts:





Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
1	-OH	-OH	H	2	2'-Me, 5'-Cl	C ₂₁ H ₂₀ ClN ₃ O ₆	446.10	446.4
2	-OH	-OH	H	2	2'- OMe, 5'-Cl	C ₂₁ H ₂₀ ClN ₃ O ₇	462.10	462.2
3	-OCH ₂ - CH ₃	-OH	H	2	2'- OMe, 5'-Cl	C ₂₃ H ₂₄ ClN ₃ O ₇	490.13	490.4
4	-OH	-OH	H	2	2'- OMe, 5'-F	C ₂₁ H ₂₀ FN ₃ O ₇	446.13	446.4
5	-OH	-OH	H	2	2'-OH, 5'-F	C ₂₀ H ₁₈ FN ₃ O ₇	432.11	432.4
6	-OH	-OH	H	2	2'-OH, 5'-Cl	C ₂₀ H ₁₈ ClN ₃ O ₇	448.08	448.0
7	-OH	-OH	H	2	2'-OH, 3'-Cl	C ₂₀ H ₁₈ ClN ₃ O ₇	448.08	448.0
8	-OH	-OH	H	2	2'-F, 5'-Cl	C ₂₀ H ₁₇ ClFN ₃ O ₆	450.08	450.2
9	-OH	-OCH ₃	H	2	2'-F, 5'-Cl	C ₂₁ H ₁₉ ClFN ₃ O ₆	464.09	464.0
10	-OCH ₂ - CH ₃	-OCH ₃	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₃ ClFN ₃ O ₆	492.13	492.2
11	-OCH- (CH ₃) ₂	-OCH ₃	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₅ ClFN ₃ O ₆	506.14	506.4
12	-OCH ₂ - CH- (CH ₃) ₂	-OCH ₃	H	2	2'-F, 5'-Cl	C ₂₅ H ₂₇ ClFN ₃ O ₆	520.16	520.2
13	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₀ ClF ₂ N ₃ O ₅	528.11	528.0
14	-OH	-CH ₂ -CH ₃	H	2	2'-F, 5'-Cl	C ₂₂ H ₂₁ ClFN ₃ O ₅	462.12	462.0
15	-OH		H	2	2'-F, 5'-Cl	C ₂₇ H ₂₃ ClFN ₃ O ₆	540.13	540.2
16	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₀ Cl ₂ FN ₃ O ₅	544.08	544.0

Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
17	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₀ Cl ₂ FN ₃ O ₅	544.08	544.0
18	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₀ ClF ₂ N ₃ O ₅	528.11	528.2
19	-O-CH ₂ -CH ₃		H	2	2'-F, 5'-Cl	C ₂₈ H ₂₄ ClF ₂ N ₃ O ₅	556.14	556.2
20			H	2	2'-F, 5'-Cl	C ₃₂ H ₃₁ ClF ₂ N ₄ O ₆	641.19	641.2
21	-OH	-OH	H	2	2'-F, 3'-Cl	C ₂₀ H ₁₇ ClFN ₃ O ₆	450.08	450.2
22	-OH	-OH	H	2	2', 5'- diCl	C ₂₀ H ₁₇ Cl ₂ N ₃ O ₆	466.05	466.2
23	-OH	-OH	H	3	2'-F, 3'-Me, 5'-Cl	C ₂₁ H ₁₉ ClFN ₃ O ₆	464.09	464.4
24	-OH	-OH	H	2	3'-F, 5'-Cl	C ₂₀ H ₁₇ ClFN ₃ O ₆	450.08	450.2
25	-OH	-OH	H	2	3', 5'- diCl	C ₂₀ H ₁₇ Cl ₂ N ₃ O ₆	466.05	466.2
26	-OH	-OH	H	2	3', 5'- diF	C ₂₀ H ₁₇ F ₂ N ₃ O ₆	434.11	434.4
27	-OH	-OH	H	2	3'-OH, 5'-Cl	C ₂₀ H ₁₈ ClN ₃ O ₇	448.08	448.0
28	-OH	-OH	H	3	2'-Me, 3', 5'- diCl	C ₂₁ H ₁₉ Cl ₂ N ₃ O ₆	480.07	480.2
29	-OH	-Cl	H	2	2'-F, 5'-Cl	C ₂₀ H ₁₆ Cl ₂ FN ₃ O ₅	468.05	468.2
30	-OH	-CH ₂ CH-(CH ₃) ₂	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₅ ClFN ₃ O ₅	490.15	490.2
31	-OH	-(CH ₂) ₂ CH ₃	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	476.2
32	-OH	-CH(CH ₃) ₂	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	476.4
33	-OH	-C(CH ₃) ₃	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₅ ClFN ₃ O ₅	490.15	489.8

- (R)-3-[N-(5'-Chloro-2'-methyl-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- (R)-3-[N-(5'-Chloro-2'-methoxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-

carbonyl)-hydrazino]-2-hydroxy-propionic acid

3. *(R)*-3-[N-(5'-Chloro-2'-methoxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

4. *(R)*-3-[N-(5'-Fluoro-2'-methoxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

5. *(S)*-3-[N-(5'-Fluoro-2'-hydroxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

6. *(S)*-3-[N-(5'-Chloro-2'-hydroxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10 7. *(R)*-3-[N-(3'-Chloro-2'-hydroxy-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

8. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

9. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

15 10. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

11. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester

20 12. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-methoxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester

13. *(R)*-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[3-(3-fluoro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid

14. *(R)*-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-ethyl-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

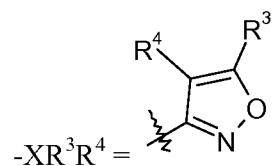
25 15. *(R)*-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[3-(2-methoxy-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid

16. *(R)*-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[3-(3-chloro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid

30 17. *(R)*-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[3-(2-chloro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid

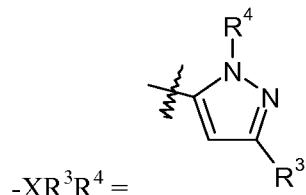
18. *(R)*-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[3-(2-fluoro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid

19. (R) -3- $\{N$ -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -[3-(2-fluoro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid ethyl ester
20. (R) -3- $\{N$ -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -[3-(2-fluoro-phenyl)-isoxazole-5-carbonyl]-hydrazino}-2-hydroxy-propionic acid 2-morpholin-4-yl-ethyl ester
- 5 21. (R) -3-[N -(3'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
22. (S) -3-[N -(2',5'-Dichloro-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
23. (S) -3-[N -(5'-Chloro-2'-fluoro-3'-methyl-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- 10 24. (S) -3-[N -(5'-Chloro-3'-fluoro-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
25. (R) -3-[N -(3',5'-Dichloro-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- 15 26. (S) -3-[N -(3',5'-Difluoro-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
27. (S) -3-[N -(5'-Chloro-3'-hydroxy-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
28. (S) -3-[N -(3',5'-Dichloro-2'-methyl-biphenyl-4-ylmethyl)- N' -(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- 20 29. (R) -3-[N -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -(3-chloro-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
30. (R) -3-[N -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -(3-isobutyl-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- 25 31. (R) -3-[N -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -(3-propyl-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
32. (R) -3-[N -(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)- N' -(3-isopropyl-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
33. (R) -3-[N' -(3-tert-Butyl-isoxazole-5-carbonyl)- N -(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid
- 30



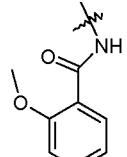
Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
34	-OH		H	2	2'-F, 5'-Cl	C ₂₅ H ₂₀ ClFN ₄ O ₅	511.11	511.2

34. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-pyridin-3-yl-isoxazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



5

Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
35	-OH	-C(O)-N(CH ₃) ₂	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₃ ClFN ₅ O ₅	504.14	504.2
36	-OH		H	2	2'-F, 5'-Cl	C ₂₅ H ₂₁ ClFN ₅ O ₄	510.13	510.2
37	-OCH ₂ -CH ₃		H	2	2'-F, 5'-Cl	C ₂₇ H ₂₅ ClFN ₅ O ₄	538.16	538.4
38	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₂ ClFN ₄ O ₅	525.13	525.2
39	-OH		H	2	2'-F, 5'-Cl	C ₂₇ H ₂₄ ClFN ₄ O ₅	539.14	539.2
40	-OH	-C(CH ₃) ₂ -OH	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₄ ClFN ₄ O ₅	491.14	491.2
41	-OH		H	2	2'-F, 5'-Cl	C ₂₆ H ₂₀ Cl ₃ FN ₄ O ₄	577.05	577.0
42	-OH	-(CH ₂) ₃ CH ₃	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₆ ClFN ₄ O ₄	489.16	489.2

Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
43	-OH	cyclopropyl	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₂ ClFN ₄ O ₄	473.13	473.2
44	-OH	-CH(CH ₃) ₂	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₄ ClFN ₄ O ₄	475.15	475.2
45	-OH	-C(O)CH ₃	H	2	2'-F, 5'-Cl	C ₂₂ H ₂₀ ClFN ₄ O ₅	475.11	475.2
46	-OCH ₂ - CH ₃	-C(O)CH ₃	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₄ ClFN ₄ O ₅	503.14	503.2
47	-OH	-C(O)CH ₃	H	2	2'- Me, 5'-Cl	C ₂₃ H ₂₃ ClN ₄ O ₅	471.14	471.4
48	-OH	-C(O)CH ₃	H	2	2', 5'- diCl	C ₂₂ H ₂₀ Cl ₂ N ₄ O ₅	491.08	491.0
49	-OH		H	2	2'-F, 5'-Cl	C ₂₈ H ₂₅ ClFN ₅ O ₆	582.15	582.2

35. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-dimethylcarbamoyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

36. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-pyridin-2-yl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

37. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-pyridin-2-yl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

38. (R)-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-(2-hydroxy-phenyl)-2H-pyrazole-3-carbonyl)-hydrazino}-2-hydroxy-propionic acid

