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NEPRILYSIN INHIBITORS**BACKGROUND OF THE INVENTION****FIELD OF THE INVENTION**

The present invention relates to novel compounds having neprilysin-inhibition activity. The invention also relates to pharmaceutical compositions comprising these
10 compounds, processes and intermediates for preparing these compounds and methods of using these compounds to treat diseases such as hypertension, heart failure, pulmonary hypertension, and renal disease.

STATE OF THE ART

Neprilysin (neutral endopeptidase, EC 3.4.24.11) (NEP), is an endothelial
15 membrane bound Zn^{2+} metallopeptidase found in many organs and tissues, including the brain, kidneys, lungs, gastrointestinal tract, heart, and the peripheral vasculature. NEP degrades and inactivates a number of endogenous peptides, such as enkephalins, circulating bradykinin, angiotensin peptides, and natriuretic peptides, the latter of which have several effects including, for example, vasodilation and natriuresis/diuresis, as well as
20 inhibition of cardiac hypertrophy and ventricular fibrosis. Thus, NEP plays an important role in blood pressure homeostasis and cardiovascular health.

NEP inhibitors, such as thiorphan, candoxatril, and candoxatrilat, have been studied as potential therapeutics. Compounds that inhibit both NEP and angiotensin-I converting enzyme (ACE) are also known, and include omapatrilat, gempatrilat, and sampatrilat.
25 Referred to as vasopeptidase inhibitors, this latter class of compounds is described in Robl et al. (1999) *Exp. Opin. Ther. Patents* 9(12): 1665-1677.

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

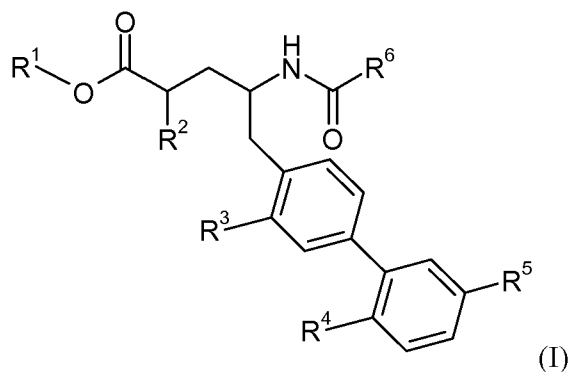
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SUMMARY OF THE INVENTION

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

as hypertension and heart failure.

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



where:

- 5 R^1 is H, $-C_{1-8}$ alkyl, $-\text{CH}(\text{CH}_3)\text{OC}(\text{O})-\text{O}-\text{cyclohexyl}$, $-(\text{CH}_2)_2-\text{morpholinyl}$, or $-\text{CH}_2-$ 5-methyl-[1,3]dioxol-2-one;
- R^2 is $-\text{CH}_2-\text{O}-R^{20}$, $-\text{C}_{0-1}$ alkylene-NHC(O)- R^{21} , $-\text{C}_{0-3}$ alkylene-NR²²R²³, $-\text{CH}_2-R^{24}$, oxetane, 2-pyridine, 3-pyridine, thiophene, tetrahydropyran, or piperidine and having H or $-\text{C}(\text{O})\text{CH}_3$ on the nitrogen, said tetrahydropyran and piperidine being attached at the 4-
- 10 position; where R^{20} is $-C_{1-6}$ alkyl, $-\text{CH}_2\text{NR}^{27}\text{CHR}^{28}$ -, $-\text{C}_{2-3}$ alkylene-OH, or $-\text{C}_{2-3}$ alkylene-NR²⁹R³⁰; R^{21} is $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{C}_{0-6}$ alkylene-NR²⁵R²⁵, $-\text{CH}(\text{NH}_2)-R^{26}$, $-\text{C}_{1-4}$ alkylene-NHC(O)O- $-C_{1-6}$ alkyl, $-\text{OCH}(\text{CH}_3)\text{OC}(\text{O})\text{CH}(\text{CH}_3)_2$, or pyrrolidine attached at a carbon atom; R^{22} is H or $-C_{1-6}$ alkyl; R^{23} is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-\text{SO}_2-C_{1-6}$ alkyl, $-\text{CH}_2\text{OC}(\text{O})-C_{1-6}$ alkyl, $-\text{C}_{2-4}$ alkylene-OH,
- 15 $-\text{C}_{2-4}$ alkylene-O-CH₃, or cyclopropyl optionally substituted with one or two R^{31} groups; or R^{22} and R^{23} are taken together to form $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$, a 2-oxa-6-aza-spiro[3.3]heptane ring, or an azetidine ring optionally substituted with one or two R^{31} groups; R^{24} is $-\text{CH}_2\text{OH}$, $-\text{CN}$, $-\text{C}(\text{O})\text{NH}_2$, triazole or imidazole attached at a nitrogen atom, or oxadiazolone or tetrazole attached at the carbon atom; each R^{25} is independently H or $-\text{CH}_3$; R^{26} is
- 20 $-\text{C}_{1-4}$ alkylene-NH₂, $-\text{CH}_2\text{OH}$, or benzyl; R^{27} is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-(\text{CH}_2)_2\text{OH}$, or $-(\text{CH}_2)_2\text{OC}_{1-6}$ alkyl; R^{28} is H, $-C_{1-6}$ alkyl, $-\text{C}_{1-2}$ alkylene-OH, or $-\text{C}_{1-2}$ alkylene-OC₁₋₆alkyl; R^{29} and R^{30} are independently H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-(\text{CH}_2)_2\text{OH}$, or $-(\text{CH}_2)_2\text{OC}_{1-6}$ alkyl; or R^{29} and R^{30} are taken together to form $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and each R^{31} is independently halo, $-C_{1-6}$ alkyl,
- 25 $-\text{C}_{0-2}$ alkylene-OH, $-\text{C}_{0-2}$ alkylene-OC₁₋₆alkyl, $-\text{CN}$, or $-\text{CONH}_2$;
- R^3 , R^4 and R^5 are independently H or halo;
- R^6 is a heterocycle selected from the group consisting of 3H-oxazol-2-one,

[1,2,4]oxadiazol-5-one, [1,2,3,5]oxatriazole, dihydro-[1,2,4]triazol-3-one, [1,2,4]triazolo[1,5- α]pyridine, triazole, pyrazole, imidazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, and pyrimidine; the heterocycle is attached at a carbon atom; and each nitrogen atom in the heterocycle is unsubstituted or substituted with an R⁶⁰ group selected from the group consisting of -OH, -(CH₂)₂OH, -C₀₋₂alkylene-O-C₁₋₆alkyl, -C₁₋₆alkyl, -CHF₂, -CF₃, and phenyl; and each carbon atom in the heterocycle is unsubstituted or substituted with an R⁶¹ group independently selected from the group consisting of halo, -OH, -C₁₋₆alkyl, -C₀₋₂alkylene-O-C₁₋₆alkyl, -C(O)CH₃, -C(O)NH(CH₃), -C(O)N(CH₃)₂, -C₃₋₆cycloalkyl, -CF₃, -CH₂SO₂CH₃, -NH₂, -CH₂NH₂, -CH₂N(CH₃)₂, pyrazine, and phenyl substituted with methyl or halo; or a pharmaceutically acceptable salt thereof.

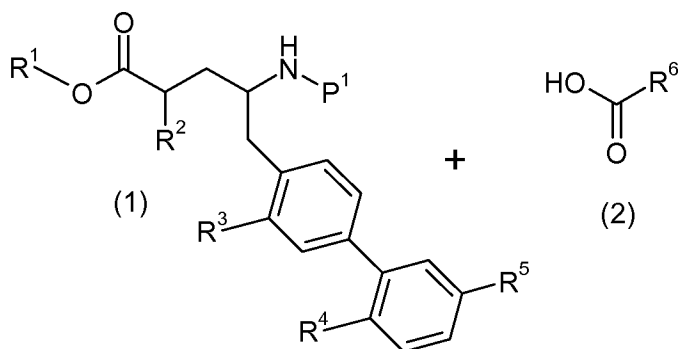
Another aspect of the invention relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the invention. Such compositions may optionally contain other therapeutic agents.

Compounds of the invention possess NEP enzyme inhibition activity, and are therefore expected to be useful as therapeutic agents for treating patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme or by increasing the levels of its peptide substrates. Thus, one aspect 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, 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 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) conducting a biological assay with a test compound to provide a first assay value; (b) conducting the biological assay with a compound of the invention to provide a second

assay value; wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include a NEP enzyme inhibition assay. Still another aspect 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 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 the group consisting of *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; and where the process further comprises deprotecting the compound of formula 1 when P^1 is an amino protecting group; and where R^1 - R^6 are as defined for formula I. In other aspects, the invention relates to products prepared by any of the processes described herein, as well as novel intermediates used in such process. In one aspect of the invention novel intermediates have formula 1, 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 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

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

5 corresponding plural forms unless the context of use clearly dictates otherwise. The terms "comprising," "including," and "having" are intended to be inclusive and mean that there may be additional elements other than the listed elements. All numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used herein are to be understood as being modified in all instances by the term
10 "about," unless otherwise indicated. Accordingly, the numbers set forth herein are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each number should at least be construed in light of the reported significant digits and by applying ordinary rounding techniques.

15 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, -C₁₋₆alkyl, meaning an alkyl group having from 1 to 6 carbon atoms where the carbon atoms are in any acceptable configuration. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl,
20 isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, *n*-hexyl, and the like.

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-, -C₀₋₂alkylene-, -C₁₋₂alkylene-, -C₁₋₆alkylene-, and so form. Representative alkylene groups include, by way
25 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 -C₀₋₂alkylene-, such terms are intended to include the absence of carbon atoms, that is, the alkylene group is not present except for a covalent bond attaching the groups separated by the alkylene term.

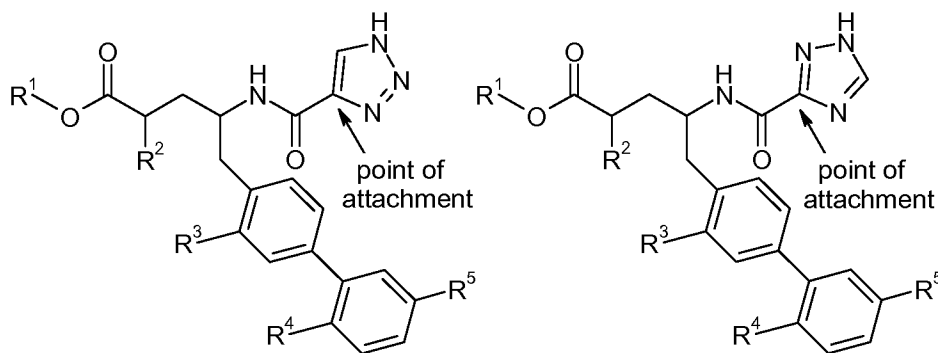
30 The term "cycloalkyl" means a monovalent saturated carbocyclic hydrocarbon group. Unless otherwise defined, such cycloalkyl groups typically contain from 3 to 10 carbon atoms and include, for example, -C₃₋₅cycloalkyl, -C₃₋₆cycloalkyl and -C₃₋₇cycloalkyl. Representative cycloalkyl groups include, by 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 (e.g., -C₁₋₇heterocycle, -C₃₋₅heterocycle, -C₂₋₆heterocycle, -C₃₋₁₂heterocycle, -C₅₋₉heterocycle, -C₁₋₉heterocycle, -C₁₋₁₁heterocycle, and -C₁₋₁₄heterocycle), and 1 to 4 are ring heteroatoms selected from nitrogen, oxygen or sulfur. Typically, 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. Exemplary heterocycles include, for example, -C₁₋₇heterocycle, -C₃₋₅heterocycle, -C₂₋₆heterocycle, -C₃₋₁₂heterocycle, -C₅₋₉heterocycle, -C₁₋₉heterocycle, -C₁₋₁₁heterocycle, and -C₁₋₁₄heterocycle. Exemplary heterocycles include 3H-oxazol-2-one, 4H-[1,2,4]oxadiazol-5-one, dihydro-[1,2,4]triazol-3-one, [1,2,3,5]oxatriazole, triazole, pyrazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, and pyrimidine.

When a heterocycle is described as being "attached at a carbon atom," it means that the point of attachment is at any available carbon ring atom. Examples of heterocycles attached at a carbon atom are the triazole rings illustrated below:



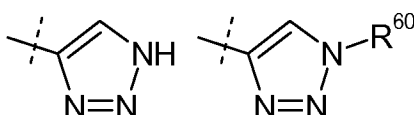
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The term "optionally substituted" means that group in question may be unsubstituted or it may be substituted one or several times, such as 1 to 3 times, or 1 to 5 times, or 1 to 8 times. For example, a heterocycle that is "optionally substituted" with one or two halo or hydroxyl groups, may be unsubstituted, or it may contain one halo group, one hydroxyl group, two halo groups, two hydroxyl group, or one halo group and one hydroxyl group. Generally, such groups can be positioned on any available atom provided that the normal valency of the designated atom is not exceeded and that the substitution

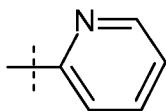
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results in a stable moiety. Such groups may be specified as being on an available nitrogen atom or an available carbon atom.

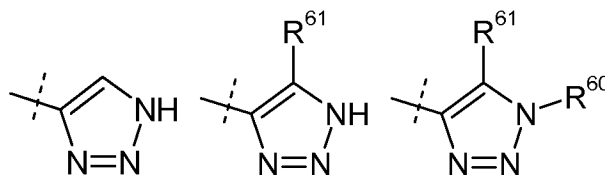
When a nitrogen atom in a heterocycle is described as being "substituted," it means that the hydrogen atom on the nitrogen is replaced with a selected moiety, provided that the normal valency of the nitrogen is not exceeded, and that the substitution results in a stable ring. Similarly, when a nitrogen atom in a heterocycle is described as being "unsubstituted," it means that a hydrogen atom is on the nitrogen or the valency of the nitrogen has already been met without substitution (for example the nitrogen atom in a pyridine ring). For example, triazole has three nitrogen atoms present. The first triazole depicted has all unsubstituted nitrogen atoms since two nitrogen atoms have their valency met without substitution and one nitrogen atom has a hydrogen present. On the other hand, the second triazole depicted is substituted on the nitrogen atom with an R^{60} group:



There are instances where the heterocycle will not be substituted with an R^{60} group. For example, pyridine has one nitrogen atom present, but the valency of the nitrogen atom is met without substitution:



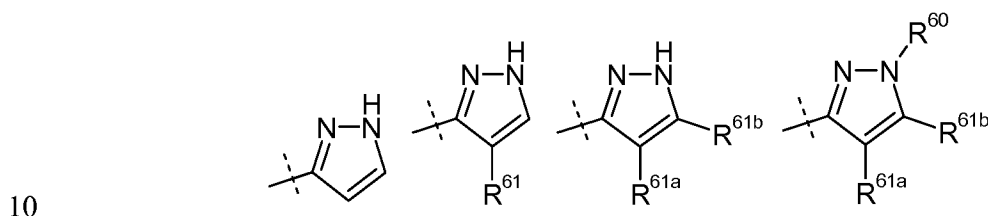
Similarly, triazole has two carbon atoms present, with one forming the point of attachment to the remainder of the compound. The first triazole has an "unsubstituted" carbon atom, while the second triazole is substituted on the carbon atom with an R^{61} group, and the third triazole is substituted on the carbon atom with an R^{61} group and on the nitrogen atom with an R^{60} group:



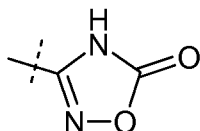
When a carbon atom in a heterocycle is described as being "substituted," it means that the hydrogen atom on the carbon is replaced with a selected moiety, provided that the normal valency of the carbon is not exceeded, and that the substitution results in a stable ring. Similarly, when a carbon atom in a heterocycle is described as being "unsubstituted,"

it means that a hydrogen atom is on the carbon atom or its valency has already been met without substitution (for example the oxo group on 4H-[1,2,4]oxadiazol-5-one). For example, pyrazole has three carbon atoms present, with one forming the point of attachment to the remainder of the compound, such that it is not available for substitution.

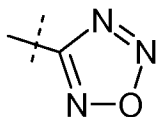
- 5 The first pyrazole has two "unsubstituted" carbon atoms, while the second pyrazole has a first "unsubstituted" carbon atom and a second carbon atom that is substituted with an R^{61} group, the third pyrazole is substituted on both carbon atoms with an R^{61} group (which may be the same or different; depicted at R^{61a} and R^{61b}), and the fourth pyrazole is substituted on both carbon atoms with an R^{61} group:



- There are instances where the heterocycle will not be substituted with an R^{61} group. For example, although 4H-[1,2,4]oxadiazol-5-one has two carbon atoms present, one carbon atom forms the point of attachment to the remainder of the compound and the other carbon atom is already substituted with an oxo group and so is not available for substitution with an R^{61} group:
- 15



Similarly, [1,2,3,5]oxatriazole has one carbon atom present, but it forms the point of attachment to the remainder of the compound:



- 20 As used herein, the phrase "of the formula" or "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.

- The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise unacceptable when used in the invention. For example, the term
- 25 "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 pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable
5 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, 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
10 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
15 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, manganous, potassium, sodium, and zinc salts, and the like. Salts derived from pharmaceutically acceptable organic bases include salts of primary, secondary and tertiary
20 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, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, hydrabamine, isopropylamine, lysine, methylglucamine, morpholine, piperazine,
25 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 (hydrobromic, hydrochloric, hydrofluoric or hydroiodic), nitric, phosphoric, sulfamic and sulfuric acids. Salts derived from pharmaceutically acceptable organic acids include salts
30 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 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, fumaric, maleic, oxalic and succinic acids), glucuronic, mandelic, mucic, nicotinic, orotic, pamoic, pantothenic, sulfonic acids (for example, benzenesulfonic, camphosulfonic, edisylic, ethanesulfonic, isethionic, methanesulfonic, naphthalenesulfonic, naphthalene-1,5-disulfonic, naphthalene-2,6-disulfonic and p-toluenesulfonic acids), xinafoic acid, and the like.

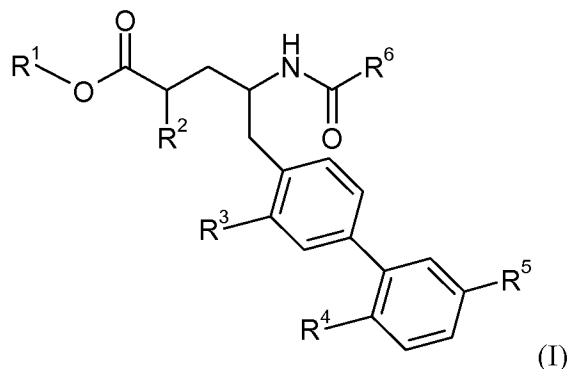
The term "therapeutically effective amount" means an amount sufficient to effect treatment when administered to a patient in need thereof, that is, the amount of drug needed to obtain the desired therapeutic effect. For example, a therapeutically effective amount for treating hypertension is an amount 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 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.

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 the crystalline compound is 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:



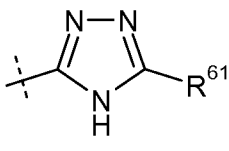
or a pharmaceutically acceptable salt thereof.

As used herein, the term "compound of the invention" includes all compounds encompassed by formula I and species thereof. Similarly, reference to compound of a given formula is intended to include all species. 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. Furthermore, solvates of compounds of formula I are included within the scope of this invention.

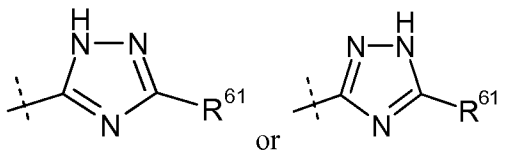
The compounds of the invention contain one or more chiral centers and therefore, these compounds may be prepared and used in various stereoisomeric forms. In some embodiments, in order to optimize the therapeutic activity of the compounds of the invention, e.g., to treat hypertension, it may be desirable that the carbon atoms have a particular (*R,R*), (*S,S*), (*S,R*), or (*R,S*) configuration or are enriched in a stereoisomeric form

having such configuration. In other embodiments, the compounds of the invention are present as racemic mixtures. Accordingly, the invention also relates to racemic mixtures, pure stereoisomers (e.g., enantiomers and diastereoisomers), stereoisomer-enriched mixtures, and the like unless otherwise indicated. When a chemical structure is depicted
 5 herein without any stereochemistry, it is understood that all possible stereoisomers are encompassed by such structure. Thus, for example, the term "compound of formula I" is intended to include all possible stereoisomers of the compound. Similarly, when a particular 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
 10 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 chromatography using a suitable chiral stationary phase or support, or by chemically converting them into diastereoisomers, separating the diastereoisomers by conventional
 15 means such as chromatography or recrystallization, then regenerating the original stereoisomer.

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 triazole is
 20 depicted as (R^{60} being hydrogen):



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



and that all such forms are covered by the invention.

25 The compounds of the invention, as well as those compounds used in their 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

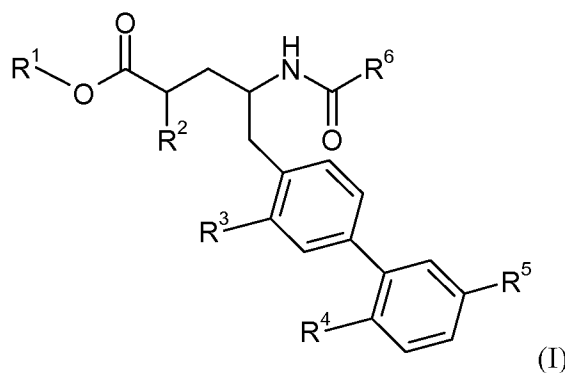
the compounds of formula I, for example, include, but are not limited to, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{36}Cl , and ^{18}F . Of particular interest are compounds of formula I enriched in tritium or carbon-14 which can be used, for example, in tissue distribution studies; compounds of the invention 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 ^{11}C , ^{18}F , ^{15}O and ^{13}N , which can be used, for example, in Positron Emission Topography (PET) studies.

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 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 indicated.