10 39. (R)-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-(2-methoxy-phenyl)-2H-pyrazole-3-carbonyl)-hydrazino}-2-hydroxy-propionic acid

40. (R)-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-(1-hydroxy-1-methyl-ethyl)-2H-pyrazole-3-carbonyl)-hydrazino}-2-hydroxy-propionic acid

41. (R)-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-(2,5-dichloro-phenyl)-2H-pyrazole-3-carbonyl)-hydrazino}-2-hydroxy-propionic acid

15 42. (R)-3-[N'-(5-Butyl-2H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

43. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-cyclopropyl-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

20 44. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-isopropyl-2H-pyrazole-3-

carbonyl)-hydrazino]-2-hydroxy-propionic acid

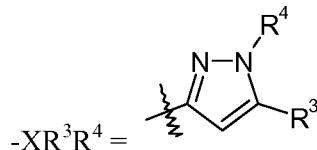
45. (S)-3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

46. (S)-3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

5 47. (S)-3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-methyl-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

48. (S)-3-[N'-(5-Acetyl-2H-pyrazole-3-carbonyl)-N-(2',5'-dichloro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

10 49. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-(2-methoxybenzoylamino)-2H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
50	-OH		H	2	2'-F, 5'-Cl	C ₂₄ H ₂₀ ClFN ₆ O ₄	511.12	511.2
51	-OH	-OH		2	2'-F, 5'-Cl	C ₂₅ H ₂₁ ClFN ₅ O ₅	526.12	526.4
52	-OH	-OH		2	2'-F, 5'-Cl	C ₂₆ H ₂₁ ClF ₂ N ₄ O ₅	543.12	543.6
53	-OH	cyclo-propyl	-CH ₂ -COOH	2	2'-F, 5'-Cl	C ₂₅ H ₂₄ ClFN ₄ O ₆	531.14	531.0
54	-OH	-CH-(CH ₃) ₂	-CH ₂ -COOH	2	2'-F, 5'-Cl	C ₂₅ H ₂₆ ClFN ₄ O ₆	533.15	533.2
55	-OH	-(CH ₂) ₃ -CH ₃	-CH ₂ -COOH	2	2'-F, 5'-Cl	C ₂₆ H ₂₈ ClFN ₄ O ₆	547.17	547.0
56	-OH	-C(CH ₃) ₂ -OH	-CH ₂ -COOH	2	2'-F, 5'-Cl	C ₂₅ H ₂₆ ClFN ₄ O ₇	549.15	549.0
57	-OH	-O-CH ₂ CH ₃	H	2	2'-F, 5'-Cl	C ₂₂ H ₂₂ ClFN ₄ O ₅	477.13	477.2

50. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-pyrazin-2-yl-1H-

15 pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

51. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-hydroxy-1-pyridin-2-yl-

1H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

52. (R)-3-{N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-[1-(2-fluoro-phenyl)-5-hydroxy-1H-pyrazole-3-carbonyl]-hydrazino}-2-hydroxy-propionic acid

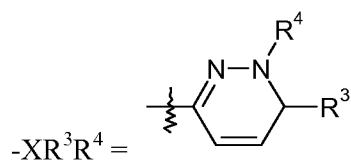
53. (R)-3-[N'-(1-Carboxymethyl-5-cyclopropyl-1H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

54. (R)-3-[N'-(1-Carboxymethyl-5-isopropyl-1H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

55. (R)-3-[N'-(5-Butyl-1-carboxymethyl-1H-pyrazole-3-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

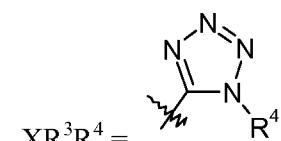
10 56. (R)-3-[N'-[1-Carboxymethyl-5-(1-hydroxy-1-methyl-ethyl)-1H-pyrazole-3-carbonyl]-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

57. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-ethoxy-1H-pyrazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
58	-OH	=O	H	2	2'-F, 5'-Cl	C ₂₁ H ₁₈ ClFN ₄ O ₅	461.10	461.2

58. *(R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(6-oxo-1,6-dihydro-pyridazine-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid*



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
59	-OH	absent	H	2	2'-Me, 5'-Cl	C ₁₉ H ₁₉ ClN ₆ O ₄	431.12	431.2
60	-OH	absent	H	2	2', 5'-diCl	C ₁₈ H ₁₆ Cl ₂ N ₆ O ₄	451.06	451.2
61	-OCH ₂ CH-(CH ₃) ₂	absent	H	2	2', 5'-diCl	C ₂₂ H ₂₄ Cl ₂ N ₆ O ₄	507.12	507.2
62	-OCH-(CH ₃) ₂	absent	H	2	2', 5'-diCl	C ₂₁ H ₂₂ Cl ₂ N ₆ O ₄	493.11	493.4
63	-OCH ₂ CH ₃	absent	H	2	2', 5'-diCl	C ₂₀ H ₂₀ Cl ₂ N ₆ O ₄	479.09	479.2

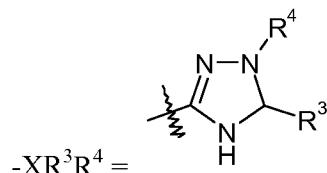
59. (R)-3-[N-(5'-Chloro-2'-methyl-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

60. (R)-3-[N-(2',5'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

5 61. (R)-3-[N-(2',5'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester

62. (R)-3-[N-(2',5'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester

10 63. (R)-3-[N-(2',5'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester



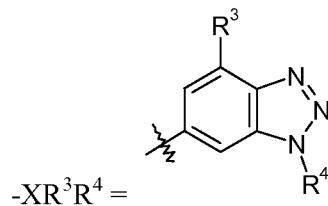
Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
64	-OH	=O	phenyl	2	2'-F, 5'-Cl	C ₂₅ H ₂₁ ClFN ₅ O ₅	526.12	526.0
65	-OH	=O	4-fluoro-phenyl	2	2'-F, 5'-Cl	C ₂₅ H ₂₀ ClF ₂ N ₅ O ₅	544.11	543.1
66	-OH	=O	2-chloro-phenyl	2	2'-F, 5'-Cl	C ₂₅ H ₂₀ Cl ₂ FN ₅ O ₅	560.08	560.1
67	-OH	=O	3-chloro-phenyl	2	2'-F, 5'-Cl	C ₂₅ H ₂₀ Cl ₂ FN ₅ O ₅	560.08	559.6

64. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-oxo-1-phenyl-4,5-dihydro-1H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

15 65. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1-(4-fluoro-phenyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

66. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1-(2-chloro-phenyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid

20 67. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1-(3-chloro-phenyl)-5-oxo-4,5-dihydro-1H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
68	-OH	-CH ₃	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₁ ClFN ₅ O ₄	498.13	498.2
69	-OH	Cl	H	2	2'-F, 5'-Cl	C ₂₃ H ₁₈ Cl ₂ FN ₅ O ₄	518.07	518.0
70	-OCH ₂ CH ₃	Cl	H	2	2'-F, 5'-Cl	C ₂₅ H ₂₂ Cl ₂ FN ₅ O ₄	546.10	546.2
71	-OCH-(CH ₃) ₂	Cl	H	2	2'-F, 5'-Cl	C ₂₆ H ₂₄ Cl ₂ FN ₅ O ₄	560.12	560.2
72	-OCH ₂ CH-(CH ₃) ₂	Cl	H	2	2'-F, 5'-Cl	C ₂₇ H ₂₆ Cl ₂ FN ₅ O ₄	574.13	574.0
73	-OH	F	H	2	2'-F, 5'-Cl	C ₂₃ H ₁₈ ClF ₂ N ₅ O ₄	502.10	502.2

68. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(7-methyl-3H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

5 69. (R)-3-[N'-(7-Chloro-3H-benzotriazole-5-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid

70. (R)-3-[N'-(7-Chloro-3H-benzotriazole-5-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

71. (R)-3-[N'-(7-Chloro-3H-benzotriazole-5-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester

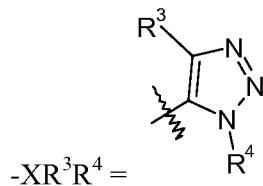
72. (R)-3-[N'-(7-Chloro-3H-benzotriazole-5-carbonyl)-N-(5'-chloro-2'-fluoro-biphenyl-4-ylmethyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester

73. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(7-fluoro-3H-benzotriazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



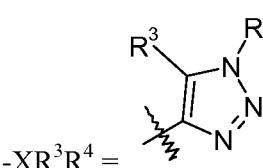
Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
74	-OH	=O	H	2	2'-F, 5'-Cl	C ₂₀ H ₁₇ ClFN ₃ O ₆	450.08	450.0

74. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(2-oxo-2,3-dihydro-oxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
75	-OH	H	H	2	2'-F, 5'-Cl	C ₁₉ H ₁₇ ClFN ₅ O ₄	434.10	434.2

75. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid



5

Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
76	-OH	H	-OH	2	2'-F, 5'-Cl	C ₁₉ H ₁₇ ClFN ₅ O ₅	450.09	450.2
77	-OCH ₂ CH ₃	H	H	2	2'-F, 5'-Cl	C ₂₁ H ₂₁ ClFN ₅ O ₄	462.13	462.2
78	-OCH-(CH ₃) ₂	H	H	2	2'-F, 5'-Cl	C ₂₂ H ₂₃ ClFN ₅ O ₄	476.14	476.2
79	-OCH ₂ -CH-(CH ₃) ₂	H	H	2	2'-F, 5'-Cl	C ₂₃ H ₂₅ ClFN ₅ O ₄	490.16	490.2
80	-OH	H	-OH	2	2'-Me, 5'-Cl	C ₂₀ H ₂₀ ClFN ₅ O ₅	446.12	446.2
81	-OH	H	-OH	2	3', 5'-diCl	C ₁₉ H ₁₇ Cl ₂ N ₅ O ₅	466.06	466.2

76. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

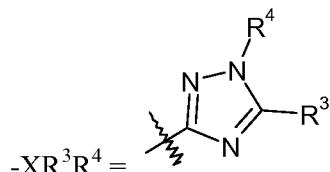
77. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid ethyl ester

78. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid isopropyl ester

79. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester

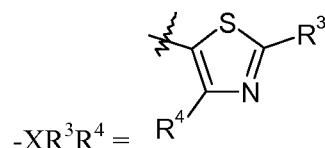
10 80. (R)-3-[N-(5'-Chloro-2'-methyl-biphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

81. (R)-3-[N-(3',5'-Dichloro-biphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
82	-OH	Cl	H	2	2'-F, 5'-Cl	C ₁₉ H ₁₆ Cl ₂ FN ₅ O ₄	468.06	468.0

82. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(5-chloro-1H-[1,2,4]triazole-3-carbonyl)-hydrazino]-2-hydroxy-propionic acid



5

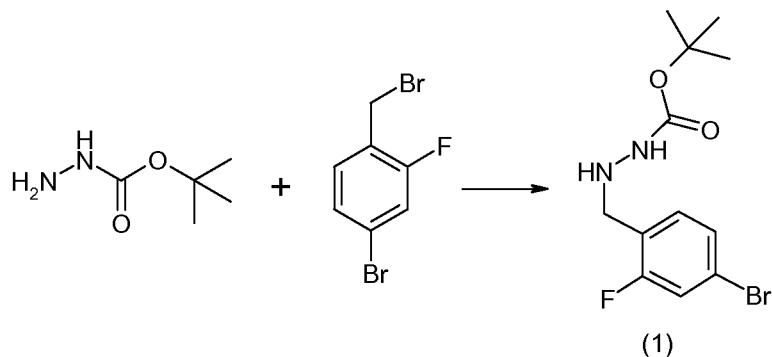
Ex.	R ¹	R ³	R ⁴	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
							calcd	found
83	-OH	-OH	H	2	2'-F, 5'-Cl	C ₂₀ H ₁₇ ClFN ₃ O ₅ S	466.06	466.0
84	-OCH ₂ CH-(CH ₃) ₂	-OH	H	2	2'-F, 5'-Cl	C ₂₄ H ₂₅ ClFN ₃ O ₅ S	522.12	522.4

83. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(2-hydroxy-thiazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10 84. (R)-3-[N-(5'-Chloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(2-hydroxy-thiazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid isobutyl ester

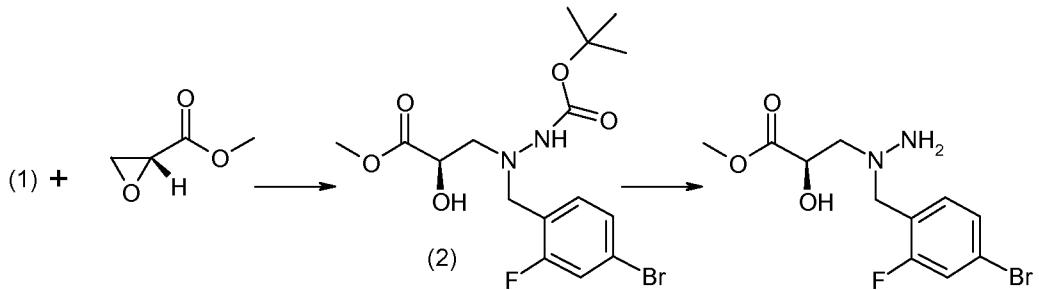
Preparation 10

(R)-3-[N-(4-bromo-2-fluoro-benzyl)-hydrazino]-2-hydroxy-propionic acid methyl ester



15 4-Bromo-2-fluorobenzyl bromide (5.0 g, 19 mmol) and DIPEA (3.3 mL, 18.7 mmol) were dissolved in DMF (20 mL). t-Butyl carbazide (7.4 g, 56.0 mmol) was added and the mixture was stirred at room temperature until the reaction was complete. The mixture was partially concentrated, then the residue was partitioned between EtOAc and a

saturated aqueous NaHCO_3 solution. The EtOAc layer was then dried over Na_2SO_4 and concentrated. The crude product was purified by flash chromatography to yield compound 1 (4.7 g).

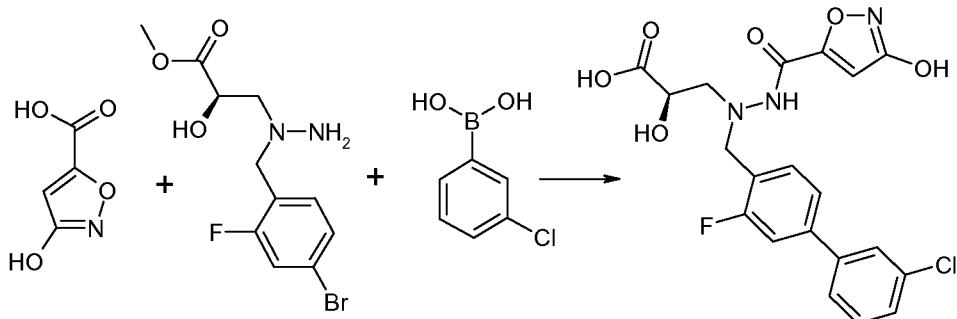


5 Compound 1 (1.9 g, 6.3 mmol) was dissolved in isopropyl alcohol (30 mL). Methyl (2R)-glycidate (3.3 mL, 37.3 mmol) was added and the mixture was refluxed at 90°C until the reaction was complete (~2 days). The mixture was concentrated to yield compound 2 (4.7 g).

10 Compound 2 was dissolved in 1:1 EtOH and 4N HCl in dioxane and stirred overnight. The mixture was then concentrated to yield the title compound (330 mg).

EXAMPLE 9

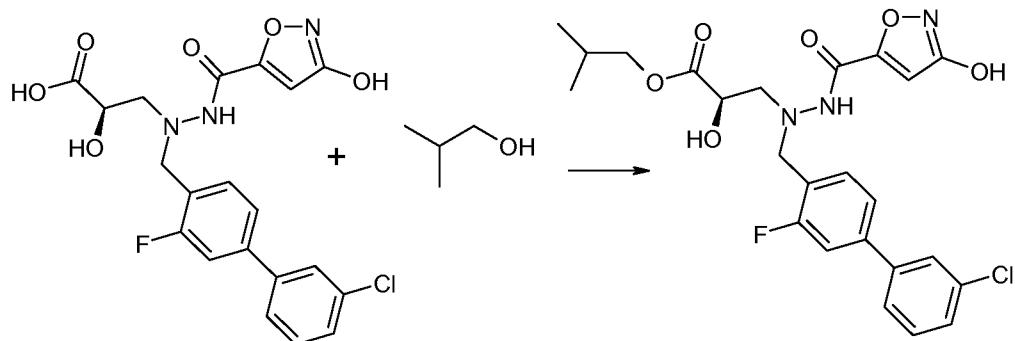
A. (R)-3-[N-(3'-Chloro-3-fluorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid



15 3-Hydroxyisoxazole-5-carboxylic acid (24.1 mg, 186 μmol) was combined with HATU (70.9 mg, 186 μmol) in DMF (2 mL) and stirred for 5 minutes at room temperature. DIPEA (54 μL , 311 μmol) and (R)-3-[N-(4-bromo-2-fluoro-benzyl)-hydrazino]-2-hydroxy-propionic acid methyl ester (50 mg, 0.2 mmol) were added and the resulting mixture was stirred for 10 minutes. The mixture was evaporated under reduced pressure 20 and the residue was diluted with EtOAc , and washed with water and saturated aqueous NaCl . The organic layer was separated and concentrated. 3-Chlorophenylboronic acid (43.8 mg, 280 μmol), K_2CO_3 (65 mg, 467 μmol), EtOH (0.8 mL), and water (0.2 mL) were

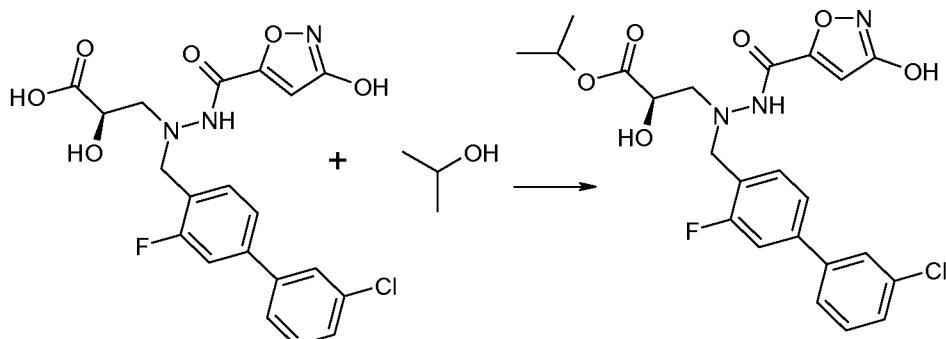
added, followed by SilicaCat®Pd(0) (0.09 mmol/g loading; 121 mg, 11 μ mol). The mixture was heated at 120°C until the reaction was complete (10 minutes). The mixture was filtered, concentrated and purified by preparative HPLC to yield the title compound as a TFA salt (9.7 mg; purity 95%). MS m/z [M+H]⁺ calc'd for C₂₀H₁₇ClFN₃O₆, 450.08; 5 found 450.2.

B. (R)-3-[N-(3'-Chloro-3-fluorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isobutyl Ester



(R)-3-[N-(3'-Chloro-3-fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (75 mg, 0.2 mmol) was dissolved in isobutyl alcohol (3 mL, 30 mmol) and 4 M HCl in dioxane (1 mL, 4 mmol) was added. The mixture was stirred at room temperature until the reaction was complete (~3 hours), then evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (26 mg; purity 95%). MS m/z [M+H]⁺ calc'd for C₂₄H₂₅ClFN₃O₆, 506.14; found 506.