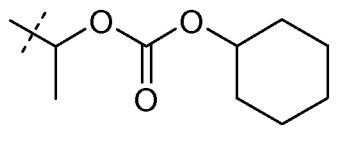
In one aspect, this invention relates to compounds of formula I:



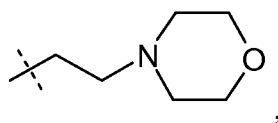
20

R^1 is selected from the group consisting of H, $-\text{C}_{1-8}\text{alkyl}$, $-\text{CH}(\text{CH}_3)\text{OC}(\text{O})-\text{O}-\text{cyclohexyl}$, $-(\text{CH}_2)_2\text{-morpholinyl}$, and $-\text{CH}_2\text{-5-methyl-[1,3]dioxol-2-one}$. In one embodiment, R^1 is H. In one embodiment, R^1 is $-\text{C}_{1-8}\text{alkyl}$, for example $-\text{CH}_2\text{CH}_3$, $-\text{CH}(\text{CH}_3)_2$, $-(\text{CH}_2)_3\text{CH}_3$, and $-(\text{CH}_2)_5\text{CH}_3$. When R^1 is $-\text{C}_{1-8}\text{alkyl}$, the compound of formula I can be referred to as an alkyl ester, for example an ethyl ester. In one embodiment, R^1 is $-\text{CH}(\text{CH}_3)\text{OC}(\text{O})-\text{O}-\text{cyclohexyl}$:

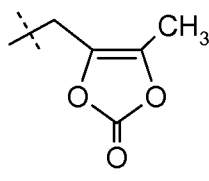
25



and the compound of formula I can be referred to as a cilexetil ester. In another embodiment, R¹ is -(CH₂)₂-morpholinyl:



- 5 and the compound of formula I can be referred to as a 2-morpholinoethyl or mofetil ester. In yet another one embodiment, R¹ is -CH₂-5-methyl-[1,3]dioxol-2-one:

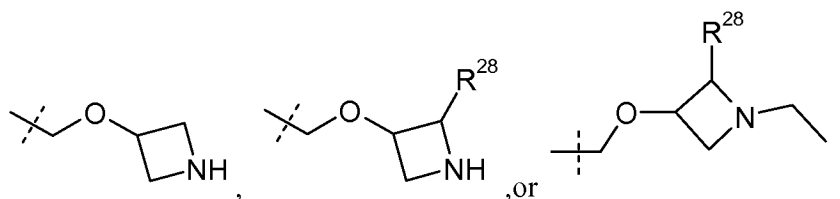


and the compound of formula I can be referred to as a medoxomil ester. In one particular embodiment, R¹ is H, -CH₂CH₃, -CH(CH₃)₂, -(CH₂)₃CH₃, or -(CH₂)₅CH₃.

- 10 R² is -CH₂-O-R²⁰, -C₀₋₁alkylene-NHC(O)-R²¹, -C₀₋₃alkylene-NR²²R²³, -CH₂-R²⁴, oxetane, 2-pyridine, 3-pyridine, thiophene, tetrahydropyran, or piperidine and having H or -C(O)CH₃ on the nitrogen, where the tetrahydropyran and piperidine rings are attached at the 4-position. The R²⁰ moiety is -C₁₋₆alkyl, -CH₂NR²⁷CHR²⁸-, -C₂₋₃alkylene-OH, or -C₂₋₃alkylene-NR²⁹R³⁰. The R²¹ moiety is -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₀₋₆alkylene-NR²⁵R²⁵,
 15 -CH(NH₂)-R²⁶, -C₁₋₄alkylene-NHC(O)O-C₁₋₆alkyl, -OCH(CH₃)OC(O)CH(CH₃)₂, or pyrrolidine attached at a carbon atom. The R²² moiety is H or -C₁₋₆alkyl. The R²³ moiety is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -SO₂-C₁₋₆alkyl, -CH₂OC(O)-C₁₋₆alkyl, -C₂₋₄alkylene-OH, -C₂₋₄alkylene-O-CH₃, or cyclopropyl optionally substituted with one or two R³¹ groups. In addition, R²² and R²³ can be taken together to
 20 form -(CH₂)₂-O-(CH₂)₂-, a 2-oxa-6-aza-spiro[3.3]heptane ring, or an azetidine ring optionally substituted with one or two R³¹ groups. The R²⁴ group is -CH₂OH, -CN, -C(O)NH₂, triazole or imidazole attached at a nitrogen atom, or oxadiazolone or tetrazole attached at the carbon atom. Each of the R²⁵ groups are independently H or -CH₃. The R²⁶ group is -C₁₋₄alkylene-NH₂, -CH₂OH, or benzyl. The R²⁷ group is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl. The R²⁸ group is
 25 H, -C₁₋₆alkyl, -C₁₋₂alkylene-OH, or -C₁₋₂alkylene-OC₁₋₆alkyl. The R²⁹ and R³⁰ groups are

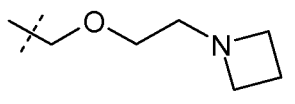
independently H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl. In addition, R²⁹ and R³⁰ can be taken together to form -CH₂-CH₂-CH₂-. Each R³¹ group is independently halo (for example, fluoro or chloro), -C₁₋₆alkyl, -C₀₋₂alkylene-OH, -C₀₋₂alkylene-OC₁₋₆alkyl, -CN, or -CONH₂.

- 5 In one embodiment, R² is -CH₂-O-R²⁰ and R²⁰ is -C₁₋₆alkyl, for example, -CH₂-O-CH₃ or -CH₂-O-CH₂CH₃. In another embodiment, R² is -CH₂-O-R²⁰ and R²⁰ is -CH₂NR²⁷CHR²⁸-, where R²⁷ is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms (e.g., -CH₂CH₂CHF₂, -CH₂CH₂CH₂F, and -CH₂CH₂CF₃), -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl, and R²⁸ is H, -C₁₋₆alkyl, -C₁₋₂alkylene-OH, or -C₁₋₂alkylene-OC₁₋₆alkyl
10 (e.g., -CH₂OCH₃, -CH₂OCH₂CH₃, and -(CH₂)₂OCH₃), for example,



In one particular embodiment, R²⁸ is H.

- In still another embodiment, R² is -CH₂-O-R²⁰ and R²⁰ is -C₂₋₃alkylene-OH, for example, -CH₂-O-(CH₂)₂OH or -CH₂-O-(CH₂)₃OH. In yet another embodiment, R² is
15 -CH₂-O-R²⁰ and R²⁰ is -C₂₋₃alkylene-NR²⁹R³⁰, where R²⁹ and R³⁰ are independently H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl, for example, -CH₂-O-(CH₂)₂NH₂, -CH₂-O-(CH₂)₃NH₂, -CH₂-O-(CH₂)₂NHCH₃, -CH₂-O-(CH₂)₃NHCH₃, -CH₂-O-(CH₂)₂N(CH₃)₂, or -CH₂-O-(CH₂)₂NH(CH₂CHF₂). In yet another embodiment, R² is -CH₂-O-R²⁰ and R²⁰ is
20 -C₂₋₃alkylene-NR²⁹R³⁰, where R²⁸ and R²⁹ are taken together to form are taken together to form -CH₂-CH₂-CH₂-, for example,

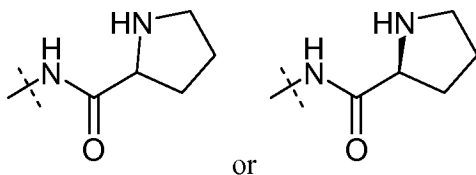


- In one embodiment, R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is -C₁₋₆alkyl, for example, -NHC(O)CH₃, -NHC(O)CH₂CH₃, or -CH₂NHC(O)CH₃. In another embodiment,
25 R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is -O-C₁₋₆alkyl, for example, -NHC(O)OCH₃. In still another embodiment, R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is -C₀₋₆alkylene-NR²⁵R²⁵ (where each R²⁵ group is independently H or -CH₃), for example, -NHC(O)CH₂NH₂, -CH₂NHC(O)CH₂NH₂, -NHC(O)(CH₂)₂NH₂, -NHC(O)(CH₂)₃NH₂,

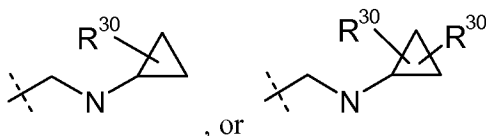
-CH₂NHC(O)(CH₂)₃NH₂, -NHC(O)(CH₂)₄NH₂, -NHC(O)(CH₂)₅NH₂,
 -NHC(O)CH(CH₃)NH₂, -CH₂NHC(O)C(CH₃)₂NH₂, -NHC(O)CH₂NH(CH₃),
 -NHC(O)CH₂N(CH₃)₂, -NHC(O)(CH₂)₃NH(CH₃), -NHC(O)(CH₂)₃N(CH₃)₂,
 -NHC(O)C(CH₃)₂NH₂, -NHC(O)CH(NH₂)-CH(CH₃)₂, or -CH₂NHC(O)C(CH₃)₂NH₂.

- 5 In yet another embodiment, R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is -CH(NH₂)-R²⁶ (where R²⁶ is -C₁₋₄alkylene-NH₂, -CH₂OH, or benzyl), for example, -NHC(O)CH(NH₂)-(CH₂)₄NH₂, -NHC(O)CH(NH₂)-CH₂OH, or -NHC(O)CH(NH₂)-benzyl. In one embodiment, R² -C₀₋₁alkylene-NHC(O)-R²¹ is and R²¹ is -C₁₋₄alkylene-NHC(O)O-C₁₋₆alkyl, for example, -NHC(O)-CH₂-NHC(O)O-CH₃ and -NHC(O)-CH[CH(CH₃)₂]-NHC(O)O-CH₃.

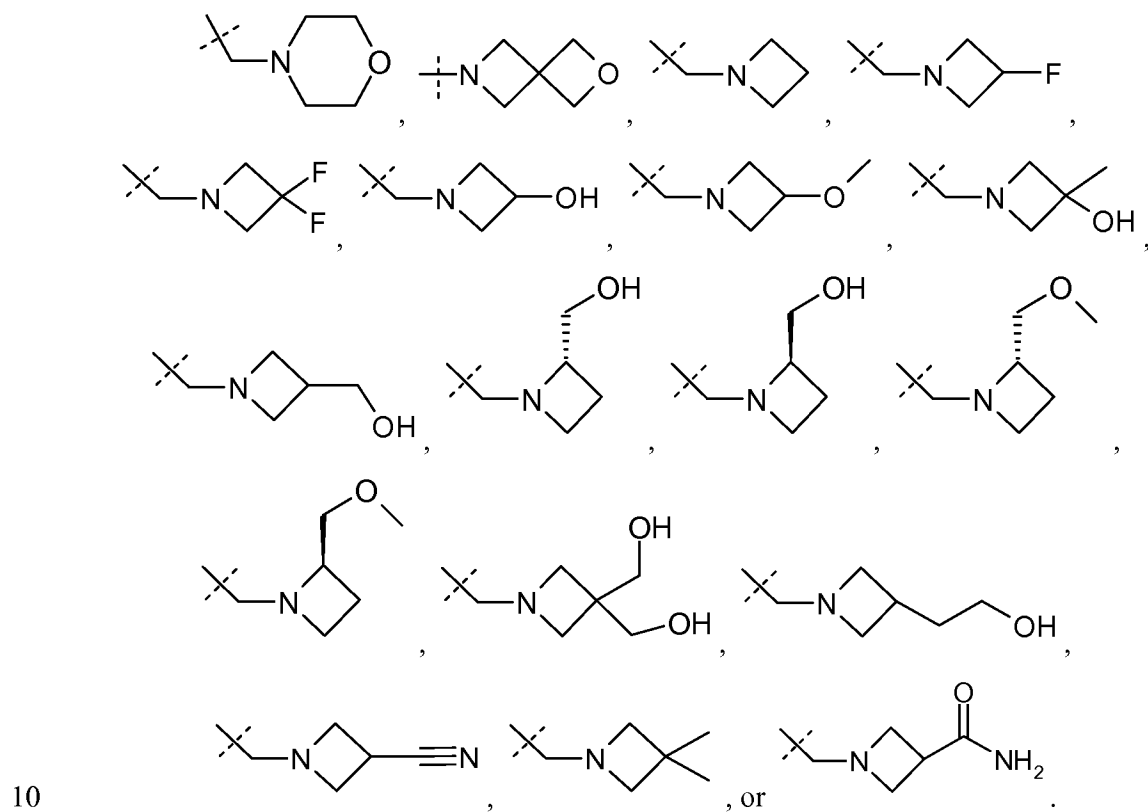
- In another embodiment, R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is -OCH(CH₃)OC(O)CH(CH₃)₂, for example, -NHC(O)OCH(CH₃)OC(O)CH(CH₃)₂ and -CH₂NHC(O)OCH(CH₃)OC(O)CH(CH₃)₂. In still another embodiment, R² is -C₀₋₁alkylene-NHC(O)-R²¹ and R²¹ is pyrrolidine, for example: (shown without stereochemistry and as the (*S*) isomer)



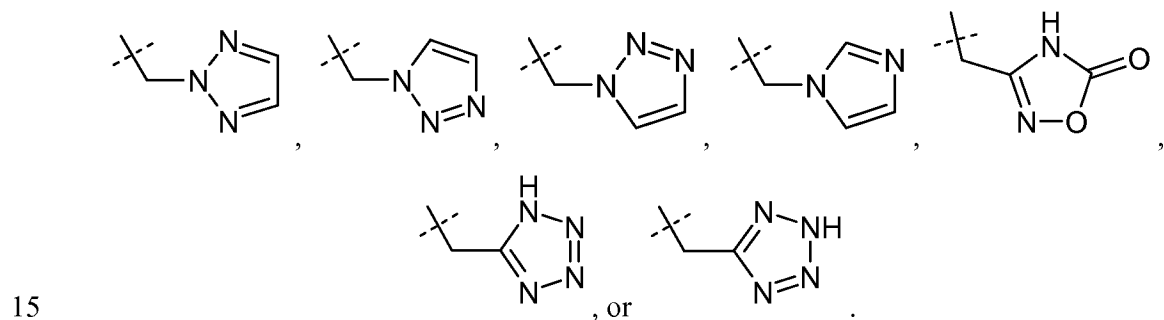
- In another embodiment, R² is -C₀₋₃alkylene-NR²²R²³ (where R²² is H or -C₁₋₆alkyl, and R²³ is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -SO₂-C₁₋₆alkyl, -CH₂OC(O)-C₁₋₆alkyl, -C₂₋₄alkylene-OH, -C₂₋₄alkylene-O-CH₃, or cyclopropyl optionally substituted with one or two R³¹ groups, where each R³¹ is independently halo, -C₁₋₆alkyl, -C₀₋₂alkylene-OH, -C₀₋₂alkylene-OC₁₋₆alkyl, -CN, or -CONH₂). Examples of this embodiment include, for example, -NH₂, -CH₂NH₂, -CH(CH₃)NH₂, -C(CH₃)₂NH₂, -(CH₂)₂NH₂, -(CH₂)₃NH₂, -CH₂NH(CH₃), -CH₂N(CH₃)₂, -CH₂NH-CH₂CH₂F, -CH₂NH-CH₂CHF₂, -NH-SO₂CH₃, -NHCH₂OC(O)CH₃, -NHCH₂OC(O)CH(CH₃)₂, -CH₂NHCH₂OC(O)CH(CH₃)₂, -CH₂-NH-(CH₂)₂-OH, -CH₂-NH-(CH₂)₃-OH, -CH₂-N(CH₃)-(CH₂)₂-OH, -NH-(CH₂)₂-O-CH₃, -CH₂-NH-(CH₂)₂-O-CH₃, -CH₂-N(CH₃)-(CH₂)₂-O-CH₃, -NH-(CH₂)₃-O-CH₃, -CH₂-NH-(CH₂)₃-O-CH₃,



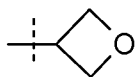
In another embodiment R² is -C₀₋₃alkylene-NR²²R²³ and R²² and R²³ taken together to form -(CH₂)₂-O-(CH₂)₂-, a 2-oxa-6-aza-spiro[3.3]heptane ring, or an azetidine ring optionally substituted with one or two R³¹ groups, where each R³¹ group is independently halo, -C₁₋₆alkyl, -C₀₋₂alkylene-OH, -C₀₋₂alkylene-OC₁₋₆alkyl, -CN, or -CONH₂. Examples of this embodiment include:



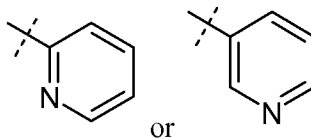
In still another embodiment, R² is -CH₂-R²⁴ and R²⁴ is -CH₂OH, -CN, -C(O)NH₂, triazole or imidazole attached at a nitrogen atom, or oxadiazolone or tetrazole attached at the carbon atom, for example, -(CH₂)₂OH, -CH₂CN, -CH₂-C(O)NH₂,



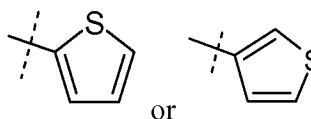
In one embodiment, R² is oxetane, for example,



In another embodiment, R^2 is 2-pyridine or 3-pyridine:

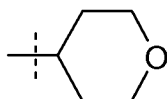


In yet another embodiment, R^2 is thiophene, for example,

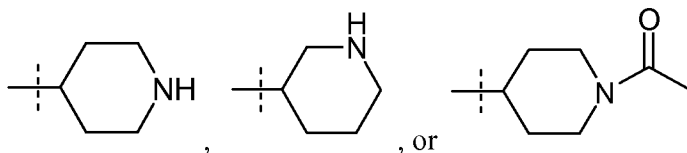


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In another embodiment, R^2 is tetrahydropyran (attached at the 4-position), for example,



In yet another embodiment, R^2 is piperidine (attached at the 4-position) having H or
10 $-C(O)CH_3$ on the nitrogen, for example,



R^3 is selected from the group consisting of H and halo, and in one embodiment, R^3 is H or Cl. R^4 is selected from the group consisting of H and halo, and in one embodiment, R^4 is H or F. R^5 is selected from the group consisting of H and halo, and in one
15 embodiment, R^5 is H, Br, or Cl, and in another embodiment R^5 is H or Cl. In other embodiments, R^3 is H, R^4 is F, and R^5 is Cl; or R^3 and R^4 are H and R^5 is Br or Cl; or R^3 , R^4 , and R^5 are H; or R^3 is Cl, R^4 is F, and R^5 is Cl; or R^3 is H, R^4 is F, and R^5 is H.

R^6 is a heterocycle selected from the group consisting of 3H-oxazol-2-one, [1,2,4]oxadiazol-5-one, [1,2,3,5]oxatriazole, dihydro-[1,2,4]triazol-3-one,
20 [1,2,4]triazolo[1,5- α]pyridine, triazole, pyrazole, imidazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, and pyrimidine, where the heterocycle is attached at a carbon atom. In one embodiment, R^6 is 3H-oxazol-2-one, 4H-[1,2,4]oxadiazol-5-one, [1,2,3,5]oxatriazole, [1,2,3]triazole, [1,2,4]triazole, pyrazole, imidazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, or pyrimidine. In another embodiment, R^6 is

3H-oxazol-2-one, 4H-[1,2,4]oxadiazol-5-one, [1,2,4]triazolo[1,5- α]pyridine, [1,2,3]triazole, [1,2,4]triazole, pyrazole, oxazole, isoxazole, isothiazole, pyridine, or pyrimidine.

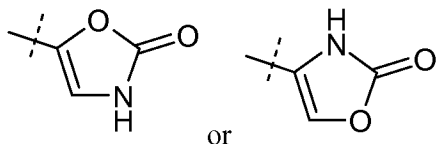
Each nitrogen atom in the heterocycle is unsubstituted or substituted with an R⁶⁰ group selected from the group consisting of -OH, -(CH₂)₂OH, -C₀₋₂alkylene-O-C₁₋₆alkyl (e.g., -OCH₃ or -OCH₂CH₃), -C₁₋₆alkyl (e.g., -CH₃), -CHF₂, -CF₃, and phenyl. In one embodiment, the nitrogen atoms in the heterocycle are unsubstituted. In another embodiment, R⁶⁰ is -OH, -(CH₂)₂OH, -OCH₃, -OCH₂CH₃, -CH₃, -CHF₂, or -CF₃; in another embodiment R⁶⁰ is phenyl; and in yet another embodiment, one nitrogen atom in the heterocycle is substituted with an R⁶⁰ moiety.

Each carbon atom in the heterocycle is unsubstituted or substituted with an R⁶¹ group independently selected from the group consisting of halo, -OH, -C₁₋₆alkyl, -C₀₋₂alkylene-O-C₁₋₆alkyl, -C(O)CH₃, -C(O)NH(CH₃), -C(O)N(CH₃)₂, -C₃₋₆cycloalkyl (e.g., cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl), -CF₃, -CH₂SO₂CH₃, -NH₂, -CH₂NH₂, -CH₂N(CH₃)₂, pyrazine, and phenyl substituted with methyl. In one embodiment, the carbon atoms in the heterocycle are unsubstituted; and in another embodiment, one carbon atom in the heterocycle is substituted with an R⁶¹ group. In another embodiment, R⁶¹ is chloro, fluoro, -OH, -CH₃, -CH₂CH₃, -(CH₂)₂CH₃, -CH(CH₃)₂, -OCH₃, -OCH₂CH₃, -CH₂-OCH₃, -C(O)CH₃, -C(O)NH(CH₃), -C(O)N(CH₃)₂, cyclopropyl, -CF₃, -CH₂SO₂CH₃, -NH₂, -CH₂NH₂, -CH₂N(CH₃)₂, pyrazine, or phenyl substituted with methyl or fluoro; and in one particular embodiment, R⁶¹ is chloro, fluoro, -OH, -CH₃, -CH₂CH₃, -(CH₂)₂CH₃, -CH(CH₃)₂, -OCH₃, -OCH₂CH₃, -C(O)CH₃, -C(O)NH(CH₃), -C(O)N(CH₃)₂, cyclopropyl, -CF₃, or phenyl substituted with methyl or fluoro.

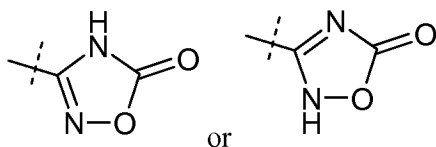
In another embodiment, two carbon atoms in the heterocycle are substituted with R⁶¹ groups, which may be the same or different; and in one specific embodiment, the R⁶¹ moiety on a first carbon is selected from the group consisting of fluoro, -OH, -CH₃, -C₀₋₂alkylene-O-C₁₋₆alkyl, -C(O)CH₃, -C₃₋₆cycloalkyl, -CF₃, -CH₂SO₂CH₃, -NH₂, and -CH₂N(CH₃)₂, and the R⁶¹ moiety on a second carbon is selected from the group consisting of halo, -OH, -CH₃, -O-CH₂CH₃, -C(O)CH₃, cyclopropyl, -CF₃, -CH₂SO₂CH₃, -NH₂, -CH₂N(CH₃)₂, and phenyl substituted with methyl or halo. In one particular embodiment, a first carbon atom in the heterocycle is substituted with an R⁶¹ group selected from the group consisting of fluoro and -CH₃; and a second carbon atom in the heterocycle is substituted with an R⁶¹ group selected from the group consisting of -CH₃, -O-CH₂CH₃,

cyclopropyl, and phenyl substituted with methyl.