C. (R)-3-[N-(3'-Chloro-3-fluorobiphenyl-4-ylmethyl)-N'-(3-hydroxyisoxazole-5-carbonyl)-hydrazino]-2-hydroxypropionic Acid Isopropyl Ester



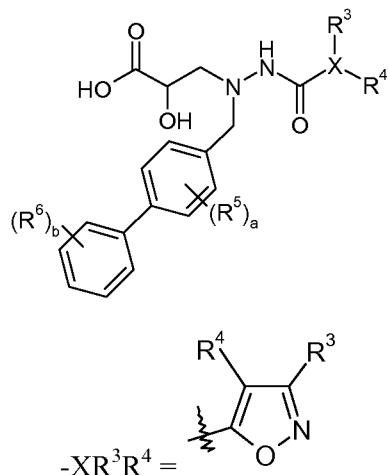
(R)-3-[N-(3'-Chloro-3-fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (75 mg, 0.2 mmol) was dissolved in isopropyl alcohol (2 mL, 20 mmol) and 4 M HCl in dioxane (1 mL, 4 mmol) was added.

The mixture was stirred at room temperature until the reaction was complete (~3 hours), then evaporated under reduced pressure and purified by preparative HPLC to yield the title compound as a TFA salt (20 mg; purity 95%). MS m/z $[M+H]^+$ calc'd for $C_{23}H_{23}ClFN_3O_6$, 492.13; found 492.2.

5

EXAMPLE 10

Following the procedures described in the examples herein, and substituting the appropriate starting materials and reagents, compounds having the following formula were prepared, either as the parent compound or as a TFA salt:



10

Ex.	R ³	R ⁴	a	R ⁵	b	R ⁶	Formula	MS m/z : $[M+H]^+$	
								calc'd	found
1	-OH	H	1	3-F	0	-	$C_{20}H_{18}FN_3O_6$	416.12	416.7
2	-OH	H	1	3-CN	1	3'-Cl	$C_{21}H_{17}ClN_4O_6$	457.08	457.4
3	-OH	H	1	2-Cl	1	3'-Cl	$C_{20}H_{17}Cl_2N_3O_6$	466.05	466.2
4	-OH	H	1	3-F	2	2'-F, 5'-Cl	$C_{20}H_{16}ClF_2N_3O_6$	468.07	468.2
5	-OH	H	1	3-F	2	2'-F, 5'-Cl	$C_{20}H_{16}ClF_2N_3O_6$	468.07	468.2
6	-OH	H	1	2-F	1	3'-Cl	$C_{20}H_{17}ClFN_3O_6$	450.08	450.2
7	-OH	H	1	3-Cl	2	2'-F, 5'-Cl	$C_{20}H_{16}Cl_2FN_3O_6$	484.04	484.4

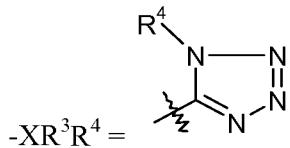
- (R)-3-[N-(3-Fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- (R)-3-[N-(3'-Chloro-3-cyano-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- (R)-3-[N-(2,3'-Dichloro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- (R)-3-[N-(5'-Chloro-3,2'-difluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid
- (R)-3-[N-(5'-Chloro-3,2'-difluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-

carbonyl)-hydrazino]-2-hydroxy-propionic acid

6. *(R)*-3-[N-(3'-Chloro-2-fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

7. *(R)*-3-[N-(3,5'-Dichloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(3-hydroxy-isoxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

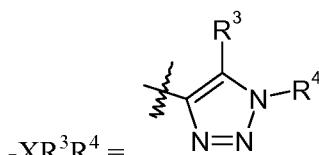
5



Ex.	R ³	R ⁴	a	R ⁵	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
								calcd	found
8	absent	H	1	3-F	1	3'-Cl	C ₁₈ H ₁₆ ClFN ₆ O ₄	435.09	435.2

8. *(R)*-3-[N-(3'-Chloro-3-fluoro-biphenyl-4-ylmethyl)-N'-(1H-tetrazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10



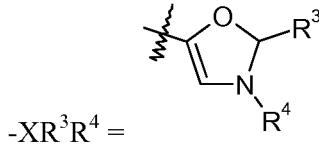
Ex.	R ³	R ⁴	a	R ⁵	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
								calcd	found
9	H	-OH	1	3-F	1	3'-Cl	C ₁₉ H ₁₇ ClFN ₅ O ₅	450.09	450.2
10	H	-OH	1	3-Cl	2	2'-F, 5'-Cl	C ₁₉ H ₁₆ Cl ₂ FN ₅ O ₄	468.06	468.2
11	H	-OH	1	3-Cl	1	3'-Cl	C ₁₉ H ₁₇ Cl ₂ N ₅ O ₄	450.07	452.0

9. *(R)*-3-[N-(3'-Chloro-3-fluoro-biphenyl-4-ylmethyl)-N'-(1-hydroxy-1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

10. *(R)*-3-[N-(3,5'-Dichloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

15. *(R)*-3-[N-(3,3'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid

11. *(R)*-3-[N-(3,3'-Dichloro-biphenyl-4-ylmethyl)-N'-(1H-[1,2,3]triazole-4-carbonyl)-hydrazino]-2-hydroxy-propionic acid



Ex.	R ³	R ⁴	a	R ⁵	b	R ⁶	Formula	MS m/z: [M+H] ⁺	
								calcd	found
12	=O	H	1	3-Cl	2	2'-F, 5'-Cl	C ₂₀ H ₁₆ Cl ₂ FN ₃ O ₆	484.04	484.0

20 12. *(R)*-3-[N-(3,5'-Dichloro-2'-fluoro-biphenyl-4-ylmethyl)-N'-(2-oxo-2,3-dihydro-oxazole-5-carbonyl)-hydrazino]-2-hydroxy-propionic acid (parent)

ASSAY 1*In vitro Assays for the Quantitation of Inhibitor Potencies (IC₅₀)**at Human and Rat NEP, and Human ACE*

The inhibitory activities of compounds at human and rat neprilysin (EC 3.4.24.11; 5 NEP) and human angiotensin converting enzyme (ACE) were determined using *in vitro* assays as described below.

Extraction of NEP Activity from Rat Kidneys

Rat NEP was prepared from the kidneys of adult Sprague Dawley rats. Whole kidneys were washed in cold phosphate buffered saline (PBS) and brought up in ice-cold 10 lysis buffer (1% Triton X-114, 150 mM NaCl, 50 mM tris(hydroxymethyl) aminomethane (Tris) pH 7.5; Bordier (1981) *J. Biol. Chem.* 256: 1604-1607) in a ratio of 5 mL of buffer for every gram of kidney. Samples were homogenized on ice using a polytron hand held tissue grinder. Homogenates were centrifuged at 1000 x g in a swinging bucket rotor for 5 minutes at 3°C. The pellet was resuspended in 20 mL of ice cold lysis buffer and 15 incubated on ice for 30 minutes. Samples (15-20 mL) were then layered onto 25 mL of ice-cold cushion buffer (6% w/v sucrose, 50 mM pH 7.5 Tris, 150 mM NaCl, 0.06%, Triton X-114), heated to 37°C for 3-5 minutes and centrifuged at 1000 x g in a swinging bucket rotor at room temperature for 3 minutes. The two upper layers were aspirated off, leaving a viscous oily precipitate containing the enriched membrane fraction. Glycerol 20 was added to a concentration of 50% and samples were stored at -20°C. Protein concentrations were quantitated using a BCA detection system with bovine serum albumin (BSA) as a standard.

Enzyme Inhibition Assays

Recombinant human NEP and recombinant human ACE were obtained 25 commercially (R&D Systems, Minneapolis, MN, catalog numbers 1182-ZN and 929-ZN, respectively). The fluorogenic peptide substrate Mca-D-Arg-Arg-Leu-Dap-(Dnp)-OH (Medeiros et al. (1997) *Braz. J. Med. Biol. Res.* 30:1157-62; Anaspec, San Jose, CA) and Abz-Phe-Arg-Lys(Dnp)-Pro-OH (Araujo et al. (2000) *Biochemistry* 39:8519-8525; Bachem, Torrance, CA) were used in the NEP and ACE assays respectively.

The assays were performed in 384-well white opaque plates at 37°C using the 30 fluorogenic peptide substrates at a concentration of 10 µM in Assay Buffer (NEP: 50 mM HEPES, pH 7.5, 100 mM NaCl, 0.01% polyethylene glycol sorbitan monolaurate (Tween-20), 10 µM ZnSO₄; ACE: 50 mM HEPES, pH 7.5, 100 mM NaCl, 0.01% Tween-20, 1 µM

ZnSO_4). The respective enzymes were used at concentrations that resulted in quantitative proteolysis of 1 μM of substrate after 20 minutes at 37°C.

Test compounds were assayed over the range of concentrations from 10 μM to 20 pM. Test compounds were added to the enzymes and incubated for 30 minute at 37°C 5 prior to initiating the reaction by the addition of substrate. Reactions were terminated after 20 minutes of incubation at 37°C by the addition of glacial acetic acid to a final concentration of 3.6% (v/v).

Plates were read on a fluorometer with excitation and emission wavelengths set to 320 nm and 405 nm, respectively. Inhibition constants were obtained by nonlinear 10 regression of the data using the equation (GraphPad Software, Inc., San Diego, CA):

$$v = v_0 / [1 + (I / K')]$$

where v is the reaction rate, v_0 is the uninhibited reaction rate, I is the inhibitor concentration and K' is the apparent inhibition constant.

Compounds of the invention were tested in this assay and found to have pK_i values 15 at human NEP as follows. In general, either the prodrug compounds did not inhibit the enzyme in this *in vitro* assay, or the prodrugs were not tested (n.d.) since activity would not be expected.

Ex.	pK_i
1	≥ 9.0
2-1	8.0-8.9
2-2	8.0-8.9
2-3	8.0-8.9
2-4	7.0-7.9
2-5	7.0-7.9
2-6	8.0-8.9
2-7	7.0-7.9
2-8	8.0-8.9
2-9	8.0-8.9
2-10	8.0-8.9
2-11	8.0-8.9
2-12	8.0-8.9
2-13	8.0-8.9
2-14	7.0-7.9
2-15	8.0-8.9
2-16	7.0-7.9
2-17	7.0-7.9
2-18	8.0-8.9
2-19	8.0-8.9
2-20	6.0-6.9
2-21	7.0-7.9

Ex.	pK_i
8-1	≥ 9.0
8-2	≥ 9.0
8-3	n.d.
8-4	8.0-8.9
8-5	8.0-8.9
8-6	8.0-8.9
8-7	8.0-8.9
8-8	≥ 9.0
8-9	≥ 9.0
8-10	n.d.
8-11	n.d.
8-12	n.d.
8-13	≥ 9.0
8-14	≥ 9.0
8-15	≥ 9.0
8-16	≥ 9.0
8-17	≥ 9.0
8-18	≥ 9.0
8-19	n.d.
8-20	n.d.
8-21	8.0-8.9
8-22	≥ 9.0

Ex.	pK _i
2-22	6.0-6.9
2-23	6.0-6.9
2-24	6.0-6.9
2-25	6.0-6.9
3A	n.d.
3B	≥9.0
3C	n.d.
3D	n.d.
3E	n.d.
3F	n.d.
3G	n.d.
3H	n.d.
3I	n.d.
3J	n.d.
3K	≥9.0
3L	n.d.
3M	n.d.
4-1	8.0-8.9
4-2	8.0-8.9
4-3	8.0-8.9
4-4	≥9.0
4-5	≥9.0
4-6	n.d.
4-7	n.d.
4-8	n.d.
4-9	8.0-8.9
4-10	8.0-8.9
4-11	≥9.0
4-12	≥9.0
4-13	≥9.0
4-14	≥9.0
4-15	≥9.0
4-16	≥9.0
4-17	≥9.0
4-18	≥9.0
4-19	8.0-8.9
4-20	8.0-8.9
4-21	8.0-8.9
4-22	≥9.0
4-23	≥9.0
4-24	8.0-8.9
4-25	≥9.0
4-26	8.0-8.9
4-27	8.0-8.9
4-28	7.0-7.9
4-29	≥9.0

Ex.	pK _i
8-23	8.0-8.9
8-24	8.0-8.9
8-25	≥9.0
8-26	7.0-7.9
8-27	≥9.0
8-28	7.0-7.9
8-29	8.0-8.9
8-30	≥9.0
8-31	≥9.0
8-32	≥9.0
8-33	8.0-8.9
8-34	8.0-8.9
8-35	≥9.0
8-36	≥9.0
8-37	n.d.
8-38	≥9.0
8-39	≥9.0
8-40	≥9.0
8-41	≥9.0
8-42	≥9.0
8-43	≥9.0
8-44	≥9.0
8-45	≥9.0
8-46	n.d.
8-47	8.0-8.9
8-48	8.0-8.9
8-49	≥9.0
8-50	≥9.0
8-51	8.0-8.9
8-52	8.0-8.9
8-53	8.0-8.9
8-54	8.0-8.9
8-55	8.0-8.9
8-56	8.0-8.9
8-57	8.0-8.9
8-58	≥9.0
8-59	≥9.0
8-60	≥9.0
8-61	n.d.
8-62	n.d.
8-63	n.d.
8-64	≥9.0
8-65	8.0-8.9
8-66	8.0-8.9
8-67	≥9.0
8-68	8.0-8.9

Ex.	pK _i	Ex.	pK _i
4-30	8.0-8.9	8-69	≥ 9.0
4-31	8.0-8.9	8-70	n.d.
4-32	8.0-8.9	8-71	n.d.
4-33	n.d.	8-72	n.d.
4-34	≥ 9.0	8-73	≥ 9.0
4-35	≥ 9.0	8-74	≥ 9.0
4-36	7.0-7.9	8-75	≥ 9.0
4-37	7.0-7.9	8-76	≥ 9.0
4-38	≥ 9.0	8-77	n.d.
4-39	8.0-8.9	8-78	n.d.
4-40	8.0-8.9	8-79	n.d.
4-41	8.0-8.9	8-80	≥ 9.0
4-42	8.0-8.9	8-81	7.0-7.9
5-1	8.0-8.9	8-82	≥ 9.0
5-2	7.0-7.9	8-83	≥ 9.0
5-3	8.0-8.9	8-84	n.d.
5-4	≥ 9.0	9A	≥ 9.0
5-5	8.0-8.9	9B	n.d.
5-6	8.0-8.9	9C	n.d.
5-7	8.0-8.9	10-1	8.0-8.9
5-8	8.0-8.9	10-2	8.0-8.9
5-9	8.0-8.9	10-3	≥ 9.0
5-10	8.0-8.9	10-4	≥ 9.0
6A	≥ 9.0	10-5	≥ 9.0
6B	n.d.	10-6	≥ 9.0
6C	n.d.	10-7	≥ 9.0
6D	n.d.	10-8	8.0-8.9
7A	≥ 9.0	10-9	≥ 9.0
7B	n.d.	10-10	≥ 9.0
7C	n.d.	10-11	≥ 9.0
7D	n.d.	10-12	n.d.

n.d. = not determined

ASSAY 2

5 Pharmacodynamic (PD) assay for ACE and NEP Activity in Anesthetized Rats

Male, Sprague Dawley, normotensive rats are anesthetized with 120 mg/kg (i.p.) of inactin. Once anesthetized, the jugular vein, carotid artery (PE 50 tubing) and bladder (flared PE 50 tubing) catheters are cannulated and a tracheotomy is performed (Teflon Needle, size 14 gauge) to facilitate spontaneous respiration. The animals are then allowed a 10 minute stabilization period and kept continuously infused with 5 mL/kg/h of saline (0.9%) throughout, to keep them hydrated and ensure urine production. Body temperature is maintained throughout the experiment by use of a heating pad. At the end of the 60

minute stabilization period, the animals are dosed intravenously (i.v.) with two doses of AngI (1.0 µg/kg, for ACE inhibitor activity) at 15 minutes apart. At 15 minutes post-second dose of AngI, the animals are treated with vehicle or test compound. Five minutes later, the animals are additionally treated with a bolus i.v. injection of atrial natriuretic peptide (ANP; 30 µg/kg). Urine collection (into pre-weighted eppendorf tubes) is started immediately after the ANP treatment and continued for 60 minutes. At 30 and 60 minutes into urine collection, the animals are re-challenged with AngI. Blood pressure measurements are done using the Notocord system (Kalamazoo, MI). Urine samples are frozen at -20 °C until used for the cGMP assay. Urine cGMP concentrations are 5 determined by Enzyme Immuno Assay using a commercial kit (Assay Designs, Ann Arbor, Michigan, Cat. No. 901-013). Urine volume is determined gravimetrically. Urinary cGMP output is calculated as the product of urine output and urine cGMP concentration. ACE inhibition is assessed by quantifying the % inhibition of pressor response to AngI. NEP inhibition is assessed by quantifying the potentiation of ANP-induced elevation in urinary 10 15 cGMP output.

ASSAY 3

In Vivo Evaluation of Antihypertensive Effects in the Conscious SHR Model of Hypertension

Spontaneously hypertensive rats (SHR, 14-20 weeks of age) are allowed a 20 minimum of 48 hours acclimation upon arrival at the testing site with free access to food and water. For blood pressure recording, these animals are surgically implanted with small rodent radiotransmitters (telemetry unit; DSI Models TA11PA-C40 or C50-PXT, Data Science Inc., USA). The tip of the catheter connected to the transmitter is inserted into the descending aorta above the iliac bifurcation and secured in place with tissue 25 adhesive. The transmitter is kept intraperitoneally and secured to the abdominal wall while closing of the abdominal incision with a non-absorbable suture. The outer skin is closed with suture and staples. The animals are allowed to recover with appropriate post operative care. On the day of the experiment, the animals in their cages are placed on top of the telemetry receiver units to acclimate to the testing environment and baseline 30 recording. After at least of 2 hours baseline measurement is taken, the animals are then dosed with vehicle or test compound and followed out to 24 hours post-dose blood pressure measurement. Data is recorded continuously for the duration of the study using Notocord software (Kalamazoo, MI) and stored as electronic digital signals. Parameters

measured are blood pressure (systolic, diastolic and mean arterial pressure) and heart rate.

ASSAY 4

In Vivo Evaluation of Antihypertensive Effects
in the Conscious DOCA-Salt Rat Model of Hypertension

5 CD rats (male, adult, 200-300 grams, Charles River Laboratory, USA) are allowed a minimum of 48 hours acclimation upon arrival at the testing site before they are placed on a high salt diet. One week after the start of the high salt diet (8% in food or 1% NaCl in drinking water), a deoxycorticosterone acetate (DOCA) pellet (100 mg, 90 days release time, Innovative Research of America, Sarasota, FL) is implanted subcutaneously and
10 unilateral nephrectomy is performed. At this time, the animals are also surgically implanted with small rodent radiotransmitters for blood pressure measurement (see Assay 3 for details). The animals are allowed to recover with appropriate post operative care. Study design, data recording, and parameters measured is similar to that described for Assay 3.

15

ASSAY 5

In Vivo Evaluation of Antihypertensive Effects
in the Conscious Dahl/SS Rat Model of Hypertension

Male, Dahl salt sensitive rats (Dahl/SS, 6-7 weeks of age from Charles River Laboratory, USA) are allowed at least 48 hours of acclimation upon arrival at the testing site before they were placed on a 8% NaCl high salt diet (TD.92012, Harlan, USA) then surgically implanted with small rodent radiotransmitters for blood pressure measurement (see Assay 3 for details). The animals are allowed to recover with appropriate post operative care. At approximately 4 to 5 weeks from the start of high salt diet, these animals are expected to become hypertensive. Once the hypertension level is confirmed, 25 these animals are used for the study while continued with the high salt diet to maintain their hypertension level. Study design, data recording, and parameters measured is similar to that described in Assay 3.