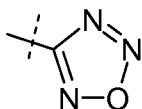
In one embodiment, R^6 is 3H-oxazol-2-one, for example:



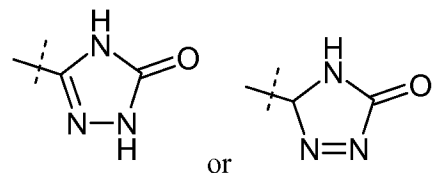
In one embodiment, R^6 is [1,2,4]oxadiazol-5-one, for example 4H-[1,2,4]oxadiazol-5-one or 2H-[1,2,4]oxadiazol-5-one:



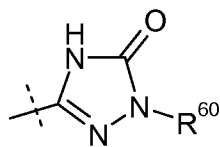
In one embodiment, R^6 is [1,2,3,5]oxatriazole, for example:



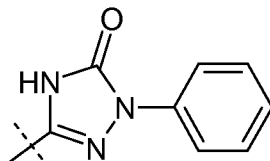
In one embodiment, R^6 is dihydro-[1,2,4]triazol-3-one, for example 2,4-dihydro-[1,2,4]triazol-3-one or 4,5-dihydro-[1,2,4]triazol-3-one:



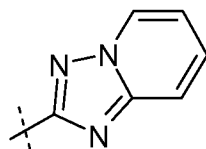
In one particular embodiment, R^6 is a 2,4-dihydro-[1,2,4]triazol-3-one ring such as:



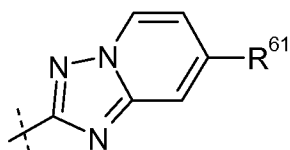
specific examples of which include:



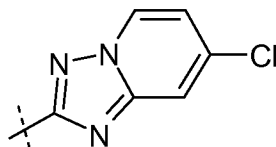
In one embodiment, R^6 is [1,2,4]triazolo[1,5- α]pyridine, for example:



In one particular embodiment, R^6 is a [1,2,4]triazolo[1,5- α]pyridine ring such as:

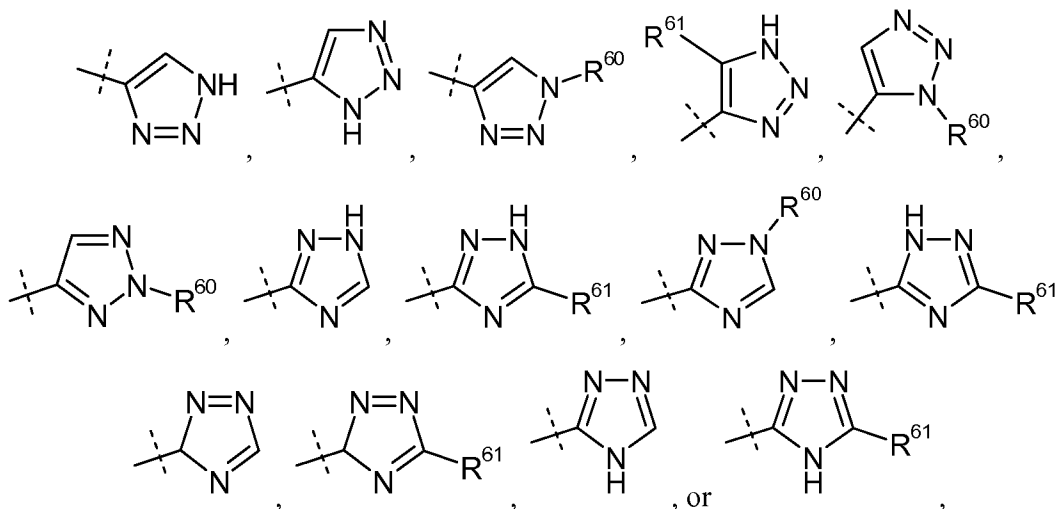


specific examples of which include:

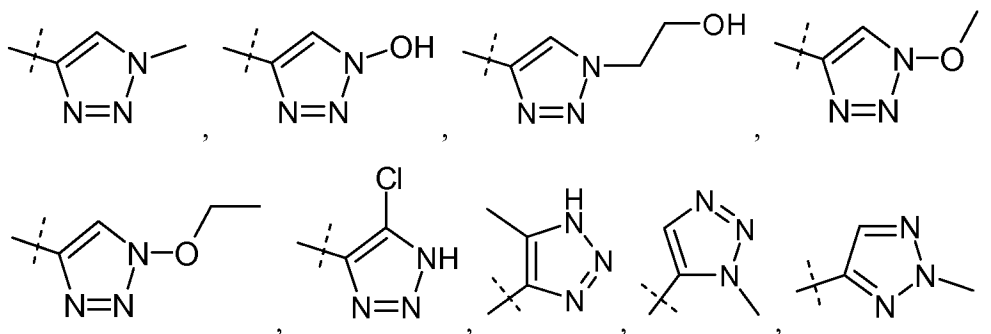


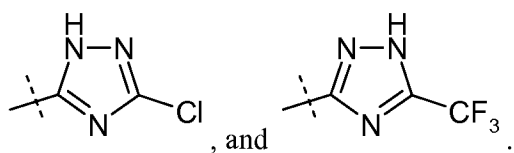
5

In one embodiment, R^6 is [1,2,3]triazole or [1,2,4]triazole, for example:

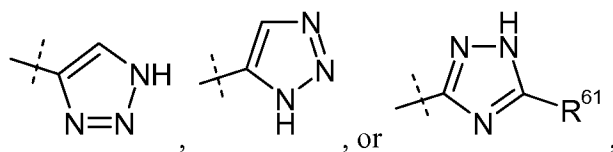


10 specific examples of which include:

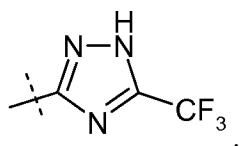




In one particular embodiment, R^6 is a triazole ring such as:

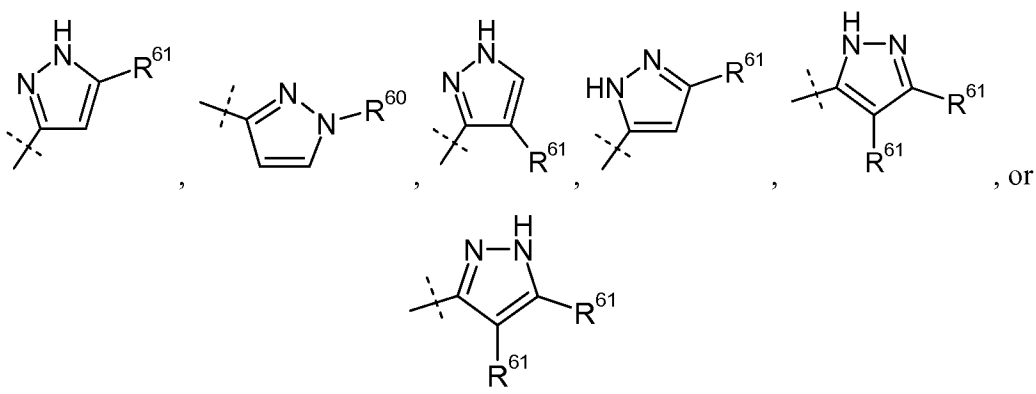


specific examples of which include:

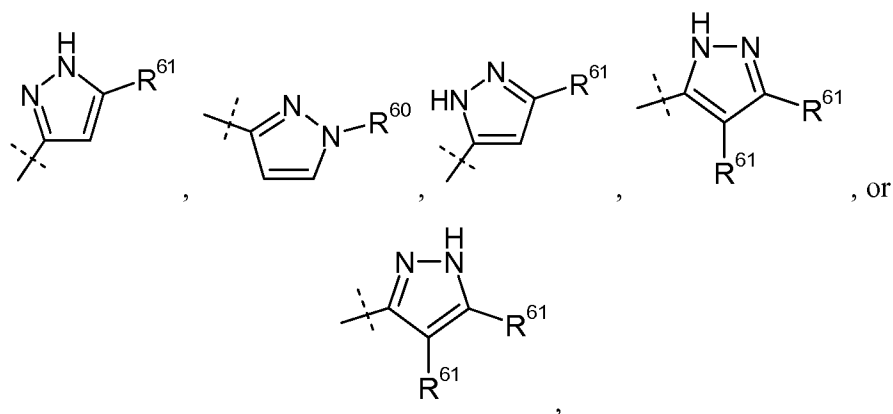


5

In one embodiment, R^6 is a pyrazole ring, for example:

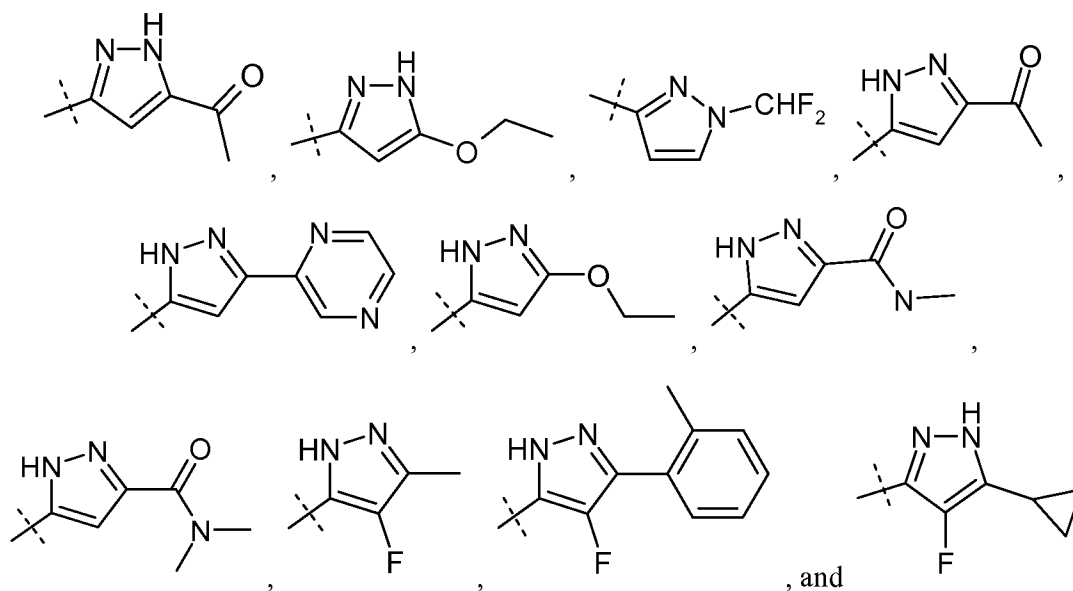


In one particular embodiment, R^6 is a pyrazole ring such as:

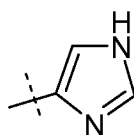


10

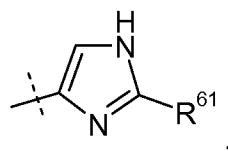
specific examples of which include:



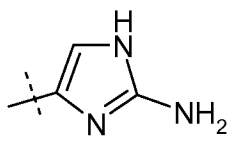
5 In one embodiment, R^6 is an imidazole ring, for example:



In one particular embodiment, R^6 is an imidazole ring such as:

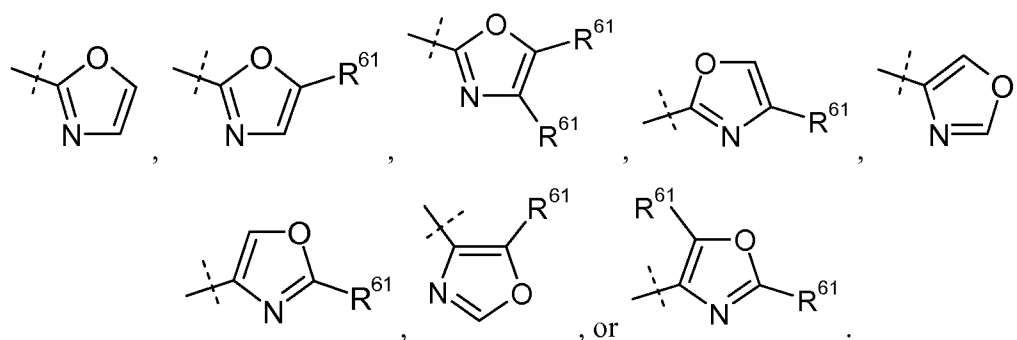


specific examples of which include:

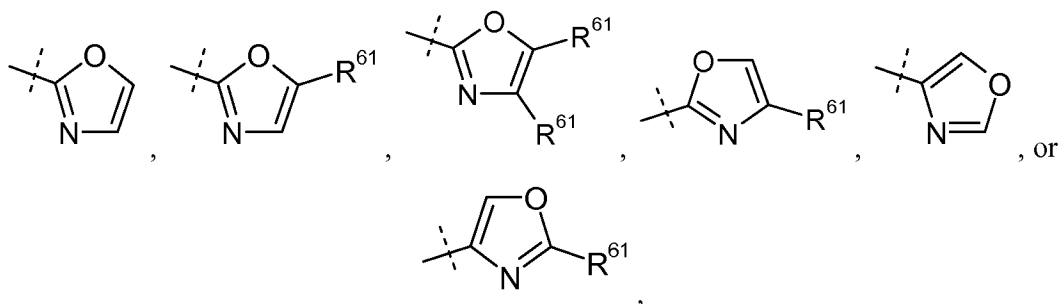


10

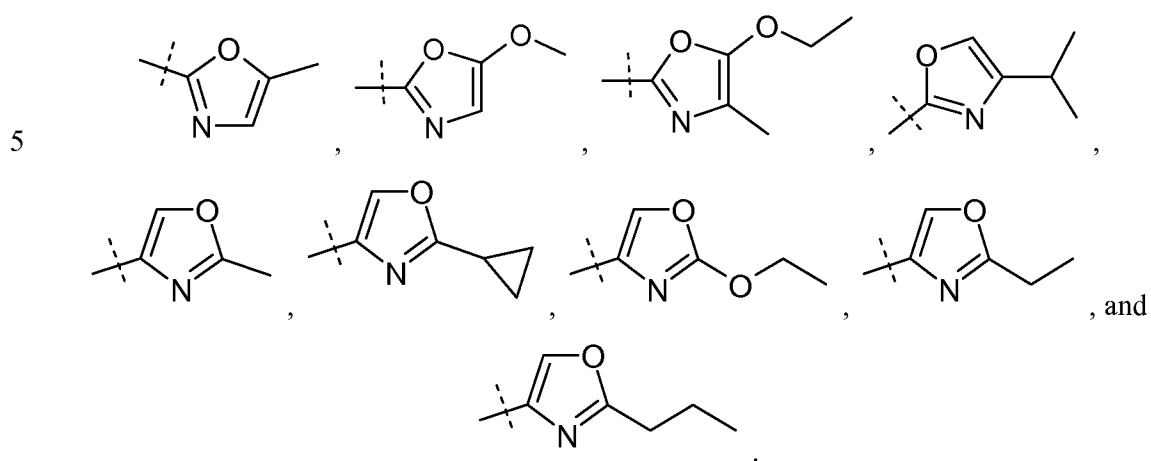
In one embodiment, R^6 is an oxazole ring, for example:



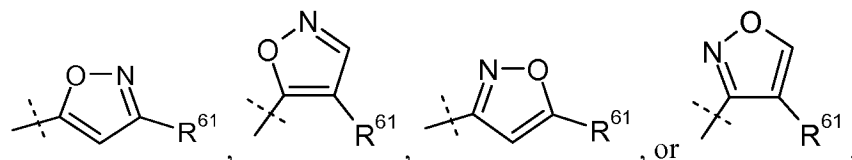
In one particular embodiment, R^6 is an oxazole ring such as:



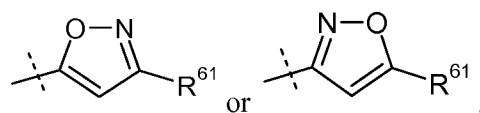
specific examples of which include:



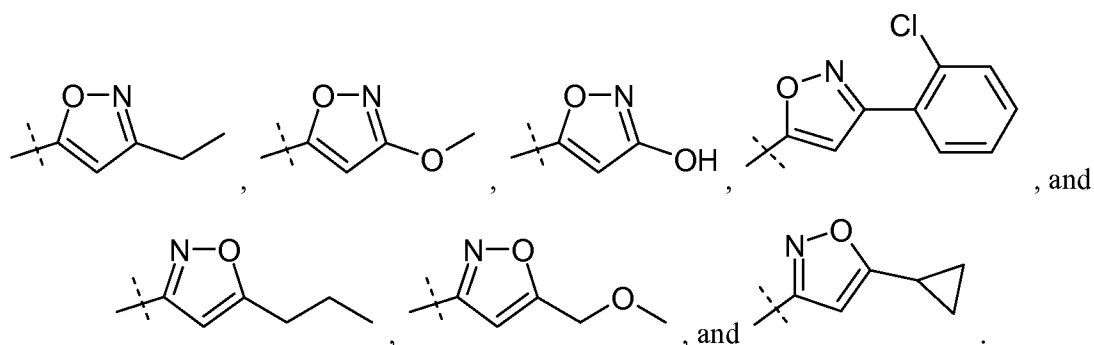
In one embodiment, R^6 is an isoxazole ring, for example:



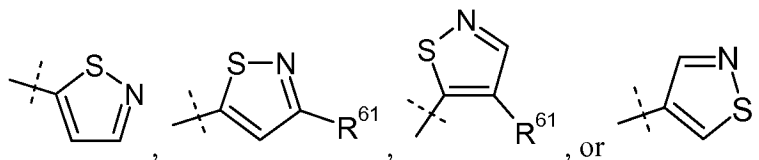
10 In one particular embodiment, R^6 is an isoxazole ring such as:



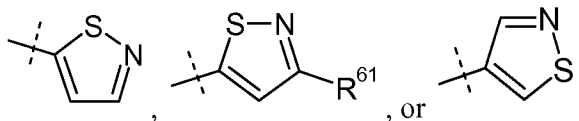
specific examples of which include:



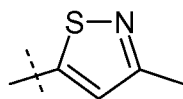
In one embodiment, R^6 is an isothiazole ring, for example:



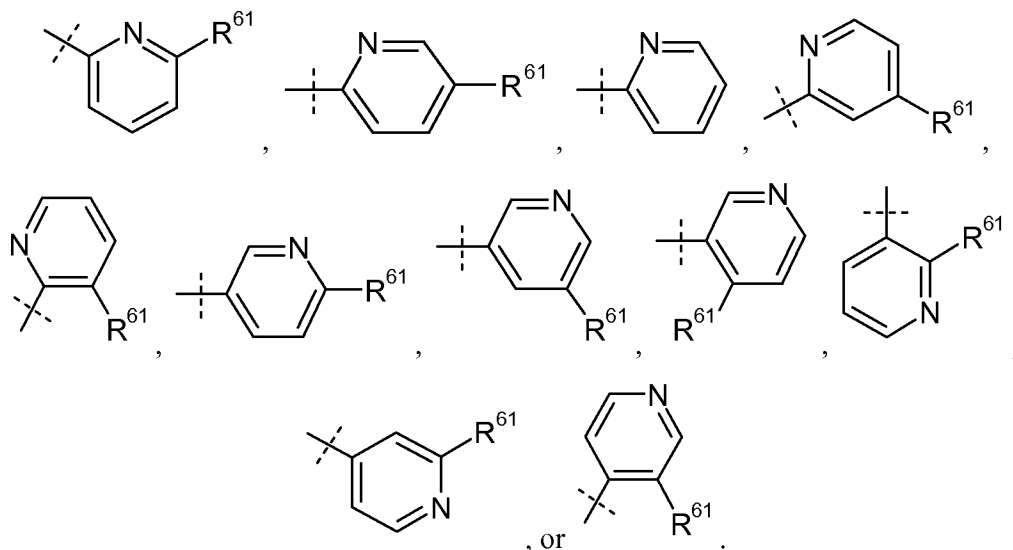
In one particular embodiment, R^6 is an isothiazole ring such as:



5 specific examples of which include:

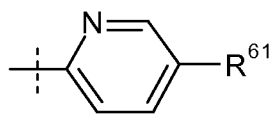


In one embodiment, R^6 is a pyridine ring, for example:

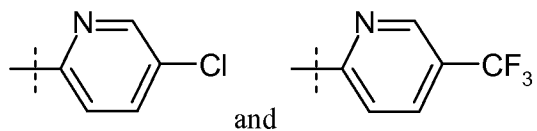


10

In one particular embodiment, R^6 is a pyridine ring such as:

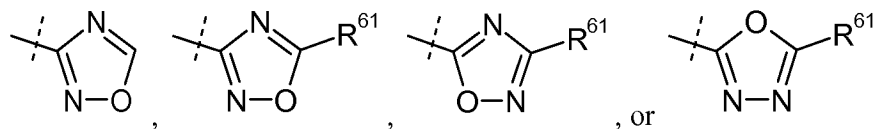


specific examples of which include:

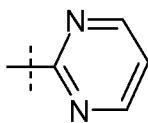


15

In one embodiment, R^6 is oxadiazole, for example [1,2,4]oxadiazole or [1,3,4]oxadiazole:



In one embodiment, R^6 is a pyrimidine ring, for example:



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

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

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.

5 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-protecting groups are suitable for preventing undesired reactions at an amino group, and
10 examples include, but are not limited to, *t*-butoxycarbonyl (BOC), trityl (Tr), benzyloxycarbonyl (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 are not limited to C₁₋₆alkyls, silyl groups including triC₁₋₆alkylsilyl groups, such as
15 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); and the like.

20 Standard deprotection techniques and reagents are used to remove the protecting groups, and may vary depending upon which group is used. For example, 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
25 ("H₂/Pd/C").

Suitable bases for use in these schemes include, by way of illustration and not limitation, potassium carbonate, calcium carbonate, sodium carbonate, triethylamine (Et₃N), pyridine, 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU), *N,N*-diisopropylethylamine (DIPEA), 4-methylmorpholine, sodium hydroxide, potassium hydroxide, potassium *t*-
30 butoxide, and metal hydrides.

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, diethyl ether, acetone, and the like.

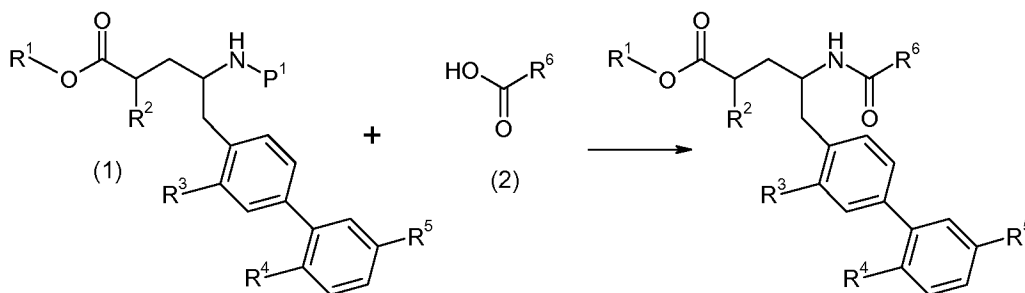
Suitable carboxylic acid/amine coupling reagents include benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP), *N,N,N',N'*-tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate (HATU), 1,3-dicyclohexylcarbodiimide (DCC), *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide (EDC), carbonyldiimidazole (CDI), 1-hydroxybenzotriazole (HOBt), and the like.

Coupling reactions are conducted in an inert diluent in the presence of a base such as
10 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), and/or LCMS until completion. Reactions may be complete in minutes, or may take hours,
15 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 water or between 5% THF in EtOAc and 1M phosphoric acid); extraction (for example,
20 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 (e.g., silica gel chromatography, flash chromatography, preparative HPLC, reverse phase-
25 HPLC, or crystallization).

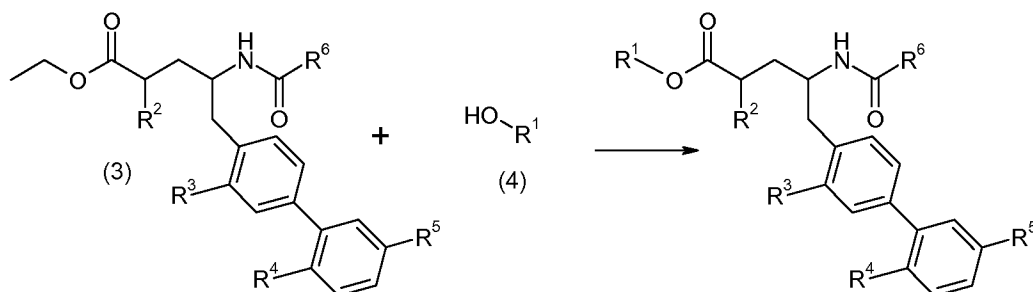
By way of illustration, compounds of formula I, as well as their salts, can be prepared as shown in Schemes I and II.

Scheme I

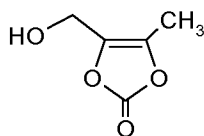


Scheme I is a coupling reaction between a compound of formula 1 (R^1 - R^5 are as defined for formula I and P^1 is H or a suitable amino-protecting group) and a compound of formula 2 (R^6 is as defined for formula I). When P^1 is an amino protecting group, the process further comprises deprotecting the compound, before or *in situ* with the coupling step. Exemplary coupling reagents include HATU, and HOBt with EDC. Generally, this reaction is conducted in the presence of a base such as DIPEA or 4-methylmorpholine, and an inert diluent or solvents such as DMF or DMA. Preparation of various amine starting materials (Compound 1) are illustrated in the Examples. The carboxylic acid starting materials (Compound 2) are generally commercially available or can be prepared using procedures that are known in the art.

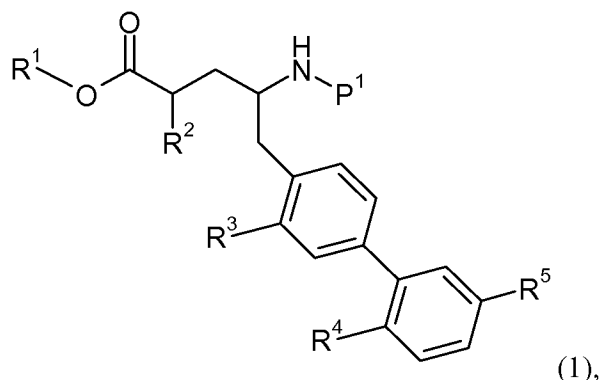
Scheme II



Scheme II is a transesterification reaction. Generally, this reaction involves reacting the ester compound of formula 3 (R^2 - R^6 are as defined for formula I) with the desired alcohol compound of formula 4 (R^1 is as defined for formula I) and a suitable acid catalyst, for example hydrochloric acid. Preparation of the compound of formula 3 from the acid (the compound of formula I) is known in the art or is described herein. The $HO-R^1$ alcohols are either commercially available or can be prepared by techniques that are known in the art or described herein. Exemplary $HO-R^1$ groups include:



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:



- 5 where R¹-R⁵ are as defined for formula I and P¹ is H or a suitable amino-protecting group selected from the group consisting of *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; or a salt thereof.

Further details regarding specific reaction conditions and other procedures for
 10 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
 15 compounds do not exhibit significant inhibitory activity of the angiotensin-converting enzyme. 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 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 7.0, and even
 20 more particularly those having a pK_i greater than or equal to 8.0; 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
 25 apparent inhibition constant (IC₅₀), which is the molar concentration of compound that results in half-maximal inhibition of substrate conversion by the NEP enzyme. The pIC₅₀

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 7.0. In another embodiment, compounds of interest have a pIC_{50} for NEP within the range of about 7.0-10.0.

- 5 It is noted that in some cases, compounds of the invention may possess weak NEP 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
10 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)
15 *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
20 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
25 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
30 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

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

5 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. Other properties and utilities of the compounds can be demonstrated using various *in vitro* and *in vivo* assays well known to those skilled in the art.

10 Depending upon the intended route of administration, oral bioavailability may be an important characteristic, as well as potency as a neprilysin inhibitor. One means of measuring oral bioavailability is by the rat PO cassette assay, where the %F is a measure of the amount of the oral drug dose that actually gets into the blood stream; an exemplary assay is described in Assay 6. Compounds tested in this assay and having a %F < 10% are
15 likely to be poorly absorbed. Similarly, compounds tested in this assay and having a %F > 10% are likely to be better absorbed. Therefore, compounds of the invention having a %F > 10% are of particular interest as orally administered drugs.

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
20 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
25 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
30 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, neurotensin, substance P and vasoactive intestinal peptide. Thus, these compounds are expected to have other physiological actions, for example, on the renal, central nervous, reproductive and gastrointestinal systems.

5

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. 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.

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, aldosterone synthase inhibitors, angiotensin-converting enzyme inhibitors and dual-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, β_1 -adrenergic receptor antagonists, dual-acting β -adrenergic receptor antagonist/ α_1 -receptor

antagonists, calcium channel blockers, diuretics, 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 particular embodiment of the invention, a compound of the invention is combined with an AT₁ receptor antagonist, a calcium channel blocker, a diuretic, 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. When used to treat resistant hypertension, the compound may be administered in combination with other therapeutic agents such as aldosterone synthase inhibitors.

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 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 receptor antagonists, β_1 -adrenergic receptor antagonists, β_2 -adrenergic receptor agonists, angiotensin-converting enzyme inhibitors, anticoagulants, calcium channel blockers, diuretics, endothelin receptor antagonists, PDE-V inhibitors, 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 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 compound may be administered in combination with other therapeutic agents such as

5 adenosine receptor antagonists, advanced glycation end product breakers, aldosterone antagonists, AT₁ receptor antagonists, β_1 -adrenergic receptor antagonists, dual-acting β -adrenergic receptor antagonist/ α_1 -receptor antagonists, chymase inhibitors, digoxin, diuretics, endothelin converting enzyme (ECE) inhibitors, endothelin receptor antagonists, natriuretic peptides and their analogs, natriuretic peptide clearance receptor antagonists,

10 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 β_1 -adrenergic receptor antagonist, an AT₁ receptor antagonist, or a diuretic, and used to treat congestive heart failure.

15 *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 example, Baumer et al. (1992) *Gut* 33:753-758; Farthing (2006) *Digestive Diseases* 24:47-

20 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 agents.

Renal Diseases

By potentiating the effects of vasoactive peptides like the natriuretic peptides and

25 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 (caused, for example, by

30 cardiovascular surgery, chemotherapy, or the use of contrast dyes in medical imaging) 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 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 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.

10 *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 antiglaucoma agents.

15 *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, the compounds of the 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

25 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 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 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 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 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 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 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 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 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 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 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 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 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 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.

5 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
10 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
15 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;
20 wherein step (a) is conducted either before, after or concurrently with step (b); and (c) comparing the first assay value from step (a) with the second assay value from step (b). Exemplary biological assays include a NEP enzyme inhibition assay.

 Still another aspect of the invention relates to a method of studying a biological system or sample comprising a NEP enzyme, the method comprising: (a) contacting the
25 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.

PHARMACEUTICAL COMPOSITIONS AND FORMULATIONS

 Compounds of the invention are typically administered to a patient in the form of a pharmaceutical composition or formulation. Such pharmaceutical compositions may be
30 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 be used in the pharmaceutical compositions discussed herein.

5 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 referred to herein as the "active agent," to distinguish it from other components of the
10 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 therapeutically effective amount of a compound of the invention. Those skilled in the art
15 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 will contain from about 0.01-95 wt% of active agent, including, from about 0.01-30 wt%,
20 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.

 Any conventional carrier or excipient may be used in the pharmaceutical
25 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 well within the scope of those skilled in the pharmaceutical arts. Additionally, carriers or
30 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, 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 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 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 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 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 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, 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 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 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.

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 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.

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 sorbitol and sorbitan esters, microcrystalline cellulose, aluminium metahydroxide, 5 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 predetermined quantity of the active agent calculated to produce the desired therapeutic 10 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 compositions are generally administered using well-known delivery devices, such as a 15 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 a suspension of micronized particles of respirable size. Dry powder inhalers administer the 20 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 amount of the active agent using compressed propellant gas. An exemplary metered-dose 25 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 compositions are typically prepared by adding chilled or pressurized hydrofluoroalkane to 30 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.

5 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, 10 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 15 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 amylase, β -cyclodextrin or cycloheptaamylose. Exemplary cyclodextrins include cyclodextrin derivatives such as hydroxypropyl and sulfobutyl ether cyclodextrins such as hydroxypropyl- β -cyclodextrin 20 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, 25 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 30 may be combined with one or more additional 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
5 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-glaucoma agents, anti-lipid agents, antinociceptive agents, anti-thrombotic agents, AT₁
10 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 inhibitors, estrogens, estrogen receptor agonists and/or antagonists, monoamine reuptake
15 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 inhibitors, selective serotonin reuptake inhibitors, sodium channel blocker, soluble
20 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 comprises a compound of the invention, a second active agent, and a pharmaceutically
25 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.

Compounds of the invention may be physically mixed with the second active agent
30 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 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 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, 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 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.

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 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 are commercially available or can be prepared using conventional procedures and reagents.

5 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.

 In one embodiment, compounds of the invention are administered in combination with an α -adrenergic receptor antagonist, representative examples of which include, but are
10 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, bevantolol, bisoprolol, bopindolol, bucindolol, bucumolol, bufetolol, bufuralol, bunitrolol,
15 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, moprolool, nadolol, nadoxolol, nebivalol, nipradilol, oxprenolol, penbutolol, perbutolol, pindolol, practolol, pronethalol, propranolol, sotalol, sufinalol, talindol, tertatolol, tilisolol, timolol,
20 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.

 In one embodiment, compounds of the invention are administered in combination
25 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 sufficient to provide from about 0.05-500 μ g per dose.

30 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 5-300 mg per day.

- 5 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).

- Compounds of the invention can also be administered in combination with an
10 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, moveltipril, pentopril, perindopril, quinapril, quinaprilat, ramipril, ramiprilat, saralasin acetate, spirapril, temocapril,trandolapril, zofenopril, and
15 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. In another embodiment, compounds of the invention are administered in combination
20 with a dual-acting angiotensin-converting enzyme/neprilysin (ACE/NEP) inhibitor, examples of which include, but are not limited to: AVE-0848 ((4*S*, 7*S*, 12*bR*)-7-[3-methyl-2(*S*)-sulfanylbutyramido]-6-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrido[2,1-*a*][2]-benzazepine-4-carboxylic acid); AVE-7688 (ilepatril) and its parent compound; BMS-182657 (2-[2-oxo-3(*S*)-[3-phenyl-2(*S*)-sulfanylpropionamido]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-1-yl]acetic acid); CGS-35601 (N-[1-[4-methyl-2(*S*)-sulfanylpentanamido]cyclopentyl-
25 carbonyl]-L-tryptophan); fasidotril; fasidotrilate; enalaprilat; ER-32935 ((3*R*, 6*S*, 9*aR*)-6-[3(*S*)-methyl-2(*S*)-sulfanylpentanamido]-5-oxoperhydrothiazolo[3,2-*a*]azepine-3-carboxylic acid); gempatrilat; MDL-101264 ((4*S*, 7*S*, 12*bR*)-7-[2(*S*)-(2-morpholinoacetylthio)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12*b*-
30 octahydropyrido[2,1-*a*][2]benzazepine-4-carboxylic acid); MDL-101287 ([4*S*-[4*α*, 7*α*(*R**), 12*bβ*]]-7-[2-(carboxymethyl)-3-phenylpropionamido]-6-oxo-1,2,3,4,6,7,8,12*b*-octahydropyrido[2,1-*a*][2]benzazepine-4-carboxylic acid); omapatrilat; RB-105 (N-[2(*S*)-(mercaptomethyl)-3(*R*)-phenylbutyl]-L-alanine); sampatrilat; SA-898 ((2*R*, 4*R*)-N-[2-(2-

hydroxyphenyl)-3-(3-mercaptopropionyl)thiazolidin-4-ylcarbonyl]-L-phenylalanine); Sch-50690 (N-[1(S)-carboxy-2-[N2-(methanesulfonyl)-L-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, 5 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.

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

15 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 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; 20 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; oxadiazolidinediones; sulfonylureas such as chlorpropamide, glimepiride, glipizide, glyburide, and tolazamide; thiazolidinediones such as pioglitazone and rosiglitazone; and 25 combinations thereof.

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

30 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 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, 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.

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), benzylosartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasartan, eprosartan, EXP3174, fonsartan, forasartan, glycylosartan, irbesartan, isoteoline, losartan, medoxomil, milfasartan, olmesartan (e.g., olmesartan medoxomil), opomisartan, prazosartan, 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, saprisartan, tasosartan, 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.

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-mercapto-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) *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
5 that this combination therapy may present the advantage of preventing angioedema or other unwanted consequences of elevated bradykinin levels.

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,
10 bepridil, clentiazem, cilnidipine, cinnarizine, diltiazem, efonidipine, elgodipine, etafenone, felodipine, fendiline, flunarizine, gallopamil, isradipine, lacidipine, lercanidipine, lidoflazine, lomerizine, manidipine, mibefradil, nicardipine, nifedipine, niguldipine, niludipine, nilvadipine, nimodipine, nisoldipine, nitrendipine, nivaldipine, perhexiline, prenylamine, ryosidine, semotiadil, terodiline, tiapamil, verapamil, and combinations
15 thereof. In a particular embodiment, the calcium channel blocker is selected from amlodipine, bepridil, diltiazem, felodipine, isradipine, lacidipine, nicardipine, nifedipine, 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.

20 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-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
25 with a diuretic. Representative diuretics include, but are not limited to: carbonic anhydrase inhibitors such as acetazolamide and dichlorphenamide; loop diuretics, which include sulfonamide derivatives such as acetazolamide, ambuside, azosemide, bumetanide, butazolamide, chloraminophenamide, clofenamide, clopamide, clorexolone, disulfamide, ethoxzolamide, furosemide, mefruside, methazolamide, piretanide, torsemide, tripamide,
30 and xipamide, as well as non-sulfonamide diuretics such as ethacrynic acid and other phenoxyacetic acid compounds such as tienilic acid, indacrinone and quincarbate; 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, benzylhydrochlorothiazide, benzthiazide, buthiazide, chlorthalidone, chlorothiazide, cyclopenthiazide, cyclothiazide, epithiazide, ethiazide, fenquizone, flumethiazide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, meticrane, 5 metolazone, paraflutizide, polythiazide, quinethazone, teclothiazide, and trichloromethiazide; and combinations thereof. In a particular embodiment, the diuretic is selected from amiloride, bumetanide, chlorothiazide, chlorthalidone, dichlorphenamide, ethacrynic acid, furosemide, hydrochlorothiazide, hydroflumethiazide, indapamide, methylclothiazide, metolazone, torsemide, triamterene, and combinations thereof. The 10 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 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 15 limited to, phosphoramidon, CGS 26303, and combinations thereof.

In a particular embodiment, compounds of the invention are administered in 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, 20 clazosentan, darusentan, sitaxentan, and zibotentan; and dual endothelin receptor antagonists that affect both endothelin A and B receptors, such as bosentan, macitentan, 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 25 statins. Representative statins include, but are not limited to, atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

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 30 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 demethylsertraline; dual serotonin-norepinephrine reuptake inhibitors (SNRIs) such as bicifadine, duloxetine, milnacipran, nefazodone, and venlafaxine; and combinations thereof.

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

- In one embodiment, compounds of the invention are administered in combination
10 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 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
15 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 inhibitor, thiorphan (Wegner (1995) *Clin.Exper.Hypert.* 17:861-876).

- In another embodiment, compounds of the invention are administered in
20 combination with a neprilysin (NEP) inhibitor. Representative NEP inhibitors include, but are not limited to: AHU-377; candoxatril; candoxatrilat; dexecadotril ((+)-N-[2(R)-(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-
25 [9(R)-(acetylthiomethyl)-10-oxo-1-azacyclodecan-2(S)-ylcarbonyl]-4(R)-hydroxy-L-proline benzyl ester); 3-(1-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; retrothiorphan; RU-42827 (2-(mercaptomethyl)-N-(4-pyridinyl)benzenepropionamide);
30 RU-44004 (N-(4-morpholinyl)-3-phenyl-2-(sulfanylmethyl)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)-(acetylsulfanylmethyl)-3-(2-

methylphenyl)propionyl]-L-methionine ethyl ester); spinorphin; SQ-28132 (N-[2-(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); thiorphan and its prodrug racecadotril; UK-69578
 5 (cis-4-[[[1-[2-carboxy-3-(2-methoxyethoxy)propyl]cyclopentyl]carbonyl]amino]cyclohexanecarboxylic acid); UK-447,841 (2-{1-[3-(4-chlorophenyl)propylcarbamoyl]-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
 10 [(3*S*,2'*R*)-3-{1-[2'-(ethoxycarbonyl)-4'-phenylbutyl]-cyclopentan-1-carbonylamino}-2,3,4,5-tetrahydro-2-oxo-1*H*-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,
 15 phosphoramidon, SCH-32615, SCH-34826, SQ-28603, thiorphan, and combinations thereof. In a particular embodiment, the NEP inhibitor is a compound such as daglutril or CGS-26303 ([N-[2-(biphenyl-4-yl)-1(*S*)-(1*H*-tetrazol-5-yl)ethyl]amino]methylphosphonic acid), which have activity both as inhibitors of the endothelin converting enzyme (ECE) and of NEP. Other dual acting ECE/NEP compounds can also be used. The NEP inhibitor
 20 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.

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;
 25 organic nitrates such as pentaerythritol tetranitrate; and sydnonimines such as linsidomine and molsidomine.

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, alefenac,
 30 alminoprofen, amfenac, amiprilose, aloxiprin, anirolac, apazone, azapropazone, benorilate, benoxaprofen, bezpiperylon, broperamole, bucloxic acid, carprofen, clidanac, diclofenac, diflunisal, diftalone, enolicam, etodolac, etoricoxib, fenbufen, fenclofenac, fenclozic acid, fenoprofen, fentiazac, feprazone, 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, 5 salsalate, sudoxicam, sulfasalazine, sulindac, suprofen, tenoxicam, tiopinac, tiaprofenic acid, tioxaprofen, tolfenamic acid, tolmetin, triflumidate, zidometacin, zomepirac, and combinations thereof. In a particular embodiment, the NSAID is selected from etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, meloxicam, naproxen, oxaprozin, piroxicam, and combinations thereof.

10 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, amantadine, dextromethorphan, dextropropoxyphene, ketamine, ketobemidone, memantine, methadone, and so forth.

In still another embodiment, compounds of the invention are administered in 15 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, levallorphan, levorphanol, meperidine, methadone, morphine, nalbuphine, nalmeferene, nalorphine, naloxone, naltrexone, nalorphine, oxycodone, oxymorphone, pentazocine, 20 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.

In a particular embodiment, compounds of the invention are administered in combination with a phosphodiesterase (PDE) inhibitor, particularly a PDE-V inhibitor. 25 Representative PDE-V inhibitors include, but are not limited to, avanafil, lodenafil, mirodenafil, sildenafil (Revatio[®]), tadalafil (Adcirca[®]), vardenafil (Levitra[®]), and udenafil.

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 30 sodium, bimatoprost, epoprostenol, iloprost, latanoprost, tafluprost, travoprost, and treprostinil, 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 inhibitor, examples of which include, but are not limited to, aliskiren, enalkiren, remikiren, and combinations thereof.

- 5 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 desmethyl-citalopram, dapoxetine, escitalopram (e.g., escitalopram oxalate), fluoxetine and the fluoxetine desmethyl metabolite norfluoxetine, fluvoxamine (e.g., fluvoxamine maleate),
10 paroxetine, sertraline and the sertraline metabolite demethylsertraline, and combinations thereof.

- In one embodiment, compounds of the invention are administered in combination 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,
15 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 limitation, carbamazepine, fosphenytoin, lamotrigine, lidocaine, mexiletine, oxcarbazepine, phenytoin, and combinations thereof.

- 20 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 atacigat, riociguat, and combinations thereof.

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

- 30 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

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 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.

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).

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).

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
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
5 (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
10 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
15 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
20 (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
25 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
30 (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 embodiments of the invention. These specific embodiments, however, are not intended to limit the scope of the invention in any way unless specifically indicated.

- 5 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:

	AcOH	acetic acid
	Bn	benzyl
10	BOC	<i>t</i> -butoxycarbonyl (-C(O)OC(CH ₃) ₃)
	(BOC) ₂ O	di- <i>t</i> -butyl dicarbonate
	Cbz	carbobenzyloxy (-C(O)O-benzyl)
	DCC	1,3-dicyclohexylcarbodiimide
	DCM	dichloromethane or methylene chloride
15	DIPEA	<i>N,N</i> -diisopropylethylamine
	DMAP	4-dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMSO	dimethylsulfoxide
	EDC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
20	EDTA	ethylenediaminetetraacetic acid
	Et ₃ N	triethylamine
	EtOAc	ethyl acetate
	EtOH	ethanol
	Et ₂ O	diethyl ether
25	HATU	<i>N,N,N',N'</i> -tetramethyl-O-(7-azabenzotriazol-1-yl)uronium hexafluorophosphate
	HOBt	1-hydroxybenzotriazole
	HMPA	Hexamethylphosphoramide
	LDA	Lithium diisopropylamide
30	LiHMDS	lithium hexamethyl disilazide
	MeCN	acetonitrile
	MeOH	methanol
	MTBE	methyl <i>t</i> -butyl ether

	NaHMDS	sodium bis(trimethylsilyl)amide
	Pd(dppf) ₂ Cl ₂	1,1-bis(diphenylphosphino)ferrocene palladium chloride
	PdOH ₂ /C	palladium hydroxide on carbon (Pearlman's catalyst)
	Pd(PPh ₃) ₄	tetrakis(triphenylphosphine)palladium(0)
5	PPh ₃	Triphenylphosphine
	PE	petroleum ether
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran

Unless noted otherwise, all materials, such as reagents, starting materials and
10 solvents, were purchased from commercial suppliers (such as Sigma-Aldrich, Fluka
Riedel-de Haën, and the like) and were used without further purification.