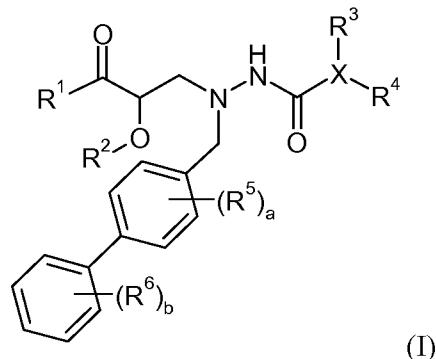
While the present invention has been described with reference to specific aspects or embodiments thereof, it will be understood by those of ordinary skilled in the art that 30 various changes can be made or equivalents can be substituted without departing from the true spirit and scope of the invention. Additionally, to the extent permitted by applicable patent statutes and regulations, all publications, patents and patent applications cited herein are hereby incorporated by reference in their entirety to the same extent as if each

document had been individually incorporated by reference herein.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of formula I:



5 where:

R¹ is selected from -OR⁷ and -NR⁸R⁹;

R² is H or -P(O)(OH)₂ or R² is taken together with R⁷ to form -CR¹⁸R¹⁹- or is taken together with R⁸ to form -C(O)-;

X is a -C₁₋₉heteroaryl;

10 R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -NH₂; -C₁₋₆alkyl; -CF₃; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; -NO₂; -C(CH₃)=N(OH); phenyl optionally substituted with one or two groups independently selected from halo, -OH, -CF₃, -OCH₃, -NHC(O)CH₃, and phenyl; naphthalenyl; pyridinyl; pyrazinyl; pyrazole optionally substituted with methyl; thiophenyl optionally substituted with methyl or halo; furanyl; and -CH₂-morpholinyl; and R³, when present, is attached to a carbon atom;

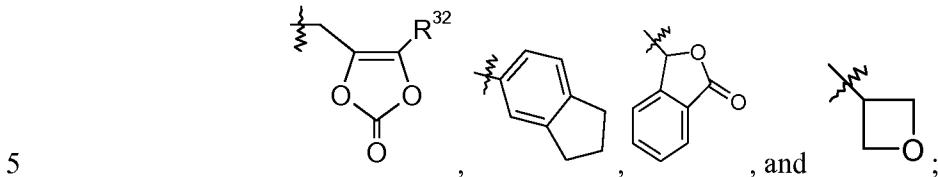
15 R⁴ is absent or is selected from H; -OH; -C₁₋₆alkyl; -C₁₋₂alkylene-COOR³⁵; -CH₂OC(O)CH(R³⁶)NH₂; -OCH₂OC(O)CH(R³⁶)NH₂; -OCH₂OC(O)CH₃; -CH₂OP(O)(OH)₂; -CH₂CH(OH)CH₂OH; -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl; pyridinyl; 20 and phenyl or benzyl optionally substituted with one or more groups selected from halo, -COOR³⁵, -OCH₃, -OCF₃, and -SCF₃; and R⁴, when present, is attached to a carbon or nitrogen atom;

or R³ and R⁴ are taken together to form -phenylene-O-(CH₂)₁₋₃- or -phenylene-O-CH₂-CHOH-CH₂-;

25 a is 0 or 1; R⁵ is selected from halo, -CH₃, -CF₃, and -CN;

b is 0 or an integer from 1 to 3; each R⁶ is independently selected from halo, -OH, -CH₃, -OCH₃, and -CF₃;

R^7 is selected from H, -C₁₋₈alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R¹⁰, -C₁₋₆alkylene-NR¹²R¹³, -C₁₋₆alkylene-C(O)R³¹, -C₀₋₆alkylenemorpholinyl; -C₁₋₆alkylene-SO₂-C₁₋₆alkyl;



R^{10} is selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₇cycloalkyl, -O-C₃₋₇cycloalkyl, phenyl, -O-phenyl, -NR¹²R¹³, -CH[CH(CH₃)₂]-NH₂, -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, and -CH(NH₂)CH₂COOCH₃; and R¹² and R¹³ are independently selected from H, -C₁₋₆alkyl, and benzyl; or R¹² and R¹³ are taken together as -(CH₂)₃₋₆-, -C(O)-(CH₂)₃-, or 10 -(CH₂)₂O(CH₂)₂-, and R³¹ is selected from -O-C₁₋₆alkyl, -O-benzyl, and -NR¹²R¹³; R³² is -C₁₋₆alkyl or -C₀₋₆alkylene-C₆₋₁₀aryl;

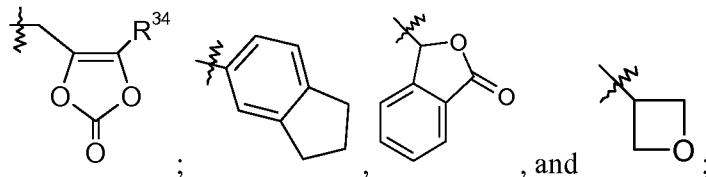
R^8 is selected from H, -OH, -OC(O)R¹⁴, -CH₂COOH, -O-benzyl, pyridyl, and -OC(S)NR¹⁵R¹⁶; R¹⁴ is selected from H, -C₁₋₆alkyl, -C₆₋₁₀aryl, -OCH₂-C₆₋₁₀aryl, -CH₂O-C₆₋₁₀aryl, and -NR¹⁵R¹⁶; and R¹⁵ and R¹⁶ are independently selected from H and -C₁₋₄alkyl;

15 R^9 is selected from H, -C₁₋₆alkyl, and -C(O)R¹⁷; and R¹⁷ is selected from H, -C₁₋₆alkyl, -C₃₋₇cycloalkyl, -C₆₋₁₀aryl, and -C₁₋₉heteroaryl;

R^{18} and R¹⁹ are independently selected from H, -C₁₋₆alkyl, and -O-C₃₋₇cycloalkyl, or R¹⁸ and R¹⁹ are taken together to form =O;

R^{20} is selected from H and -C₁₋₆alkyl;

20 R^{21} and R³⁵ are independently selected from H, -C₁₋₆alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R²⁵, -C₁₋₆alkylene-NR²⁷R²⁸, -C₁₋₆alkylene-C(O)R³³, -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-SO₂-C₁₋₆alkyl,



25 R^{25} is selected from -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₃₋₇cycloalkyl, -O-C₃₋₇cycloalkyl, phenyl, -O-phenyl, -NR²⁷R²⁸, -CH[CH(CH₃)₂]-NH₂, -CH[CH(CH₃)₂]-NHC(O)O-C₁₋₆alkyl, and -CH(NH₂)CH₂COOCH₃; R²⁷ and R²⁸ are independently selected from H, -C₁₋₆alkyl, 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 -CONH₂; 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 15 two $-C_{1-6}alkyl$ groups or cyclopropyl;

or a pharmaceutically acceptable salt thereof.

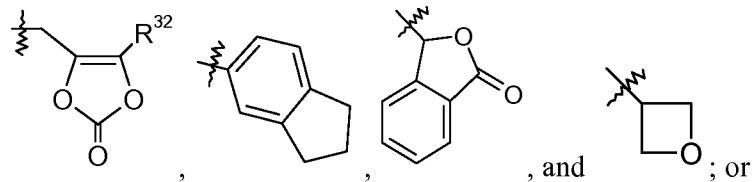
2. The compound of Claim 1, where X is selected from pyrazole, imidazole, triazole, benzotriazole, furan, pyrrole, tetrazole, pyrazine, thiophene, oxazole, isoxazole, thiazole, isothiazole, oxadiazole, thiadiazole, pyridazine, pyridine, pyrimidine, pyran, 20 benzimidazole, benzoxazole, benzothiazole, pyridylimidazole, and pyridyltriazole.

3. The compound of Claim 2, where X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, pyrimidine, and pyridyltriazole.

4. The compound as claimed in any one of Claims 1 to 3, where R^1 is selected from 25 $-OR^7$ and $-NR^8R^9$, where R^7 is H, R^8 is H or -OH, and R^9 is H.

5. The compound claimed in any one of Claims 1 to 3, where:

R^1 is $-OR^7$; and R^7 is selected from $-C_{1-8}alkyl$, $-C_{1-3}alkylene-C_{6-10}aryl$, $-C_{1-3}alkylene-C_{1-9}heteroaryl$, $-C_{3-7}cycloalkyl$, $-[(CH_2)_2O]_{1-3}CH_3$, $-C_{1-6}alkylene-OC(O)R^{10}$, $-C_{1-6}alkylene-NR^{12}R^{13}$, $-C_{1-6}alkylene-C(O)R^{31}$, $-C_{0-6}alkylenemorpholinyl$, $-C_{1-6}alkylene-30 SO_2-C_{1-6}alkyl$,



5 R^1 is $-NR^8R^9$; R^8 is selected from $-OC(O)R^{14}$, $-CH_2COOH$, $-O\text{-benzyl}$, pyridyl, and $-OC(S)NR^{15}R^{16}$; and R^9 is H; or

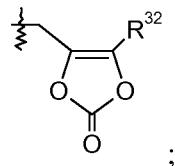
5 R^1 is $-NR^8R^9$; R^8 is selected from $-OC(O)R^{14}$, $-CH_2COOH$, $-O\text{-benzyl}$, pyridyl, and $-OC(S)NR^{15}R^{16}$; and R^9 is $-C_{1-6}\text{alkyl}$ or $-C(O)R^{17}$;

10 R^1 is $-NR^8R^9$; R^8 is selected from H or $-OH$; and R^9 is selected from $-C_{1-6}\text{alkyl}$, and $-C(O)R^{17}$;

R^1 is $-OR^7$ and R^2 is taken together with R^7 to form $-CR^{18}R^{19}$; or

R^1 is $-NR^8R^9$ and R^2 is taken together with R^8 to form $-C(O)-$.