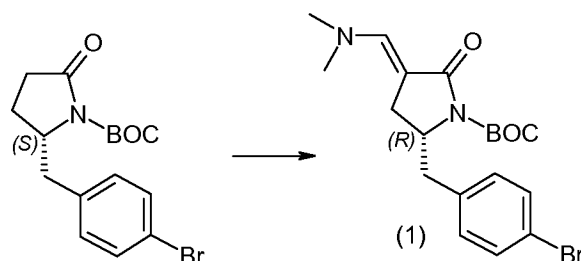
Reactions were run under nitrogen atmosphere, unless noted otherwise. The
progress of reactions were monitored by thin layer chromatography (TLC), analytical high
performance liquid chromatography (anal. HPLC), and mass spectrometry, the details of
15 which are given in specific examples. Solvents used 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
20 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).
25 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
30 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.

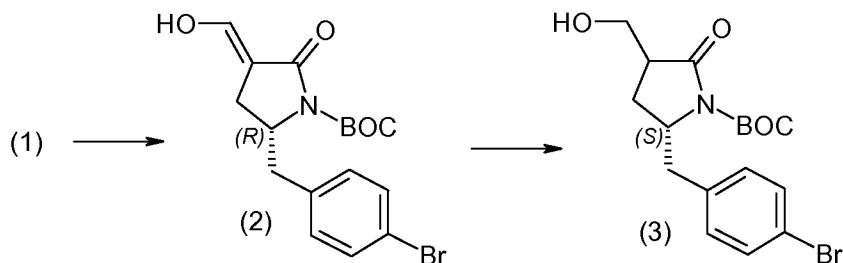
It is understood that many of the compounds described in the Preparations and
Examples can exist in a tautomer form, and that both forms are intended to be covered.

For example, (2*S*,4*S*)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid is depicted in Example 2-1 but it is understood that this compound can exist in a tautomer form, for example, as (2*S*,4*S*)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid.

Preparation 1: (2*S*,4*S*)-5-(4-Bromophenyl)-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic Acid Ethyl Ester



A mixture of (S)-2-(4-bromobenzyl)-5-oxopyrrolidine-1-carboxylic acid *t*-butyl ester (52 g, 147 mmol) and *t*-butoxy-*N,N,N',N'*-tetramethylmethanedi-
 10 amine (50 g, 286 mmol) was stirred at 80°C for 4 hours under argon. The mixture was diluted with EtOAc (500 mL) and washed with water (300 mL) and saturated aqueous NaCl (300 mL), dried over NaSO₄, and concentrated to yield Compound 1 (60 g) as a red oil. LC-MS: [M+H]⁺:410.

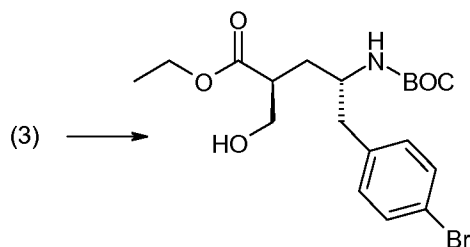


To a solution of Compound 1 (60 g, 147 mmol) in THF (600 mL) was added 1 M HCl (175 mL, 175 mmol) at 0°C under nitrogen. After stirring for 1 hour at room temperature, the mixture was diluted with EtOAc (500 mL) and adjusted with saturated aqueous NaHCO₃ to pH 7. The aqueous layer was extracted with EtOAc (2x300 mL) and
 20 the combined organic layers were washed with water (2x500 mL) and saturated aqueous NaCl (500 mL), dried over NaSO₄, and concentrated to yield Compound 2 (56 g) as a yellow solid. LC-MS: [2M+Na]⁺: 787

To a solution of Compound 2 (20 g, 52 mmol) in MeOH (600 mL) was added 1M HCl (210 mL, 210 mmol) at 0°C under nitrogen. The mixture was stirred at 0°C for 1

hour, then NaBH_3CN (13.2 g, 210 mmol) was added in small portions over 30 minutes. After stirring for 2 hours at 0°C , the mixture was adjusted with saturated aqueous NaHCO_3 to pH 7 and concentrated. The aqueous layers were extracted with EtOAc (3x200 mL) and the combined organic layers were washed with water (2x100 mL) and saturated aqueous

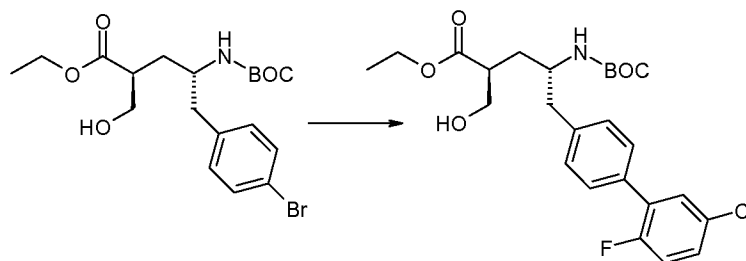
5 NaCl (100 mL), dried over Na_2SO_4 , filtered, and concentrated to yield the crude residue, which was further purified by silica gel chromatography (PE:EtOAc=5:1) to yield Compound 3 (10 g) as a white solid. LC-MS: $[2\text{M}+\text{Na}]^+$: 791



To a solution of Compound 3 (10 g, 26 mmol) in anhydrous EtOH (800 mL) was

10 added anhydrous K_2CO_3 (14.3 g, 104 mmol) at 0°C under nitrogen. After stirring for 1 hour at 0°C , the mixture was warmed to room temperature and stirred for 16 hours. After filtration, the filtrate was concentrated and the residue was purified by silica gel chromatography (PE:EtOAc=5:1 to 2:1) to yield the title compound (2.5 g) as a colorless oil. LC-MS: $[\text{M}+\text{Na}]^+$: 453

15 Preparation 2: (2S,4S)-4-t-Butoxycarbonylamino-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)-2-hydroxymethylpentanoic Acid Ethyl Ester

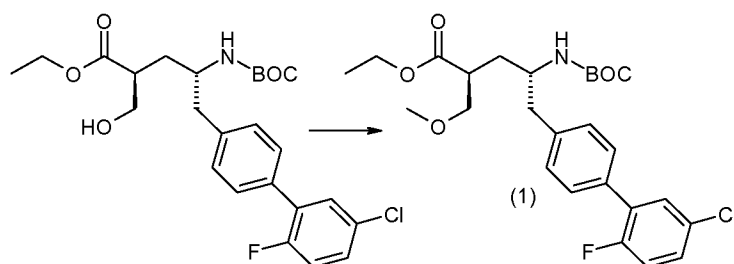


(2S,4S)-5-(4-Bromophenyl)-4-t-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (6 g, 13.9 mmol), 5-chloro-2-fluorophenylboronic acid (2.7 g, 15.3 mmol),

20 $\text{Pd}(\text{dppf})\text{Cl}_2$ (500 mg, 683 μmol), and KF (1.6 g, 27.8 mmol) in dioxane (50 mL) and water (50 mL) were combined in a flask that had been evacuated and back-filled with nitrogen. The mixture was stirred at 80°C for 4 hours, then extracted with EtOAc (2x50 mL), and the organic layers were concentrated and purified by silica gel chromatography (PE:EtOAc=5:1) to yield the title compound (4 g) as a yellow oil. LC-MS: $[2\text{M}+\text{Na}]^+$:

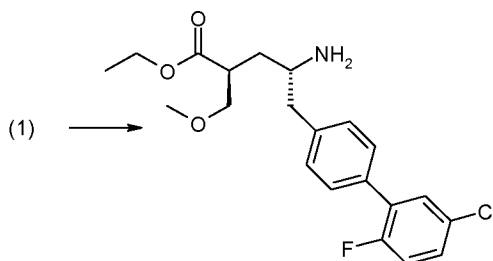
982; ^1H NMR (300 MHz, CDCl_3): δ ppm 7.05~7.44 (m, 7H), 4.4 (s, 1H), 4.1~4.2 (m, 2H), 3.85 (s, 1H), 3.76 (m, 2H), 2.7~2.85 (m, 3H), 1.94~2.02 (m, 2H), 1.59 (s, 1H), 1.40 (s, 9H), 1.24~1.29 (t, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ ppm 174.65, 159.98, 156.71, 155.50, 138.16, 129.87, 129.04, 128.61, 117.78, 117.45, 79.63, 63.77, 61.16, 50.34, 44.91, 41.73, 33.30, 28.70, 14.54.

Preparation 3: (2*S*,4*S*)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethylpentanoic Acid Ethyl Ester



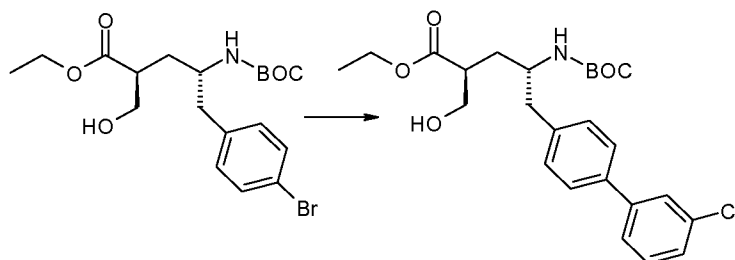
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-

hydroxymethylpentanoic acid ethyl ester (1.5 g, 3.1 mmol) was combined with 10N NaOH (2.2 mL, 21.9 mmol), DCM (12 mL), and tetrabutylammonium hydrogen sulfate (212 mg, 625 μmol). Dimethyl sulfate (512 mg, 4.1 mmol) was added, the reaction flask was capped and stirred vigorously overnight. The DCM layer was extracted and concentrated under reduced pressure. The residue was purified by normal phase chromatography (0-80% EtOAc/hexanes) to yield Compound 1 (630 mg).



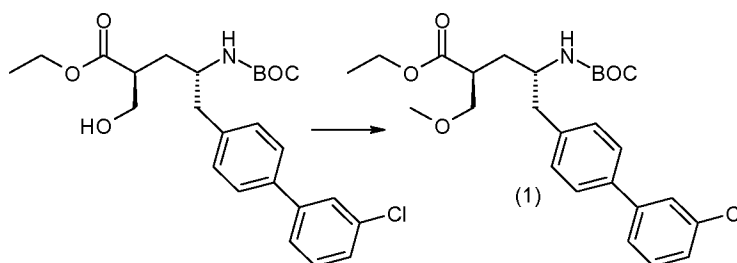
Compound 1 (292 mg, 591 μmol) was dissolved in MeCN (2 mL) and 4N HCl in dioxane (0.6 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

Preparation 4: (2S,4S)-4-*t*-Butoxycarbonylamino-5-(3'-chlorobiphenyl-4-yl)-2-hydroxymethylpentanoic Acid Ethyl Ester

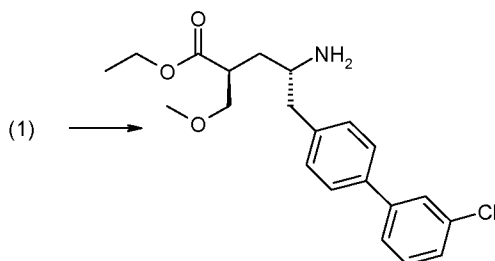


- (2S,4S)-5-(4-Bromophenyl)-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (5.5 g, 12.8 mmol), 3-chlorophenylboronic acid (2.2 g, 14 mmol), Pd(dppf)Cl₂ (500 mg, 683 μmol), and KF (1.5 g, 25.6 mmol) in dioxane (50 mL) and water (50 mL) were combined in a flask that had been evacuated and back-filled with nitrogen. The mixture was stirred at 80°C for 4 hours, then extracted with EtOAc (2x50 mL), and the organic layers were concentrated and purified by silica gel chromatography (PE:EtOAc=5:1) to yield the title compound (3.3 g) as a yellow oil. LC-MS: [2M+Na]⁺: 947; ¹H NMR (300 MHz, CDCl₃): δ ppm 7.23~7.54 (m, 8H), 4.4 (s, 1H), 4.1~4.2 (m, 2H), 3.85 (s, 1H), 3.7 (m, 2H), 2.69~2.85 (m, 3H), 1.93~2.09 (m, 2H), 1.59 (s, 1H), 1.40 (s, 9H), 1.24~1.29 (t, 3H).

Preparation 5: (2S,4S)-4-Amino-5-(3'-chlorobiphenyl-4-yl)-2-methoxymethylpentanoic Acid Ethyl Ester

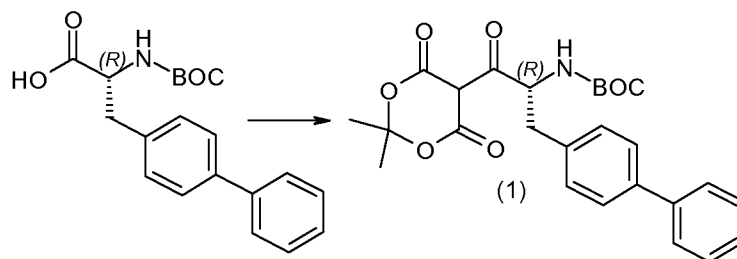


- (2S,4S)-4-*t*-Butoxycarbonylamino-5-(3'-chlorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (1.4 g, 3.1 mmol) was combined with 10N NaOH (2.2 mL, 21.9 mmol), DCM (12 mL), and tetrabutylammonium hydrogen sulfate (212 mg, 625 μmol). Dimethyl sulfate (512 mg, 4.1 mmol) was added, the reaction flask was capped and stirred vigorously overnight. The DCM layer was extracted and concentrated under reduced pressure. The residue was purified by normal phase chromatography (0-80% EtOAc/hexanes) to yield Compound 1 (650 mg).

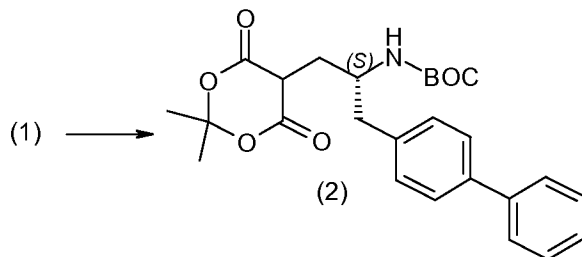


Compound 1 (281 mg, 591 μ mol) was dissolved in MeCN (2 mL) and 4N HCl in dioxane (0.6 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

Preparation 6: (2S,4S)-5-Biphenyl-4-yl-4-t-butoxycarbonylamino-2-hydroxymethylpentanoic Acid Ethyl Ester

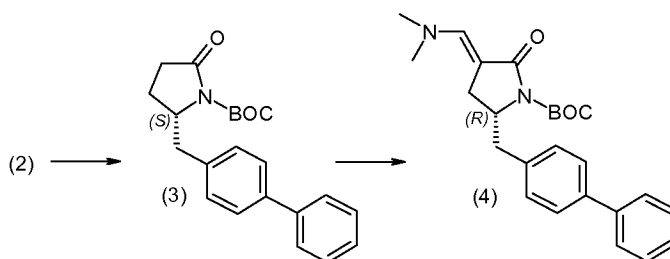


To a solution of (*R*)-3-biphenyl-4-yl-2-*t*-butoxycarbonylamino-propionic acid (50 g, 146 mmol), Meldrum's acid (23.3 g, 161 mmol) and DMAP (27.8 g, 227 mmol) in anhydrous DCM (500 mL) was added a solution of DCC (33.3 g, 161 mmol) in anhydrous DCM (200 mL) over 1 hour at -5°C under nitrogen. The mixture was stirred at -5°C for 8 hours, then refrigerated overnight, during which time, tiny crystals of dicyclohexylurea precipitated. After filtration, the mixture was washed with 5% KHSO₄ (4x200 mL) and saturated aqueous NaCl (200 mL), then dried under refrigeration with MgSO₄ overnight. The solution was filtered and evaporated to yield Compound 1 (68 g) as a light yellow solid, which was used without further purification. LC-MS: 490 [M+Na], 957 [2M+Na].



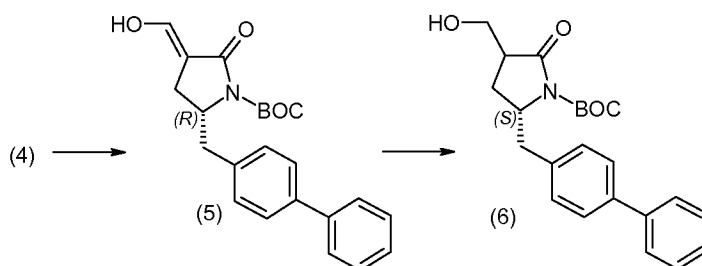
To a solution of crude Compound 1 (68 g, 147 mmol) in anhydrous DCM (1 L) was

added AcOH (96.7 g, 1.6 mol) at -5°C under nitrogen. The mixture was stirred at -5°C for 0.5 hour, then NaBH₄ (13.9 g, 366 mmol) was added in small portions over 1 hour. After stirring for an additional one hour at -5°C, saturated aqueous NaCl (300 mL) was added. The organic layer was washed with saturated aqueous NaCl (2x300 mL) and water (2x300 mL), dried over MgSO₄, filtered, and evaporated to yield the crude residue, which was further purified by chromatography (hexanes:EtOAc=5:1) to yield Compound 2 (46 g) as a light yellow solid. LC-MS: 476 [M+Na], 929 [2M+Na].



A solution of Compound 2 (46 g, 101 mmol) in anhydrous toluene (300 mL) was refluxed under nitrogen for 3 hours. After evaporation of the solvent, the residue was purified by chromatography (hexanes:EtOAc=10:1) to yield Compound 3 (27 g) as a light yellow solid. LC-MS: 374 [M+Na], 725 [2M+Na]. ¹H NMR (300 MHz, CDCl₃): δ 7.64-7.62 (m, 4H), 7.51-7.46 (m, 2H), 7.42-7.39 (m, 1H), 7.39-7.30 (m, 2H), 4.50-4.43 (m, 1H), 3.27-3.89 (m, 1H), 2.88-2.80 (m, 1H), 2.48-2.42 (m, 2H), 2.09-1.88 (m, 2H), 1.66 (s, 9H).

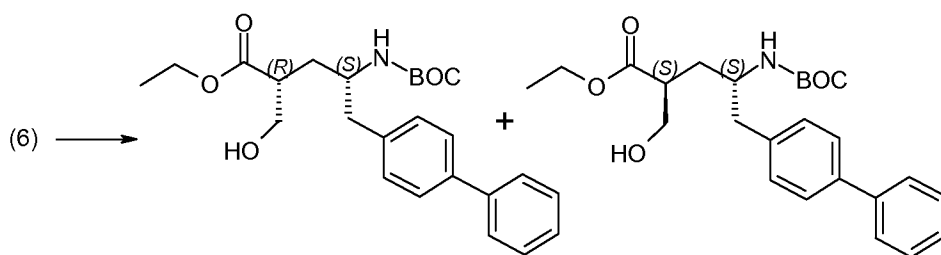
A mixture of Compound 3 (27 g, 77 mmol) and *t*-butoxy-*N,N,N',N'*-tetramethylmethanediimine (40.3 g, 231 mmol) was heated to 80°C under nitrogen. After stirring for 3 hours at 80°C, the mixture was diluted with EtOAc (300 mL), washed with water (2x150 mL) and saturated aqueous NaCl (2x150 mL), dried over MgSO₄, filtered, and evaporated to yield crude Compound 4 (29.7 g, light yellow oil). LC-MS: 425 [M+H], 835 [2M+H].



To a solution of crude Compound 4 (29.7 g, 73 mmol) in THF (200 mL) was added 1 M HCl (81 mL) at 0°C under nitrogen. After stirring for 1 hour at room temperature, the mixture was diluted with EtOAc (100 mL) and adjusted with saturated aqueous NaHCO₃ to

pH 7. The aqueous layer was extracted with EtOAc (2x150 mL) and the combined organic layers were washed with water (2x150 mL) and saturated aqueous NaCl (150 mL), dried over MgSO₄, filtered, and evaporated to yield crude Compound 5 (29.4 g, yellow oil). LC-MS: 402 [M+Na], 781 [2M+Na].

- 5 To a solution of Compound 5 (29.4 g, 77 mmol) in anhydrous THF (300 mL) was added anhydrous EtOH (30 mL) and AcOH (92.5 g, 1.5 mol) at -5°C under nitrogen. The mixture was stirred at -5°C for 0.5 hour, then NaBH₃CN (19.4 g, 308 mmol) was added in small portions over 1 hour. After stirring for one additional hour at -5°C, the mixture was adjusted with saturated aqueous NaHCO₃ to pH 7. The aqueous layers were extracted with
- 10 EtOAc (2x200 mL) and the combined organic layers were washed with water (2x150 mL) and saturated aqueous NaCl (150 mL), dried over MgSO₄, filtered, and concentrated to yield the crude residue, which was further purified by chromatography (hexanes:EtOAc=5:1) to yield Compound 6 (11.2 g) as a light yellow solid. LC-MS: 404 [M+Na], 785 [2M+Na].



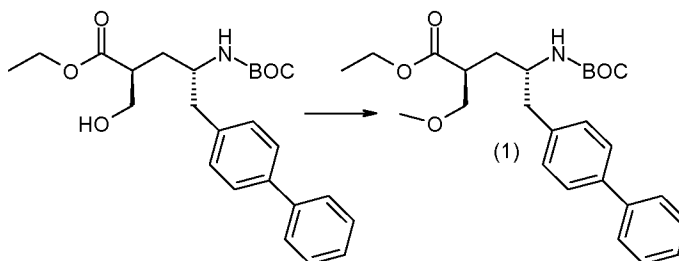
15

- To a solution of Compound 6 (11.2 g, 29 mmol) in anhydrous EtOH (500 mL) was added anhydrous K₂CO₃ (8.0 g, 58 mmol) at 0°C under nitrogen. After stirring for 1 hour at 0°C, the mixture was warmed to room temperature and stirred for 16 hours. After filtration, the filtrate was concentrated and the residue was diluted with water (150 mL),
- 20 DCM (200 mL) and saturated aqueous NaCl (50 mL). After separation, the aqueous layer was extracted with DCM (2x150 mL). The combined organic layers were washed with saturated aqueous NaCl (2x200 mL), dried over MgSO₄, and concentrated to yield the crude residue which was further purified by column chromatography (hexanes:EtOAc=5:1) to yield the (*S,S*) title compound (8.3 g) as a light yellow solid, as well as the (*R,S*) isomer.
- 25 (*S,S*) title compound: LC-MS: 450 [M+Na], 877 [2M+Na]. ¹H NMR (300 MHz, CDCl₃): δ 7.58-7.23 (m, 9H), 4.46-4.43 (d, 1H), 4.20-4.13 (m, 2H), 3.94 (s, 1H), 3.82-3.70 (m, 2H), 2.85-2.70 (m, 3H), 2.25-2.22 (d, 1H), 2.01-1.92 (m, 1H), 1.47 (s, 9H), 1.26-1.24 (m, 3H).