10 6. The compound claimed in any one of Claims 1 to 3, where R^1 is $-OR^7$, where R^7 is selected from H, $-C_{1-8}\text{alkyl}$, $-C_{1-3}\text{alkylene-C}_{6-10}\text{aryl}$, $-C_{0-6}\text{alkylenemorpholinyl}$, and



where R^{32} is $-C_{1-6}\text{alkyl}$; and where each alkyl group is optionally substituted with 1 to 8 fluoro atoms.

15 7. The compound as claimed in any one of Claims 1 to 6, where R^2 is H.

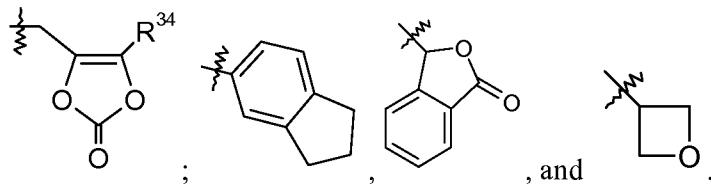
8. The compound as claimed in any one of Claims 1 to 7, where R^3 is absent or is selected from H; halo; $-C_{0-5}\text{alkylene-OH}$; $-NH_2$; $-C_{1-6}\text{alkyl}$; $-CF_3$; $-C_{3-7}\text{cycloalkyl}$; $-C_{0-2}\text{alkylene-O-C}_{1-6}\text{alkyl}$; $-C(O)R^{20}$; $-C_{0-1}\text{alkylene-COOR}^{21}$; $-C(O)NR^{22}R^{23}$; $-NHC(O)R^{24}$; $=O$; $-NO_2$; $-C(CH_3)=N(OH)$; phenyl optionally substituted with one or two groups

20 independently selected from halo, $-OH$, $-CF_3$, $-OCH_3$, $-NHC(O)CH_3$, and phenyl; naphthalenyl; pyridinyl; pyrazinyl; pyrazolyl optionally substituted with methyl; thiophenyl optionally substituted with methyl or halo; furanyl; and $-CH_2\text{-morpholinyl}$; and R^{21} is H.

9. The compound as claimed in any one of Claims 1 to 7, where R^3 is

25 $-C_{0-1}\text{alkylene-COOR}^{21}$; and R^{21} is selected from $-C_{1-6}\text{alkyl}$, $-C_{1-3}\text{alkylene-C}_{6-10}\text{aryl}$, $-C_{1-3}\text{alkylene-C}_{1-9}\text{heteroaryl}$, $-C_{3-7}\text{cycloalkyl}$, $-[(CH_2)_2O]_{1-3}CH_3$, $-C_{1-6}\text{alkylene-OC(O)R}^{25}$; $-C_{1-6}\text{alkylene-NR}^{27}R^{28}$, $-C_{1-6}\text{alkylene-C(O)R}^{33}$, $-C_{0-6}\text{alkylenemorpholinyl}$, $-C_{1-6}\text{alkylene-}$

SO₂-C₁₋₆alkyl,

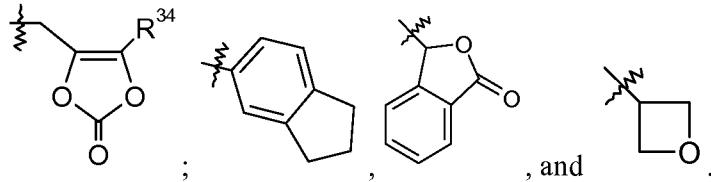


, and

10. The compound as claimed in any one of Claims 1 to 7, where R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -C₁₋₆alkyl; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; phenyl optionally substituted with one or two groups independently selected from halo, -OH, and -OCH₃; pyridinyl; and pyrazinyl; R²⁰ is -C₁₋₆alkyl; R²¹ is H; R²² is H or -C₁₋₆alkyl; R²³ is selected from -C₁₋₆alkyl, -(CH₂)₂OH, -(CH₂)₂OCH₃, -(CH₂)₂SO₂NH₂, and -C₀₋₁alkylene-C₃₋₇cycloalkyl; or R²² and R²³ are taken together to form a saturated or partially unsaturated C₃₋₅heterocycle optionally substituted with halo or -OH, and optionally containing an oxygen atom in the ring; and R²⁴ is phenyl substituted with -OCH₃.

11. The compound as claimed in any one of Claims 1 to 10, where R⁴ is absent or is selected from H; -OH; -C₁₋₆alkyl; -C₁₋₂alkylene-COOR³⁵; -CH₂OC(O)CH(R³⁶)NH₂, -CH₂CH(OH)CH₂OH; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo, -COOR³⁵, -OCH₃, -OCF₃, and -SCF₃; and R³⁵ is H.

12. The compound as claimed in any one of Claims 1 to 10, where R⁴ is selected from -OCH₂OC(O)CH₃; -CH₂OP(O)(OH)₂; -C₁₋₂alkylene-COOR³⁵; and phenyl or benzyl substituted with at least one -COOR³⁵ group; where R³⁵ is selected from -C₁₋₆alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₁₋₃alkylene-C₁₋₉heteroaryl, -C₃₋₇cycloalkyl, -[(CH₂)₂O]₁₋₃CH₃, -C₁₋₆alkylene-OC(O)R²⁵; -C₁₋₆alkylene-NR²⁷R²⁸, -C₁₋₆alkylene-C(O)R³³, -C₀₋₆alkylenemorpholinyl, -C₁₋₆alkylene-SO₂-C₁₋₆alkyl,



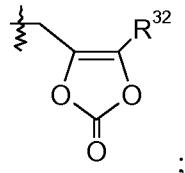
, and

13. The compound as claimed in any one of Claims 1 to 10, where R⁴ is selected from H; -OH; -C₁₋₂alkylene-COOR³⁵; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo and -OCH₃; and R³⁵ is H.

14. The compound as claimed in any one of Claims 1 to 13, where a is 0; or a is 1 and R⁵ is selected from halo and -CN.

15. The compound as claimed in any one of Claims 1 to 14, where b is 0; or b is 1 and R⁶ is selected from Cl, F, -OH, -CH₃, -OCH₃, and -CF₃; or b is 2 and each R⁶ is independently halo, -OH, -CH₃, or -OCH₃; or b is 3 and each R⁶ is independently halo or -CH₃.

5 16. The compound of Claim 1, where R¹ is OR⁷; R² is H; X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, pyrimidine, and pyridyltriazole; R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -C₁₋₆alkyl; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; phenyl optionally substituted with one or two groups independently selected from halo, -OH, and -OCH₃; pyridinyl; and pyrazinyl; R⁴ is selected from H; -OH; -C₁₋₂alkylene-COOR³⁵; pyridinyl; and phenyl or benzyl optionally substituted with one or more groups selected from halo and -OCH₃; a is 0; or a is 1 and R⁵ is selected from halo and -CN; b is 0; or b is 1 and R⁶ is selected from Cl, F, -OH, -CH₃, -OCH₃, and -CF₃; or b is 2 and each R⁶ is independently halo, -OH, -CH₃, or -OCH₃; or b is 3 and each R⁶ is independently halo or -CH₃; R⁷ is selected from H, -C₁₋₈alkyl, -C₁₋₃alkylene-C₆₋₁₀aryl, -C₀₋₆alkylenemorpholinyl, and



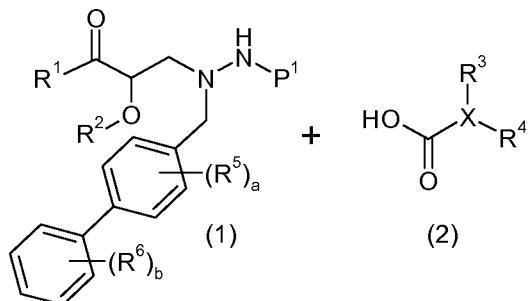
R³² is -C₁₋₆alkyl; R²⁰ is -C₁₋₆alkyl; R²¹ is H; R²² is H or -C₁₋₆alkyl; R²³ is selected from -C₁₋₆alkyl, -(CH₂)₂OH, -(CH₂)₂OCH₃, -(CH₂)₂SO₂NH₂, and -C₀₋₁alkylene-C₃₋₇cycloalkyl;

20 or R²² and R²³ are taken together to form a saturated or partially unsaturated -C₃₋₅heterocycle optionally substituted with halo or -OH, and optionally containing an oxygen atom in the ring; R²⁴ is phenyl substituted with -OCH₃; and R³⁵ is H; and where each alkyl group in R¹ is optionally substituted with 1 to 8 fluoro atoms.

17. The compound of Claim 1, where R¹ is OR⁷; R² is H; X is selected from pyrazole, triazole, benzotriazole, tetrazole, oxazole, isoxazole, thiazole, pyridazine, and pyrimidine; R³ is absent or is selected from H; halo; -C₀₋₅alkylene-OH; -C₁₋₆alkyl; -C₃₋₇cycloalkyl; -C₀₋₂alkylene-O-C₁₋₆alkyl; -C(O)R²⁰; -C₀₋₁alkylene-COOR²¹; -C(O)NR²²R²³; -NHC(O)R²⁴; =O; phenyl substituted with one or two groups independently selected from halo, -OH, and -OCH₃; pyridinyl; and pyrazinyl; R⁴ is selected from H, -OH, and phenyl optionally substituted with a halo group; a is 0; or a is 1 and R⁵ is halo; b is 0; or b is 1 and R⁶ is halo

or -CH₃; or b is 2 and each R⁶ is independently halo, -OH, -CH₃, or -OCH₃; R²⁰ is -C₁₋₆alkyl; R²¹ is H; R²² is -C₁₋₆alkyl; R²³ is -C₁₋₆alkyl or -C₀₋₁alkylene-C₃₋₇cycloalkyl; or R²² and R²³ are taken together to form a saturated -C₃₋₅heterocycle optionally substituted with halo or -OH; and R²⁴ is phenyl substituted with -OCH₃.