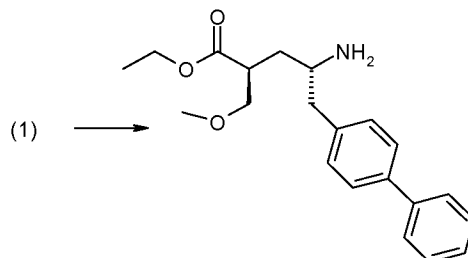
(*R,S*) isomer: LC-MS: 450 [M+Na], 877 [2M+Na]. ¹H NMR (300 MHz, CDCl₃): 87.58-7.55 (m, 4H), 7.50-7.43 (m, 2H), 7.40-7.30 (m, 1H), 7.26-7.23 (m, 1H), 4.46 (m, 1H), 4.21-4.13 (m, 2H), 3.94 (m, 1H), 3.82-3.77 (m, 2H), 2.83-2.81 (d, 2H), 2.66-2.63 (m, 1H), 2.24 (m, 1H), 1.83-1.81 (m, 2H), 1.38 (s, 9H), 1.30-1.25 (m, 3H).

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Preparation 7: (*2S,4S*)-4-Amino-5-biphenyl-4-yl-2-methoxymethylpentanoic Acid Ethyl Ester

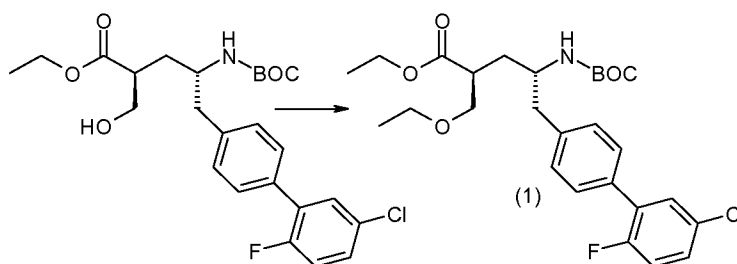


(*2S,4S*)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (69 mg, 140 μmol) was combined with DCM (1 mL), 10N NaOH (98 μL, 982 μmol), tetrabutylammonium hydrogen sulfate (9.5 mg, 28 μmol) and dimethyl sulfate (54 μL, 561 μmol). The mixture was stirred overnight and the DCM layer was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (30 mg).

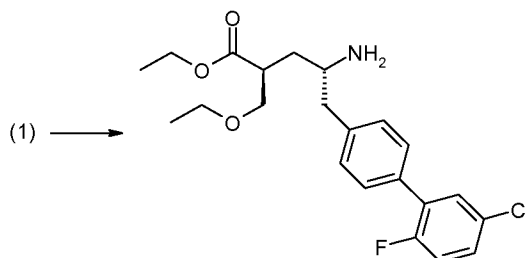


Compound 1 (21.7 mg, 49 μmol) was dissolved in MeCN (0.3 mL) and 4N dioxane (0.3 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt.

Preparation 8: (*2S,4S*)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethylpentanoic Acid Ethyl Ester

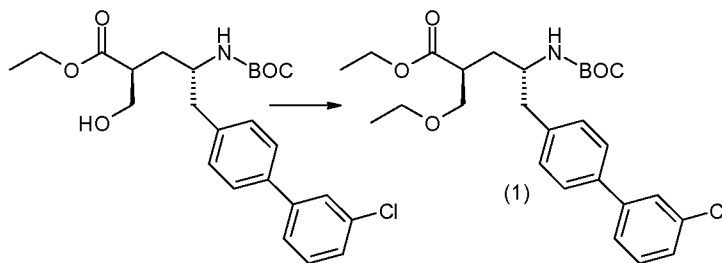


(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (1.5 g, 3.1 mmol) was combined with 10N NaOH (2.2 mL, 21.9 mmol), DCM (12 mL), and tetrabutylammonium hydrogen sulfate (212 mg, 625 μ mol). Diethyl sulfate (626 mg, 4.1 mmol) was added, the reaction flask was capped and stirred vigorously overnight. The DCM layer was extracted and concentrated under reduced pressure. The residue was purified by normal phase chromatography (0-80% EtOAc/hexanes) to yield Compound 1 (300 mg).

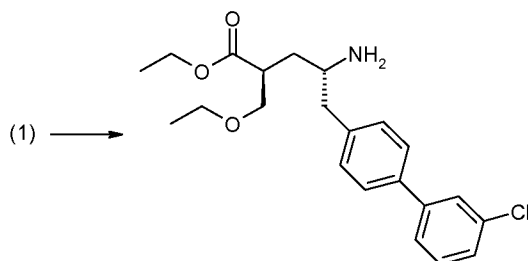


Compound 1 (300 mg, 591 μ mol) was dissolved in MeCN (2 mL) and 4N HCl in dioxane (0.6 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

Preparation 9: (2*S*,4*S*)-4-Amino-5-(3'-chlorobiphenyl-4-yl)-2-ethoxymethylpentanoic Acid Ethyl Ester



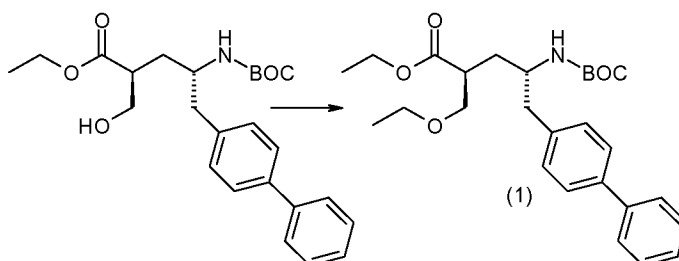
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(3'-chlorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (1.4 g, 3.1 mmol) was combined with 10N NaOH (2.2 mL, 21.9 mmol), DCM (12 mL), and tetrabutylammonium hydrogen sulfate (212 mg, 625 μ mol). Diethyl sulfate (626 mg, 4.1 mmol) was added, the reaction flask was capped and stirred vigorously overnight. The DCM layer was extracted and concentrated under reduced pressure. The residue was purified by normal phase chromatography (0-80% EtOAc/hexanes) to yield Compound 1 (350 mg).



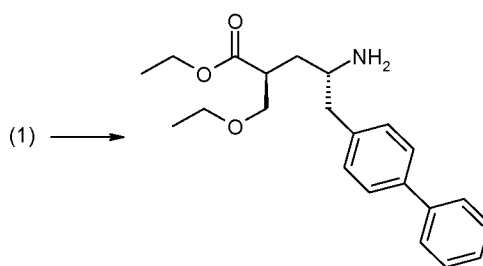
Compound 1 (289 mg, 591 μ mol) was dissolved in MeCN (2 mL) and 4N HCl in dioxane (0.6 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound, which was used without further purification.

5

Preparation 10: (2S,4S)-4-Amino-5-biphenyl-4-yl-
2-ethoxymethylpentanoic Acid Ethyl Ester

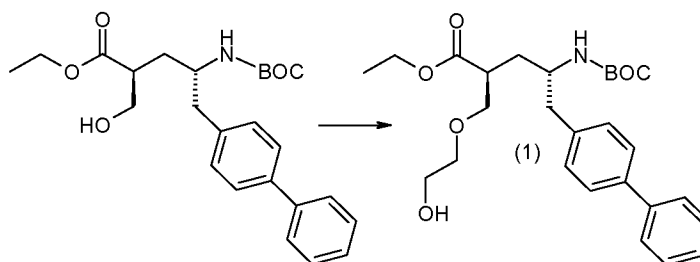


(2S,4S)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (60 mg, 140 μ mol) was combined with 10N NaOH (98 μ L, 982 μ mol), DCM (1 mL), tetrabutylammonium hydrogen sulfate (9.5 mg, 28 μ mol), and diethyl sulfate (87 mg, 561 μ mol). The mixture was stirred overnight and the DCM layer was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (15 mg).

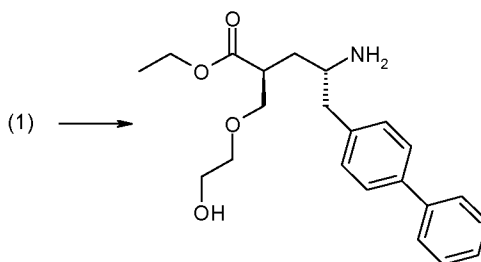


Compound 1 (22.4 mg, 49 μ mol) was dissolved in MeCN (0.3 mL) and 4N HCl in dioxane (0.3 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

Preparation 11: (2*S*,4*S*)-4-Amino-5-biphenyl-4-yl-2-(2-hydroxyethoxymethyl)pentanoic Acid Ethyl Ester



(2*S*,4*S*)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (60 mg, 140 μ mol) was combined with 10N NaOH (98 μ L, 982 μ mol), DCM (1 mL), tetrabutylammonium hydrogen sulfate (9.5 mg, 28 μ mol), and [1,3,2]dioxathiolane 2,2-dioxide (70 mg, 561 μ mol). The mixture was stirred overnight and the DCM layer was separated, dried over Na₂SO₄, and purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (8 mg).

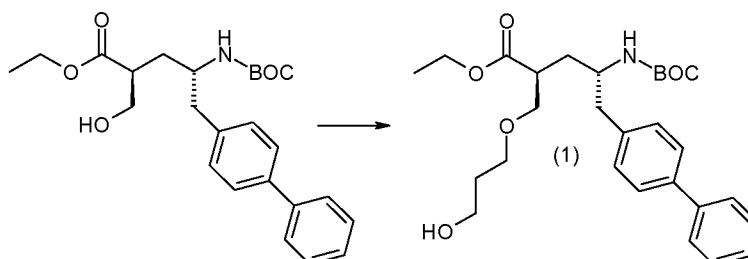


10

Compound 1 (23.2 mg, 49 μ mol) was dissolved in MeCN (0.3 mL) and 4N HCl in dioxane (0.3 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

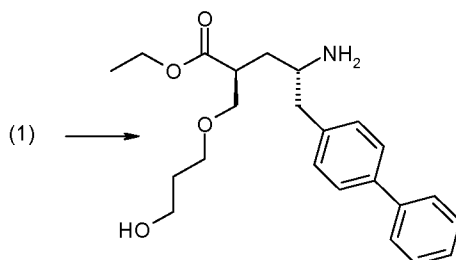
15

Preparation 12: (2*S*,4*S*)-4-Amino-5-biphenyl-4-yl-2-(3-hydroxypropoxymethyl)pentanoic Acid Ethyl Ester



(2*S*,4*S*)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (60 mg, 140 μ mol) was combined with 10N NaOH (98 μ L, 982 μ mol), DCM (1

mL), tetrabutylammonium hydrogen sulfate (9.5 mg, 28 μ mol), and [1,3,2]dioxathiane 2,2-dioxide (78 mg, 561 μ mol). The mixture was stirred overnight and the DCM layer was separated, dried over Na_2SO_4 , and purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (9 mg).

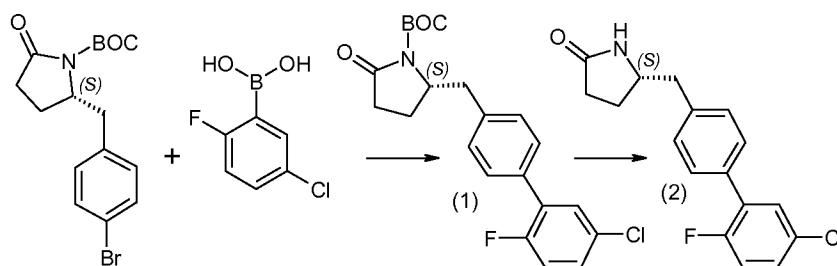


5

Compound 1 (23.9 mg, 49 μ mol) was dissolved in MeCN (0.3 mL) and 4N HCl in dioxane (0.3 mL) and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

10

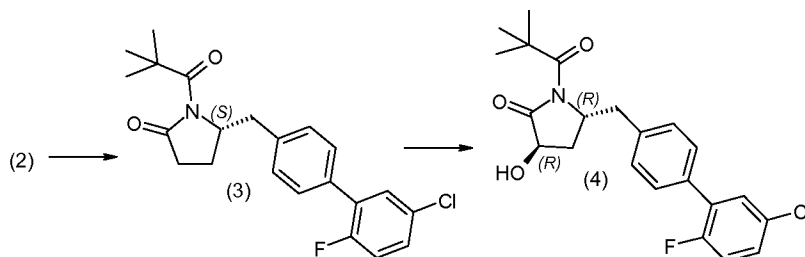
Preparation 13: (2R,4R)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxypentanoic Acid Ethyl Ester



To a solution of (*S*)-2-(4-bromobenzyl)-5-oxopyrrolidine-1-carboxylic acid *t*-butyl ester (25 g, 70.6 mmol) in 1,4-dioxane (500 mL) was added 5-chloro-2-fluorophenylboronic acid (24.6 g, 141 mmol), $\text{Pd}(\text{PPh}_3)_4$ (4.1 g, 3.5 mmol) and a solution of K_2CO_3 (17.8 g, 141 mmol) in water (90 mL), at room temperature under nitrogen. The mixture was heated to 60°C and stirred overnight. Water (500 mL) was added and the solvent evaporated. The mixture was extracted with EtOAc (3x200 mL). The combined organic layers were washed with saturated aqueous NaCl (300 mL) and filtered. The filtrate was concentrated to yield the crude residue which was purified by chromatography to yield Compound 1 (22.7 g) as a light yellow solid. LC-MS: 829.2 $[2\text{M}+\text{Na}^+]$.

To a solution of Compound 1 (4.9 g, 12.1 mol) in DCM (100 mL) was added TFA (4.5 mL, 60.7 mmol) at 0°C under nitrogen, and stirred for 1 hour. The mixture was warmed to room temperature for 1.5 hours. After evaporation of the solvent, the residue

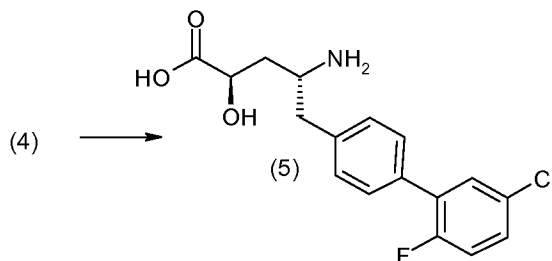
was diluted with EtOAc (100 mL), then washed with saturated aqueous NaHCO_3 (3x100 mL), water (2x100 mL), saturated aqueous NaCl (100 mL), then dried over Na_2SO_4 . The mixture was filtered and the filtrate was concentrated to yield crude Compound 2. LC-MS: 304 $[\text{M}+\text{H}]^+$.



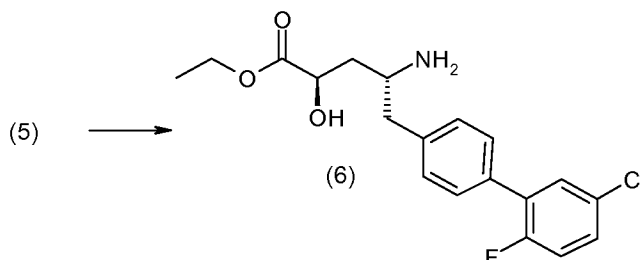
5

To a solution of NaH (2.4 g, 695 mmol) in THF (200 mL) was added dropwise a solution of Compound 2 (8.5 g, 278 mmol) in THF (50 mL) at 0°C under nitrogen. The mixture was warmed to room temperature and stirred for 2 hours. After cooling to 0°C , pivaloyl chloride (5 g, 41.7 mmol) was added dropwise over 30 minutes. The mixture was warmed to room temperature and stirred for 9.5 hours. The reaction was quenched with saturated aqueous NH_4Cl (250 mL) and extracted with EtOAc (3x400 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield the crude residue which was purified by chromatography to yield Compound 3 (18 g) as a yellow solid. LC-MS: 388 $[\text{M}+\text{H}]^+$.

To a solution of Compound 3 (9 g, 23.2 mmol) in THF (200 mL) was added dropwise NaHMDS (20.9 mL, 41.8 mmol) at -78°C under nitrogen. After stirring for 1 hour at -78°C , a solution of (+)-(8,8-dichlorocamphorylsulfonyl)oxaziridine (10.4 g, 34.8 mmol) in THF (50 mL) was added dropwise. After stirring at -78°C for 1 hour, the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with EtOAc (3x400 mL). The combined organic layers were washed with 1M HCl (400 mL), saturated aqueous NaHCO_3 (400 mL), and saturated aqueous NaCl (400 mL), dried over Na_2SO_4 , and concentrated to give the crude residue which was purified by chromatography to yield Compound 4 (8.8 g) as a white semi-solid. LC-MS: 426.1 $[\text{M}+\text{Na}]^+$.

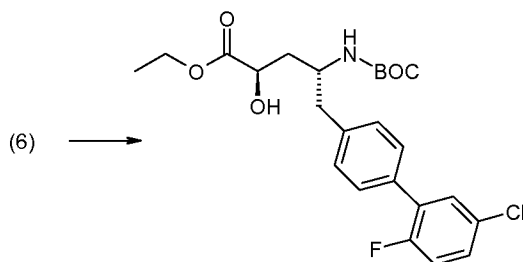


A solution of Compound 4 (8.8 g, 21.8 mmol) in EtOH (12 mL) was added to concentrated HCl (200 mL) and heated at 100°C and stirred overnight. The mixture was then concentrated to give the crude residue which was purified by washing with Et₂O (100 mL) to yield Compound 5 (7.5 g) as a solid HCl salt. LC-MS: 338 [M+ H⁺].



5

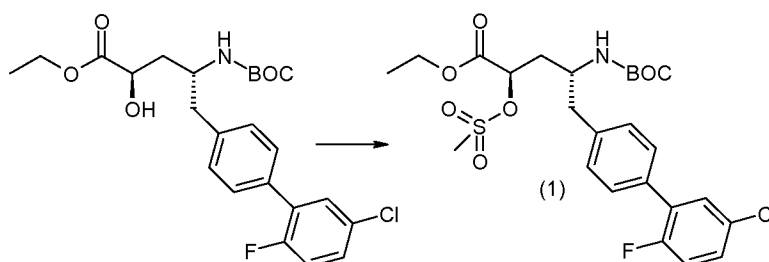
A solution of Compound 5 (7.5 g, 20.1 mmol) in EtOH/HCl (100 mL) was heated at 50°C overnight. The mixture was concentrated and the crude residue was purified by washing with Et₂O (200 mL) to yield Compound 6 (6.5 g) as a white solid HCl salt. LC-MS: 366.1 [M+ H⁺].



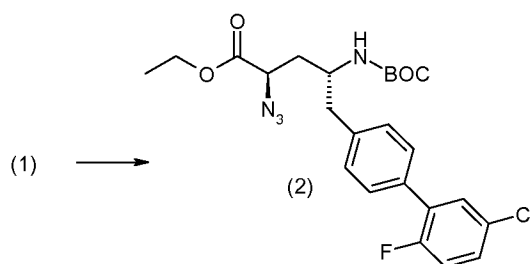
10

Compound 6 (2 g, 5.5 mmol) and di-*t*-butyl dicarbonate (1.5 mL, 6.6 mmol) were mixed in DCM (10 mL) followed by DIPEA (1.9 mL, 10.9 mmol). The mixture was stirred at room temperature for 3 hours, at which time LCMS indicated the mass of the desired compound. The solvent was removed and the residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield the title compound (2.5 g).

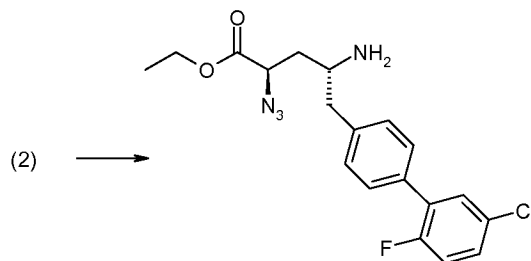
Preparation 14: (2*R*,4*R*)-4-Amino-2-azido-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic Acid Ethyl Ester



(2*R*, 4*R*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-pentanoic acid ethyl ester (2.5 g, 5.4 mmol) was dissolved in DCM (10 mL). Methanesulfonyl chloride (460 μ L, 6.0 mmol) was added, followed by Et₃N (1.5 mL, 10.8 mmol). The mixture was stirred at room temperature for 10 minutes, at which time LCMS indicated the mass of the desired compound. EtOAc and a saturated aqueous NH₄Cl were added. The organic layer was extracted, separated, dried over MgSO₄, filtered, and evaporated to yield crude Compound 1, which was used directly in the next step.

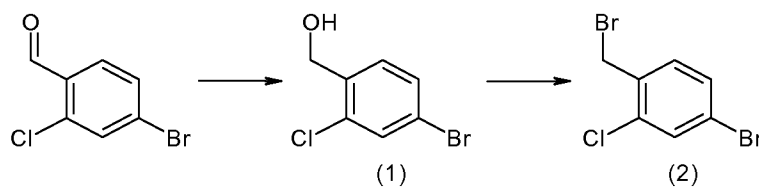


Compound 1 (2.9 g, 5.4 mmol) in DMF (6 mL) was combined with sodium azide (422 mg, 6.5 mmol), and the resulting mixture was stirred at 50°C for 4 hours, at which time LCMS indicated the mass of the desired compound. EtOAc and water were added. The organic layer was extracted, separated and dried over MgSO₄, filtered, and evaporated. The residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield Compound 2 (2.1 g) as a yellow oil.



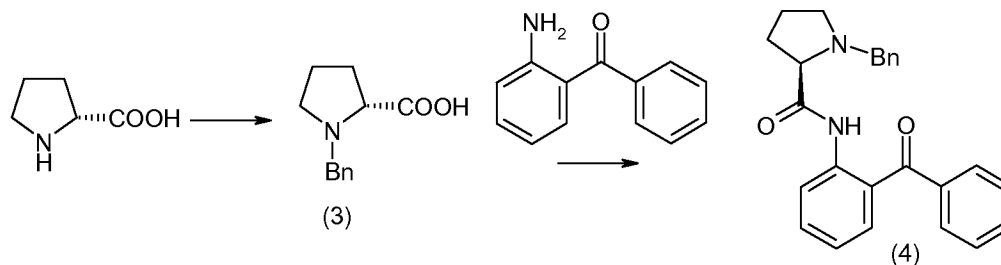
Compound 2 (2.1 g, 4.2 mmol) was dissolved in MeCN (6 mL). A solution of 4N HCl in dioxane (10.5 mL, 42.2 mmol) was added, and the mixture was stirred at room temperature for 20 minutes then concentrated *in vacuo* to yield the crude title compound as an HCl salt, which was used without further purification.

Preparation 15: (2R,4R)-4-Amino-5-(4-bromo-2-chlorophenyl)-
2-hydroxypentanoic Acid Ethyl Ester



To a suspension of 4-bromo-2-chlorobenzaldehyde (50g, 22.8mmol) in MeOH (500 mL) was added NaBH₄ (17.3 g, 45.6 mmol) in portions at 0°C. The mixture was stirred for 30 minutes and then aqueous NH₄Cl was added to quench the reaction. The mixture was concentrated *in vacuo*. The residue was extracted with EtOAc (200 mL×2) and the combined organic layers were dried over Na₂SO₄, and concentrated *in vacuo* to yield Compound 1 (48g) as a white solid.

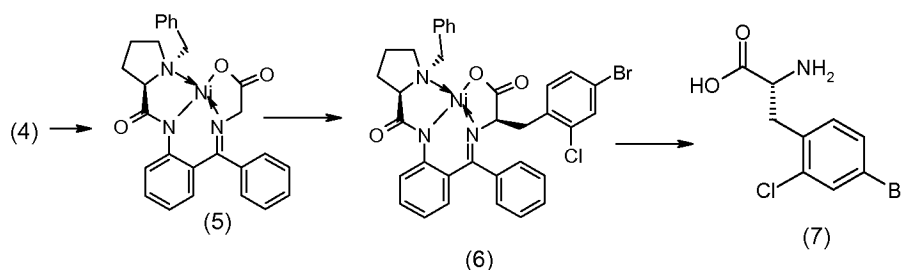
To a solution of Compound 1 (46.8 g, 21.1 mmol) in dry DCM (500 mL) was added phosphorous tribromide (68.6 g, 25.3 mmol) dropwise at 0°C under nitrogen. The mixture was stirred for 2 hours and then washed with saturated aqueous NaHCO₃ (200 mL×2) and saturated aqueous NaCl (200 mL), dried over Na₂SO₄, concentrated *in vacuo* to yield Compound 2 (36 g) as a colorless oil.



To a stirred solution of (R)-pyrrolidine-2-carboxylic acid (57.7 g, 0.5 mol) and KOH (84 g, 1.5 mol) in isopropyl alcohol (330 mL) was added benzyl chloride (70 mL, 0.6 mol) dropwise at 0°C over 3 hours. The mixture was then stirred overnight at the same temperature. The resulting mixture was neutralized with concentrated HCl to pH 6, followed by the addition of chloroform (200 mL). The mixture was stirred for 30 minutes, then filtered and the precipitate was washed with chloroform (100 mL×3). The combined chloroform solutions were dried over Na₂SO₄, and concentrated *in vacuo* to yield Compound 3 (52 g) as a white solid. LC-MS: 206 [M+H]⁺.

To a solution of Compound 3 (10 g, 48.8 mmol) in dry DCM (50 mL) was added SO₂Cl₂ (7.3 g, 61 mmol) at -20°C under nitrogen. The mixture was stirred at -20°C for 3

- hours followed by the addition of a solution of (2-aminophenyl)(phenyl)methanone (6 g, 30.5 mmol) in dry DCM (25 mL) and the mixture was stirred overnight at room temperature. A solution of Na_2CO_3 (10.3 g) in water (40 mL) was added at 0 °C. The organic layer was separated and the aqueous layer was extracted with DCM (50 mL×3).
- 5 The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was washed with MTBE (50 mL×2) to yield Compound 4 (8.5 g) as a yellow solid. LC-MS: 385 $[\text{M}+\text{H}]^+$.

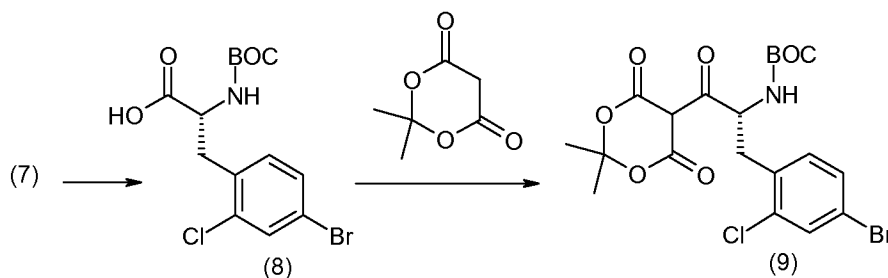


- To a solution of Compound 4 (29.4 g, 76.5 mmol), glycine (28.7 g, 382.4 mmol) and $\text{Ni}(\text{NO}_3)_2 \cdot 6\text{H}_2\text{O}$ (44.5 g, 152.9 mmol) in MeOH (280 mL) was added a solution of KOH (30 g, 535.3 mmol) in MeOH (100 mL) at 45°C under nitrogen. The mixture was stirred at 60°C for an hour. The resulting solution was neutralized with AcOH (31 mL) and poured into ice water (380 mL). The resulting solid was filtered and dissolved in DCM (450 mL), which was washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4
- 10 and concentrated. The residue was washed with EtOAc (50 mL×2) to yield compound 5 (38 g) as a red solid. LC-MS: 498 $[\text{M}+\text{H}]^+$.

- Compound 5 (14.3 g, 28.7 mmol) and NaOH (3.4 g, 81.6 mmol) were added to a flask which was purged with nitrogen twice. Anhydrous DMF (100 mL) was added and the mixture was stirred for 5 minutes at 0°C before a solution of Compound 2 (8.6 g, 30.1 mmol) in DMF (20 mL) was added. The reaction mixture was stirred at room temperature for 30 minutes until complete consumption of Compound 4 (checked by TLC). The resulting mixture was poured into a 5% AcOH aqueous solution (120 mL) which was then extracted with DCM (150 mL×3) and the combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The
- 20 residue was recrystallized with DCM/Et₂O (1:1) to yield Compound 6 (15.5 g) as a red solid. LC-MS: 702 $[\text{M}+\text{H}]^+$.

To a solution of Compound 6 (46 g, 65.6 mmol) in MeOH (300 mL) was added 3N HCl (200 mL). The mixture was refluxed until the red color turned green. The resulting

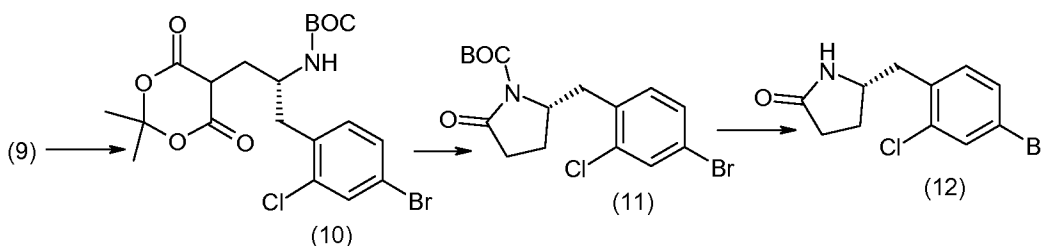
solution was concentrated *in vacuo* before concentrated $\text{NH}_3 \cdot \text{H}_2\text{O}$ (100 mL) was added. The solution was extracted with DCM (200 mL $\times$ 2) and the aqueous phase was concentrated *in vacuo* and subjected to the cation exchange resin (eluted with $\text{NH}_3 \cdot \text{H}_2\text{O}$ /EtOH, 1:1) to yield Compound 7 (15 g) as a white solid. LC-MS: 280 $[\text{M}+\text{H}]^+$.



5

To a suspension of Compound 7 (15 g, 53.9 mmol) in MeCN (150 mL) was added a solution of NaOH (4.3 g, 107.7 mmol) in water (150 mL) at 0 °C, followed by the addition of (BOC) $_2$ O (17.6 g, 80.8 mmol). The mixture was stirred overnight at room temperature. The resulting solution was concentrated *in vacuo*, followed by extraction with DCM (150 mL $\times$ 2). The layers were separated and the aqueous phase was acidified with 1N HCl to pH 3 and extracted with EtOAc (150 mL $\times$ 3). The combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over Na_2SO_4 , filtered and concentrated *in vacuo* to yield Compound 8 (12.3 g, 60%) as a white solid. LC-MS: 402 $[\text{M}+\text{Na}]^+$.

To a suspension of Compound 8 (18.4 g, 48.5 mmol) and Meldrum's acid (8.4 g, 58.2 mmol) in DCM (400 mL) was added DMAP (9.5 g, 77.6 mmol) at -5 °C. After stirring for 10 minutes, a solution of DCC (12 g, 58.2 mmol) in DCM (100 mL) was added dropwise at -5 °C. The mixture was stirred overnight at room temperature. The resulting solution was cooled to 0°C and filtered. The filtrate was washed with aqueous citric acid (200 mL $\times$ 3) and saturated aqueous NaCl (200 mL), dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The residue was triturated with Et $_2$ O (50 mL $\times$ 2) to yield Compound 9 (22 g) as a light yellow solid.

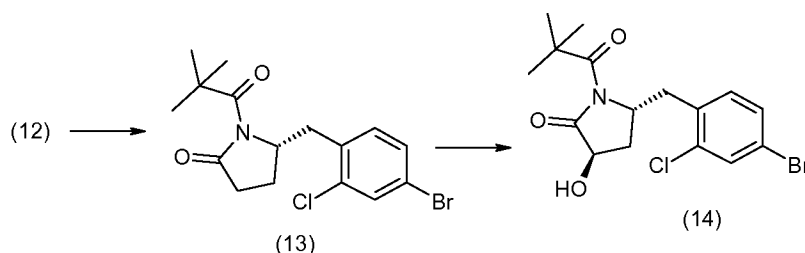


To a solution of Compound 9 (22 g, 43.6 mmol) in DCM (400 mL) was added

AcOH (28.8 g, 479.4 mmol) at 0°C. After stirring for 10 minutes, NaBH₄ (4.1 g, 109 mmol) was added in portions. The mixture was stirred for an hour at 0°C. The resulting solution was washed with saturated aqueous NaHCO₃ (200 mL×2) and saturated aqueous NaCl (200 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was washed
 5 with ether (100 mL×2) to yield Compound 10 (18.6 g) as an off-white solid. LC-MS: 514 [M+Na]⁺.

A solution of Compound 10 (18.6 g, 37.9 mmol) in toluene (350 mL) was heated under reflux for 2 hours. Upon cooling, the mixture was evaporated to dryness to yield Compound 11 (14 g) as a yellow syrup. LC-MS: 334 [M-*t*Bu+H]⁺.

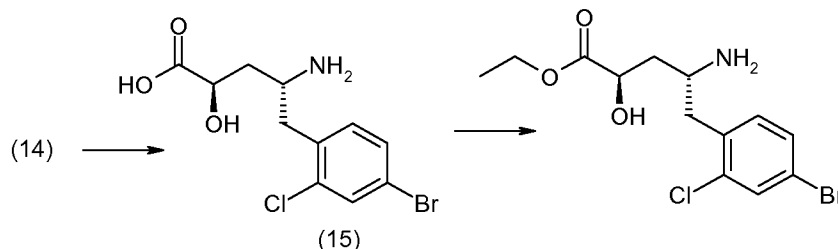
10 To a solution of Compound 11 (14 g, 36.0 mmol) in DCM (250 mL) was added TFA (20 mL). The mixture was stirred for 4 hours at 0°C. The resulting solution was concentrated *in vacuo* to remove TFA. The residue was dissolved in DCM (400 mL) and washed with saturated aqueous NaHCO₃ (200 mL×2), dried over Na₂SO₄ and concentrated to yield Compound 12 (10 g) as a yellow solid. LC-MS: 290 [M+H]⁺.



15 To a solution of Compound 12 (10 g, 34.7 mmol) in dry THF (250 mL) was added NaH (2.4 g, 69.3 mmol, 70%) at 0 °C. The mixture was stirred for one hour at 0°C under nitrogen, then pivaloyl chloride (5 g, 41.6 mmol) was added. After stirring for another 2 hours, saturated aqueous NaHCO₃ (100 mL) was added to quench the reaction. The
 20 resulting mixture was concentrated and extracted with EtOAc (100 mL×3) and the combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over Na₂SO₄ and concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexanes/EtOAc, 5:1) to yield Compound 13 (11.8 g) as a white solid. LC-MS: 374[M+H]⁺.

25 To a solution of Compound 13 (11.8 g, 31.8 mmol) in dry THF (70 mL) was added NaHMDS (24 mL, 47.7 mmol, 2.0 M in THF) dropwise at -78 °C under nitrogen. After stirring for 30 minutes, a solution of (+)-(8,8-dichlorocamphorylsulfonyl)-oxaziridine (15.2 g, 50.8 mmol) in THF (70 mL) was added dropwise at -78 °C. The mixture was stirred for another hour at the same temperature before aqueous NH₄Cl (70 mL) was added to quench

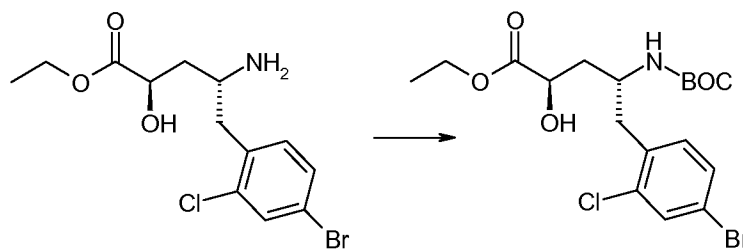
the reaction. The resulting mixture was extracted with EtOAc (150 mL×3) and the combined organic layers were washed with saturated aqueous NaCl (150 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (hexanes/EtOAc, 20:1~5:1) to yield the crude residue (5 g), which was further purified by preparative HPLC to yield Compound 14 (4 g) as a yellow solid. LC-MS: 390 [M+H]⁺.



A solution of Compound 14 (4 g, 10.3 mmol) in concentrated HCl (50 mL) was heated under reflux overnight. The mixture was concentrated *in vacuo* and the resulting solid was washed with Et₂O (50 mL×2) to yield Compound 15 (3.1 g) as a white solid HCl salt. LC-MS: 324 [M+H]⁺.

A solution of Compound 15 (3.1 g, 8.6 mmol) in HCl/EtOH (6.7M, 40 mL) was stirred overnight at 50°C. The resulting mixture was concentrated *in vacuo* and the residue was washed with ether (50 mL×2) to yield the title compound (2.9 g) as an off-white solid HCl salt. LC-MS: 352 [M+H]⁺. ¹H NMR: (CD₃OD) 1.268 (t, *J* = 6.9 Hz, 3H), 1.862-1.946 (m, 1H), 2.068-2.143 (m, 1H), 3.104-3.199 (m, 2H), 3.769-3.809 (m, 1H), 4.162-4.209 (m, 2H), 4.274-4.881 (m, 1H), 7.325 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.522 (dd, *J* = 8.3, 3.0 Hz, 1H), 7.696 (d, *J* = 1.8 Hz, 1H).

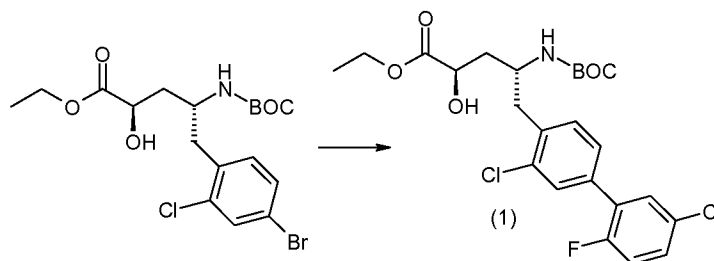
20 Preparation 16: (2R,4R)-5-(4-Bromo-2-chlorophenyl)-4-*t*-butoxycarbonylamino-2-hydroxypentanoic Acid Ethyl Ester



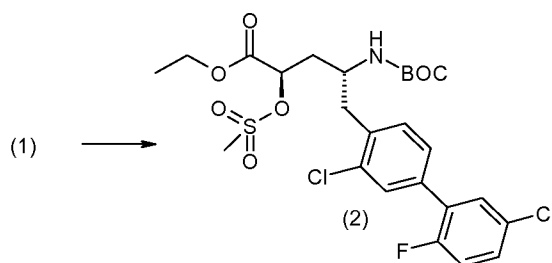
(2R,4R)-4-Amino-5-(4-bromo-2-chlorophenyl)-2-hydroxypentanoic acid ethyl ester (160 mg, 460 μmol) and di-*t*-butyl dicarbonate (99.6 mg, 456 μmol) were mixed in DCM (5 mL) followed by the addition of DIPEA (120 μL, 680 μmol). The mixture was stirred at

room temperature for 1 hour. EtOAc was added and the mixture was washed with 1N HCl (10 mL) followed by aqueous NaHCO₃ (10 mL) and saturated aqueous NaCl (10 mL). The organic layer was retained and dried over MgSO₄, then filtered and dried *in vacuo* to yield the title compound (200 mg).

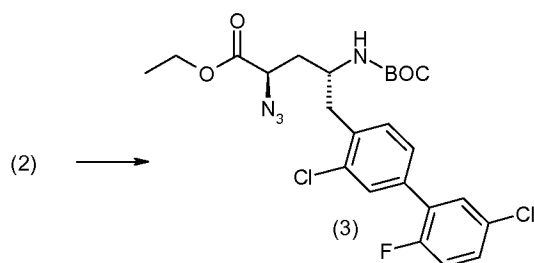
5 Preparation 17: (2*R*,4*R*)-4-Amino-2-azido-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)pentanoic Acid Ethyl Ester



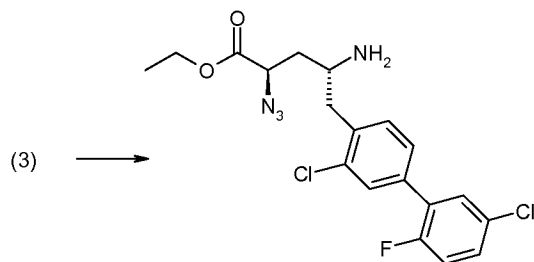
A microwave flask was charged with (2*R*,4*R*)-5-(4-Bromo-2-chlorophenyl)-4-*t*-butoxycarbonylamino-2-hydroxypentanoic acid ethyl ester (400 mg, 887 μmol), 5-chloro-2-fluorophenylboronic acid (170 mg, 976 μmol), Na₂CO₃ (282 mg, 2.7 mmol), Pd(PPh₃)₄ (154 mg, 133 μmol), EtOH (4 mL) and water (1 mL), then placed under nitrogen. The mixture was microwaved for 45 minutes at 110°C, at which time LCMS indicated the mass of the desired compound. The solvent was removed *in vacuo* and the crude residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield Compound 1 (218 mg).



Compound 1 (218 mg, 436 μmol) was dissolved in DCM (5 mL). Methanesulfonyl chloride (37 μL, 479 μmol) was added, followed by Et₃N (152 μL, 1.1 mmol). The mixture was stirred at room temperature for 10 minutes. EtOAc and a saturated aqueous NH₄Cl were added. The organic layer was extracted, separated, dried over MgSO₄, filtered, and evaporated, to yield crude Compound 2, which was used directly in the next step without purification.



Compound 2 (252 mg, 436 μ mol) in DMF (4 mL) was combined with sodium azide (85 mg, 1.3 mmol), and the resulting mixture was stirred at 50°C for 7 hours. EtOAc and water were added. The organic layer was extracted, separated and dried over MgSO_4 ,
 5 filtered, and evaporated. The solvent was evaporated and the residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield Compound 3 (181 mg) as a yellow oil.



Compound 3 (162 mg, 308 μ mol) was dissolved in MeCN (3 mL). A solution of
 10 4N HCl in dioxane (1.2 mL, 4.6 mmol) was added, and the mixture was stirred at room temperature for 20 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was then concentrated *in vacuo* to yield the crude title compound as an HCl salt, which was used without further purification.

15 Preparation 18: Oxodiperoxymolybdenum(pyridine)-
(hexamethylphosphorictriamide)



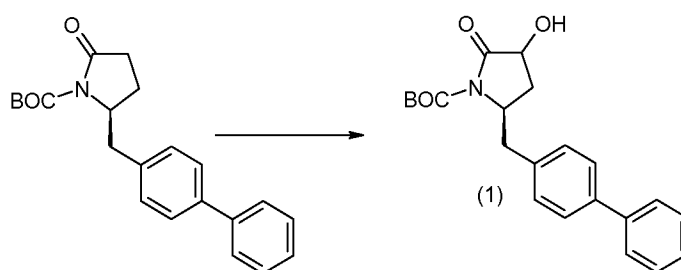
Molybdenum oxide (MoO_3 ; 30 g, 0.2 mol) and 30% hydrogen peroxide (150 mL) were combined, with stirring. The reaction flask was placed in an oil bath equilibrated at 40°C and heated until the internal temperature reached 35°C. The heating bath was then
 20 removed and replaced by a water bath to control the mildly exothermic reaction so that an internal temperature of 35-40°C was maintained. After the initial exothermic period (~30 minutes), the reaction flask was returned to the 40°C oil bath and stirred for a total of 3.5 hours to form a yellow solution with a small amount of suspended white solid. After

cooling to 20°C, the solution was filtered and the resulting yellow filtrate was cooled to 10°C (with stirring) and hexamethylphosphoric triamide ((Me₂N)₃PO; HMPA; 37.3 g, 0.2 mol) was added dropwise over 5 minutes, resulting in the formation of a yellow crystalline precipitate. Stirring was continued for a total of 15 minutes at 10°C, and the residue was
 5 filtered and pressed dry. After 30 minutes *in vacuo*, the filter cake was dissolved in MeOH (20 mL) and stirred at 40°C. Additional MeOH was slowly added until the solids dissolved. The saturated solution was cooled in the refrigerator, yielding a yellow solid (appeared as needles). The solid mass was physically broken, filtered and washed with cold MeOH (20-30 mL) to yield oxodiperoxymolybdenum(aqua) (hexamethylphosphoric
 10 triamide) (MoO₅•H₂O•HMPA, 46-50 g).