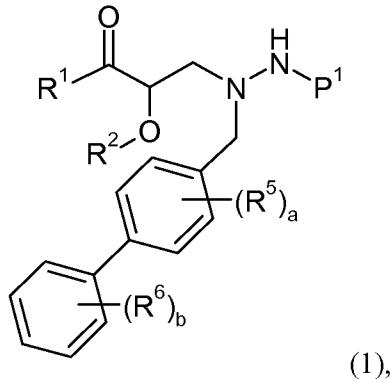
5 18. A process for preparing a compound as claimed in any one of Claims 1 to 17, comprising the step of coupling a compound of formula 1 with a compound of formula 2:



to produce a compound of formula I; where P¹ is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl,

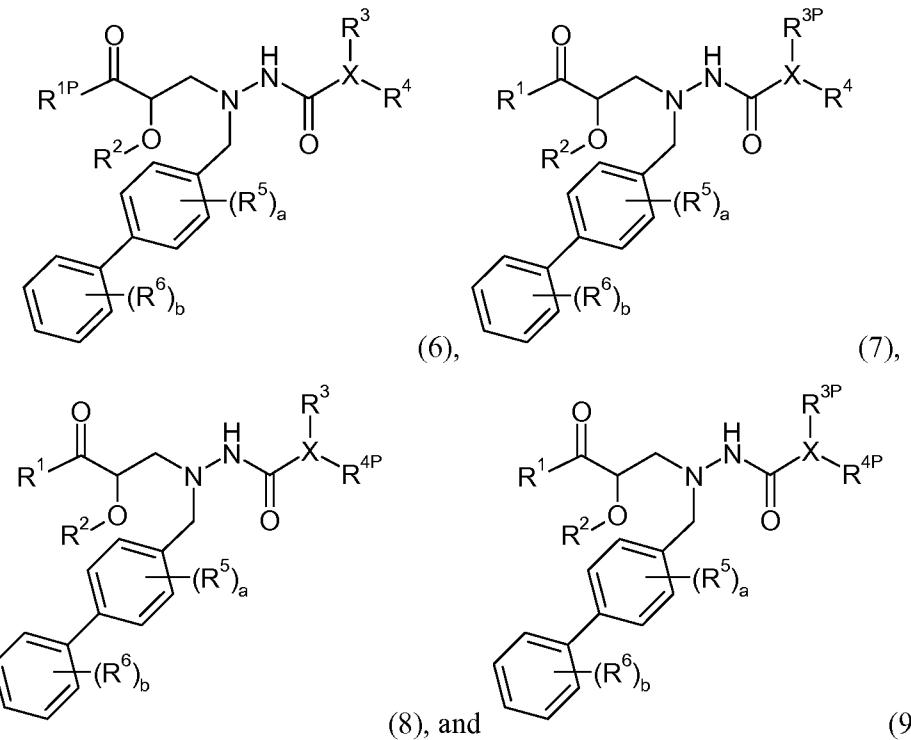
10 trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises deprotecting the compound of formula 1 when P¹ is an amino protecting group.

19. An intermediate useful in the synthesis of a compound as claimed in any one of Claims 1 to 17, having formula 1:



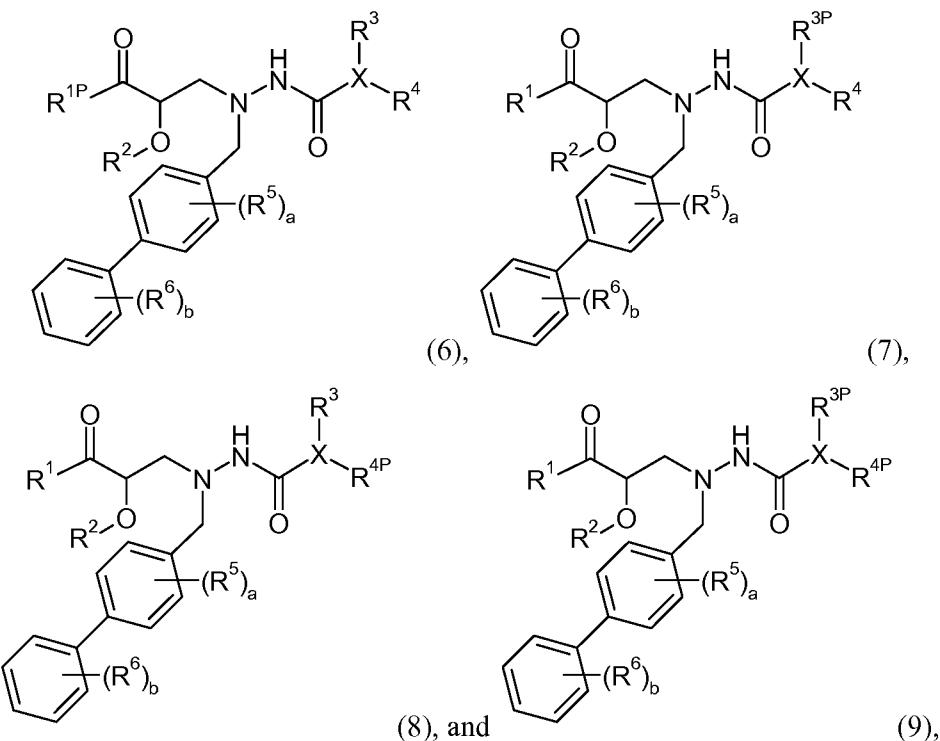
15 where P¹ is H or an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; or a salt thereof.

20. A process for preparing a compound as claimed in any one of Claims 1 to 17, comprising the step of deprotecting a compound selected from:



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 $-C_{0.5}\text{alkylene}-O-P^4$, $-C_{0.1}\text{alkylene}-COO-P^3$, and phenyl substituted with $-O-P^4$; R^{4P} is selected from $-O-P^4$; $-C_{1.2}\text{alkylene}-COO-P^3$; and phenyl or benzyl substituted with $-COO-P^3$; P^2 is an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzoyloxycarbonyl, 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 $-C_{1-6}\text{alkyl}$, $triC_{1-6}\text{alkylsilyl}$, $-C_{1-6}\text{alkanoyl}$, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl.

21. An intermediate useful in the synthesis of a compound as claimed in any one of Claims 1 to 17, selected from:



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 $-C_{0.5}\text{alkylene}-O-P^4$, $-C_{0.1}\text{alkylene}-COO-P^3$, and phenyl substituted with $-O-P^4$; R^{4P} is selected from $-O-P^4$; $-C_{1.2}\text{alkylene}-COO-P^3$; and phenyl or benzyl substituted with $-COO-P^3$; P^2 is an amino-protecting group selected from *t*-butoxycarbonyl, trityl, benzoyloxycarbonyl, 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 $-C_{1-6}\text{alkyl}$, $triC_{1-6}\text{alkylsilyl}$, $-C_{1-6}\text{alkanoyl}$, benzoyl, benzyl, *p*-methoxybenzyl, 9-fluorenylmethyl, and diphenylmethyl.

22. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 17 and a pharmaceutically acceptable carrier.

15 23. The pharmaceutical composition of Claim 22, further comprising a therapeutic agent selected from adenosine receptor antagonists, α -adrenergic receptor antagonists, β_1 -adrenergic receptor antagonists, β_2 -adrenergic receptor agonists, dual-acting β -adrenergic receptor antagonist/ α_1 -receptor antagonists, advanced glycation end product breakers, aldosterone antagonists, aldosterone synthase inhibitors, aminopeptidase N inhibitors, 20 androgens, angiotensin-converting enzyme inhibitors and dual-acting angiotensin-

converting enzyme/neprilysin inhibitors, angiotensin-converting enzyme 2 activators and stimulators, angiotensin-II vaccines, anticoagulants, anti-diabetic agents, antidiarrheal agents, anti-glaucoma agents, anti-lipid agents, antinociceptive agents, anti-thrombotic agents, AT₁ receptor antagonists and dual-acting AT₁ receptor antagonist/neprilysin

5 inhibitors and multifunctional angiotensin receptor blockers, bradykinin receptor antagonists, calcium channel blockers, chymase inhibitors, digoxin, diuretics, dopamine agonists, endothelin converting enzyme inhibitors, endothelin receptor antagonists, HMG-CoA reductase inhibitors, estrogens, estrogen receptor agonists and/or antagonists, monoamine reuptake inhibitors, muscle relaxants, natriuretic peptides and their analogs,

10 natriuretic peptide clearance receptor antagonists, neprilysin inhibitors, nitric oxide donors, non-steroidal anti-inflammatory agents, N-methyl d-aspartate receptor antagonists, opioid receptor agonists, phosphodiesterase inhibitors, prostaglandin analogs, prostaglandin receptor agonists, renin inhibitors, selective serotonin reuptake inhibitors, sodium channel blocker, soluble guanylate cyclase stimulators and activators, tricyclic antidepressants,

15 vasopressin receptor antagonists, and combinations thereof.

24. The pharmaceutical composition of Claim 23, wherein the therapeutic agent is an AT₁ receptor antagonist.

25. A compound as claimed in any one of Claims 1 to 17, for use in therapy.

26. A compound as claimed in Claim 25, for use in treating hypertension, heart failure,

20 or renal disease.

27. The use of a compound as claimed in any one of Claims 1 to 17, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2011/064837

A. CLASSIFICATION OF SUBJECT MATTER				
INV.	C07D231/14	C07D231/20	C07D231/22	C07D231/40
	C07D239/36	C07D239/54	C07D249/04	C07D249/10
	C07D249/18	C07D257/04	C07D261/18	C07D263/34
				C07D263/38

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/136474 A2 (NOVARTIS AG [CH]; COPPOLA GARY MARK [US]; IWAKI YUKI [US]; KARKI RAJES) 2 December 2010 (2010-12-02) claims 1, 12-19 examples 49-1	1-15, 18-27
A	----- WO 2010/136493 A1 (NOVARTIS AG [CH]; COPPOLA GARY MARK [US]; IWAKI YUKI [US]; KARKI RAJES) 2 December 2010 (2010-12-02) claims 1,13-18	16,17
A	-----	1-27



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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INTERNATIONAL SEARCH REPORT

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