MoO₅•H₂O•HMPA was dried over phosphorus oxide in a vacuum desiccator, shielded from the light, for 24 hours at 0.2 mm Hg to yield a somewhat hygroscopic yellow solid, MoO₅•HMPA. MoO₅•HMPA (36.0 g, 0.1 mol) was dissolved in THF (150 mL) and the solution was filtered to remove any precipitate. The filtrate was then stirred at 20°C
 15 while dry pyridine (8.0 g, 0.1 mol) was added over 10 minutes. The crystalline, yellow residue was collected, washed with dry THF (25 mL) and anhydrous ether (200 mL) and dried in a vacuum desiccator (1 hour, 0.2 mm Hg) to yield the title compound (36-38 g; MoO₅•Py•HMPA) as a finely divided yellow solid.

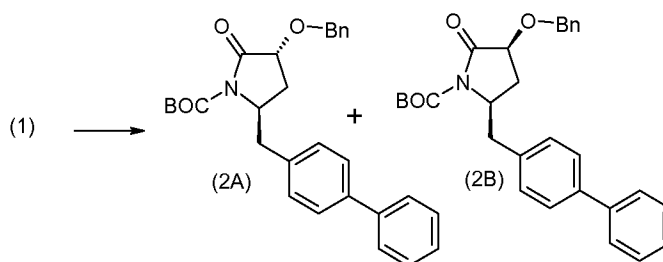
Preparation 19: (2*R*,4*R*)-4-Amino-5-biphenyl-4-yl-2-hydroxypentanoic

20 Acid Ethyl Ester and (2*R*,4*S*)-4-Amino-5-biphenyl-4-yl-2-hydroxypentanoic Acid Ethyl Ester



To a stirred solution of (*S*)-2-biphenyl-4-ylmethyl-5-oxopyrrolidine-1-carboxylic acid *t*-butyl ester (4.4 g, 12.4 mmol) in anhydrous THF (70 mL) was added a solution of 1
 25 M LiHMDS in THF (28 mL) over 15 minutes at -65°C under nitrogen. After stirring for 3 hours at -65°C, oxodiperoxymolybdenum (pyridine) (hexamethylphosphoric triamide) (9 g, 18.6 mmol) was added. The mixture was stirred for another 2 hours at -35°C, then saturated aqueous Na₂S₂O₃ (60 mL) was added. The organic layer was collected and washed with saturated aqueous NH₄Cl (3x60 mL) and saturated aqueous NaCl (2x60 mL),

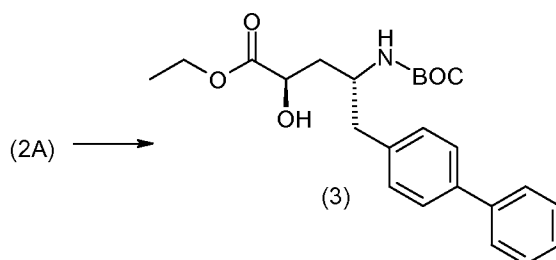
then dried over Na_2SO_4 , and the solvent was removed under reduced pressure to yield the crude residue which was further purified by chromatography (hexanes:EtOAc=5:1) to yield Compound 1 (1.8 g) as a white solid. LC-MS: $[2\text{M}+\text{Na}]$:757.



To a solution of Compound 1 (1.8 g, 5.0 mmol) in anhydrous DCM (50 mL) was added DMAP (122 mg, 1 mmol) and Et_3N (1.5 g, 14.9 mmol) at 0°C under nitrogen. After stirring for 0.5 hour at 0°C , benzyl chloride (1.0 g, 7.4 mmol) was added over 15 minutes. The mixture was stirred for an additional 2 hours at 0°C , then saturated aqueous NaHCO_3 (50 mL) was added. The organic layer was collected and washed with saturated aqueous NaHCO_3 (2x50 mL) and saturated aqueous NaCl (50 mL), then dried over Na_2SO_4 . The mixture was filtered and the filtrate was concentrated to yield the crude residue which was further purified by chromatography (hexanes:EtOAc = 4:1) to yield Compound 2A (471 mg) and Compound 2B (883 mg) as white solids. LC-MS: $[\text{M}+\text{Na}]$:494; $[2\text{M}+\text{Na}]$:965.

Compound 2A: ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 8.02 (m, 2H), 7.57-7.25 (m, 12H), 5.42 (m, 1H), 4.50 (m, 1H), 3.26-3.21 (m, 1H), 2.90 (m, 1H), 2.58 (m, 1H), 2.15-2.05 (m, 1H), 1.62 (m, 9H)

Compound 2B: ^1H NMR (300 MHz, CDCl_3): δ (ppm) = 8.06 (m, 2H), 7.58-7.18 (m, 12H), 5.53-5.41 (m, 1H), 4.39 (m, 1H), 3.57-3.54 (m, 1H), 2.87-2.80 (m, 1H), 2.48-2.44 (m, 1H), 1.98 (m, 1H), 1.63 (m, 9H).

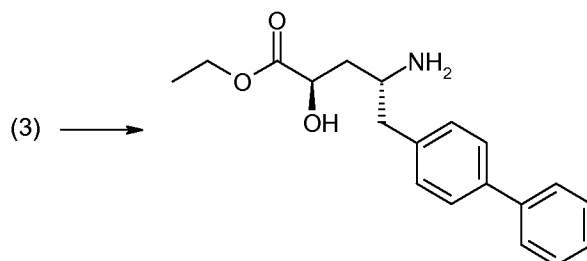


20

To a stirred solution of Compound 2A (471 mg, 1 mmol) in anhydrous EtOH (10 mL) was added anhydrous K_2CO_3 (691 mg, 5 mmol) at room temperature under nitrogen. After stirring for 20 hours at room temperature, the mixture was filtered. To the filtrate was added water (30 mL), DCM (30 mL) and saturated aqueous NaCl (5 mL). The

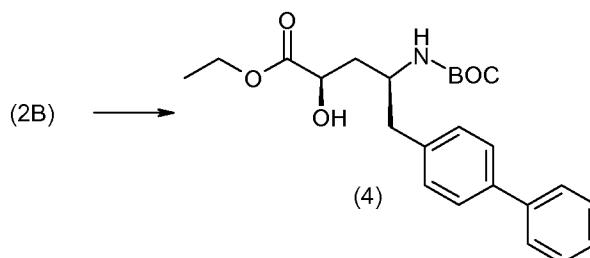
aqueous layer was separated and extracted with DCM (30 mL x 3). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over Na₂SO₄, and concentrated to yield the crude residue which was further purified by chromatography (hexanes:EtOAc = 6:1) to yield Compound 3 (275 mg) as a white solid. LC-MS:

5 [M+Na]⁺:436, [2M+Na]⁺:849.



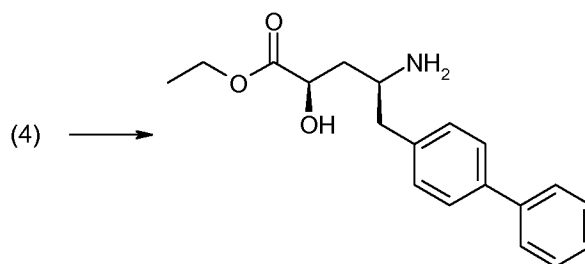
To EtOH (5 mL) was added acetyl chloride (685 mg) at -30°C. After stirring for 1 hour at -30°C, a solution of Compound 3 (275 mg, 665 μmol) in anhydrous EtOH (5 mL) was added. The mixture was heated to 25°C and stirred for 3 hours at 25°C. After
 10 evaporation of the solvent, the residue was washed with cold anhydrous Et₂O (10 mL) to yield (2*R*,4*R*)-4-amino-5-biphenyl-4-yl-2-hydroxypentanoic acid ethyl ester (207 mg) as a white solid HCl salt. LC-MS: [M+H]⁺:314, [2M+Na]⁺:649.

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 7.99 (m, 3H), 7.66-7.64 (m, 4H), 7.48-7.35 (m, 5H), 6.08 (m, 1H), 4.21 (m, 1H), 4.09-4.05 (m, 2H), 3.52 (m, 1H), 2.97-2.95 (m, 2H),
 15 1.89-1.87 (m, 2H), 1.19-1.14 (m, 3H).



To a stirred solution of Compound 2B (883 mg, 1.9 mmol) in anhydrous EtOH (15 mL) was added anhydrous K₂CO₃ (1293 mg, 9.4 mmol) at room temperature under nitrogen. After stirring for 20 hours at room temperature, the mixture was filtered. To the
 20 filtrate was added water (30 mL), DCM (30 mL) and saturated aqueous NaCl (5 mL). The aqueous layer was separated and extracted with DCM (30 mL x 3). The combined organic layers were washed with saturated aqueous NaCl (50 mL), dried over Na₂SO₄, and concentrated to yield the crude residue which was further purified by chromatography (hexanes:EtOAc = 6:1) to yield Compound 4 (524 mg) as a white solid. LC-MS:

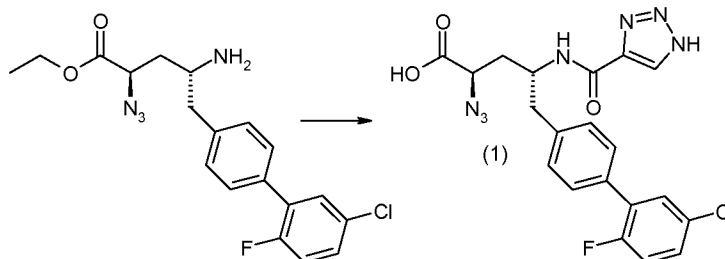
$[M+Na]^+$:436, $[2M+Na]^+$:849.



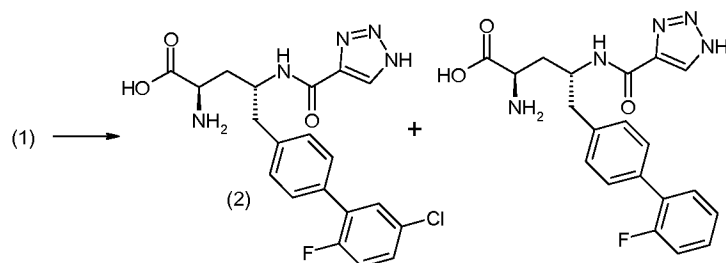
To EtOH (8 mL) was added acetyl chloride (1.3 g) at -30°C. After stirring for 1 hour at -30°C, a solution of Compound 4 (524 mg, 1.3 mmol) in anhydrous EtOH (8 mL) was added. The mixture was heated to 25°C and stirred for 3 hours at 25°C. After evaporation of the solvent, the residue was washed with cold anhydrous Et₂O (10 mL) to yield (2*R*,4*S*)-4-amino-5-biphenyl-4-yl-2-hydroxypentanoic acid ethyl ester (395 mg) as a white solid HCl salt. LC-MS: $[M+H]^+$:314, $[2M+Na]^+$:649.

¹H NMR (300 MHz, CDCl₃): δ (ppm) = 8.14 (m, 3H), 7.66-7.62 (m, 4H), 7.47-7.31 (m, 5H), 5.87-5.85 (m, 1H), 4.34 (m, 1H), 4.08-4.00 (m, 2H), 3.48 (m, 1H), 3.09 (m, 1H), 2.85-2.81 (m, 1H), 1.88(m, 1H), 1.76 (m, 1H), 1.15-1.10 (m, 3H).

Preparation 20: (2*R*,4*R*)-2-Amino-5-(2'-fluoro-biphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



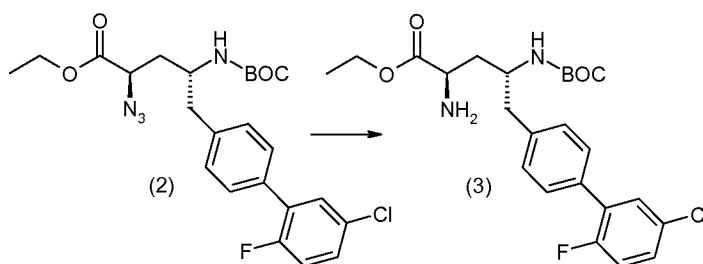
1H-1,2,3-triazole-4-carboxylic acid (50.8 mg, 449 μ mol) and HATU (171 mg, 449 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. (2*R*,4*R*)-4-Amino-2-azido-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (160 mg, 409 μ mol) and DIPEA (214 μ L, 1.2 mmol) were added, and the mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was then concentrated *in vacuo* to yield Compound 1, which was used in the next step without purification.



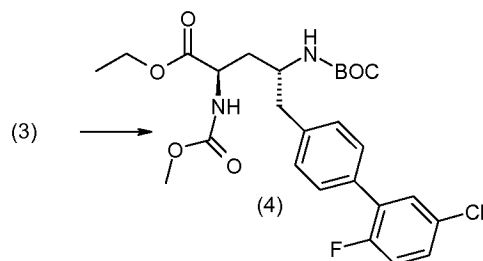
Compound 1 (50 mg, 109 μmol) and palladium hydroxide (15.3 mg, 109 μmol) were stirred in dry MeOH (2 mL) and AcOH (2 mL). The reaction flask was placed *in vacuo* and flushed a few times with nitrogen, then placed under hydrogen and stirred at room temperature for 2 hours. LC/MS showed conversion to Compound 2, also yielding the title compound (having lost the Cl atom on the ring). The hydrogen was removed *in vacuo* and the flask was purged with nitrogen. The mixture was filtered and the solution was concentrated *in vacuo* to yield the crude title compound.

Preparation 21: (2R,4R)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylaminopentanoic Acid Ethyl Ester

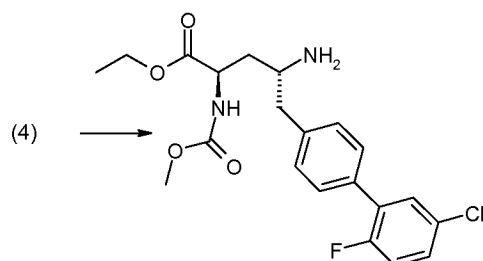
Compound 2 was prepared as described herein.



Compound 2 (210 mg, 428 μmol) and palladium hydroxide (60.1 mg, 428 μmol) were dissolved in dry MeOH (5 mL) and AcOH (5 mL). The reaction flask was placed *in vacuo* and flushed a few times with nitrogen, then placed under hydrogen and stirred at room temperature for 1 hour. LC/MS showed reaction completion. The hydrogen was removed *in vacuo* and the flask was purged with nitrogen. The mixture was filtered and the solution was concentrated *in vacuo* to yield crude Compound 3, which was used in the next step without purification.

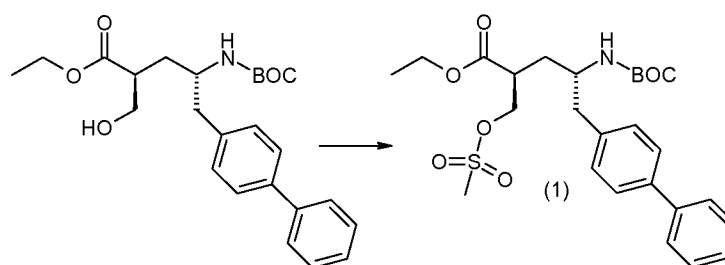


Compound 3 (199 mg, 428 μmol) was dissolved in DCM (5 mL). Methyl chloroformate (36.5 μL , 471 μmol) was added, followed by DIPEA (187 μL , 1.2 mmol). The resulting mixture was stirred at room temperature for 10 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield Compound 4.



Compound 4 (30 mg, 57 μmol) was dissolved in MeCN (3 mL). A solution of 4N HCl in dioxane (215 μL , 860 μmol) was added and the resulting mixture was stirred at room temperature for 10 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* to yield the crude title compound as an HCl salt, which was used without further purification.

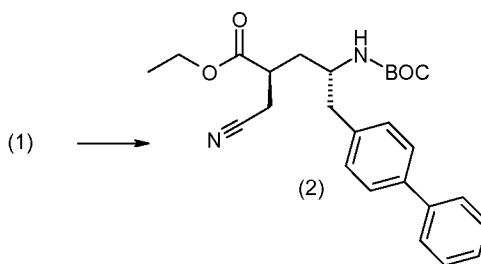
Preparation 22: (2S,4S)-4-Amino-5-biphenyl-4-yl-2-cyanomethylpentanoic Acid Ethyl Ester



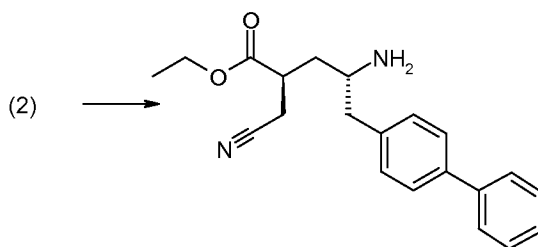
15

(2S,4S)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (450 mg, 1.1 mmol) was dissolved in DCM (2 mL). Methanesulfonyl chloride (98 μL , 1.3 mmol) was added, followed by Et₃N (293 μL , 2.1 mmol). The mixture was stirred at room temperature for 30 minutes, then was purified by normal phase

chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (405 mg).

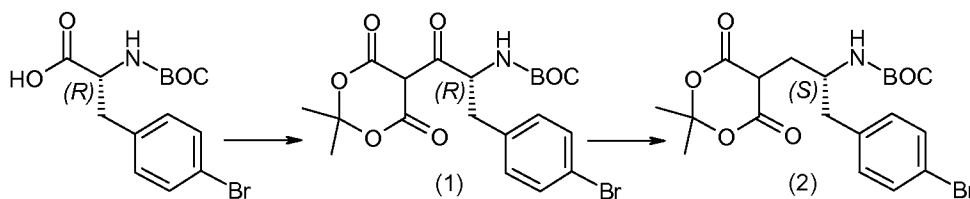


Compound 1 (200 mg, 396 μ mol) in DMF (2 mL) was combined with sodium cyanide (25 mg, 514 μ mol), and the resulting mixture was stirred at 50°C overnight. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed (3x) with water, dried over Na₂SO₄, then concentrated under reduced pressure followed by purification by normal phase chromatography (0-60% EtOAc/hexanes) to yield Compound 2 (90 mg).



Compound 2 (90 mg, 206 μ mol) was dissolved in MeCN and 4N HCl in dioxane, and the mixture was stirred at room temperature for 10 minutes. The mixture was concentrated under reduced pressure to yield the title compound as an HCl salt, which was used without further purification.

Preparation 23: (2R,4S)-4-*t*-butoxycarbonylamino-5-(3'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic Acid Ethyl Ester (compound 23a) and (2S,4S)-4-*t*-butoxycarbonylamino-5-(3'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic Acid Ethyl Ester (compound 23-b)



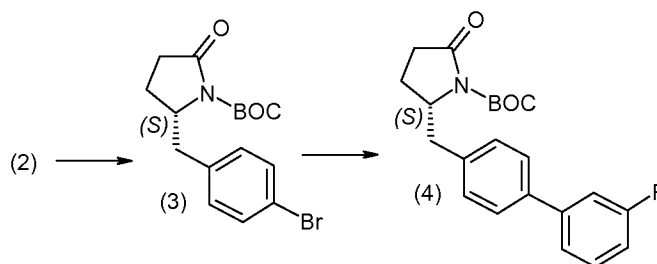
To a solution of (*R*)-3-(4-bromophenyl)-2-*t*-butoxycarbonylamino propionic acid (50 g, 145 mmol), Meldrum's acid (23 g, 160 mmol) and DMAP (27.8 g, 227 mmol) in anhydrous DCM (500 mL) was added a solution of DCC (33.3 g, 161 mmol) in anhydrous

DCM (200 mL) over 1 hour at -5°C under nitrogen. The mixture was stirred at -5°C for 8 hours, then refrigerated overnight, during which time tiny crystals of dicyclohexylurea precipitated. After filtration, the mixture was washed with 5% KHSO_4 (4x200 mL) and saturated aqueous NaCl (200 mL), then dried under refrigeration with MgSO_4 overnight.

- 5 The solution was evaporated to yield the crude Compound 1 (65.9 g) as a light yellow solid. LC-MS: $[\text{M}+\text{Na}]^+$:493, $[\text{2M}+\text{Na}]^+$:963.

To a solution of crude Compound 1 (65.9 g, 140 mmol) in anhydrous DCM (1 L) was added AcOH (92.5 g, 1.5 mol) at -5°C under nitrogen. The mixture was stirred at -5°C for 0.5 hour, then NaBH_4 (13.2 g, 350 mmol) was added in small portions over 1 hour.

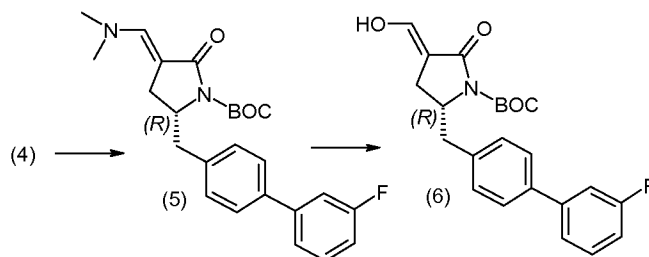
- 10 After stirring for another 1 hour at -5°C , saturated aqueous NaCl (300 mL) was added. The organic layer was washed with saturated aqueous NaCl (2x300 mL) and water (2x300 mL), dried over MgSO_4 , filtered, and concentrated to yield the crude residue, which was further purified by chromatography (hexanes: EtOAc =6:1) to yield Compound 2 (33 g) as a light yellow solid. LC-MS: $[\text{M}+\text{Na}]^+$:479, $[\text{2M}+\text{Na}]^+$:935.



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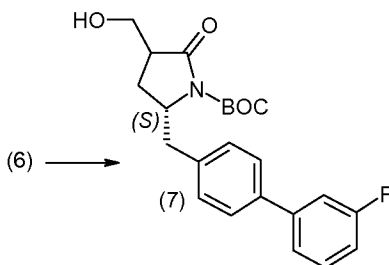
A solution of Compound 2 (33 g, 72.3 mmol) in anhydrous toluene (300 mL) was refluxed under nitrogen for 3 hours. After evaporation of the solvent, the residue was purified by chromatography (hexanes: EtOAc =10:1) to yield Compound 3 (21 g) as a light yellow oil. LC-MS: $[\text{M}+\text{Na}]^+$:377, $[\text{2M}+\text{Na}]^+$:731.

- 20 To a solution of Compound 3 (21 g, 60 mmol) in 1,4-dioxane (250 mL) was added 3-fluorophenylboronic acid (8.8 g, 63 mmol) and $\text{Pd}(\text{dppf})_2\text{Cl}_2$ (4.4 g, 6 mmol) at room temperature under nitrogen. After stirring for 10 minutes, a solution of K_2CO_3 (16.6 g, 120 mmol) in water (250 mL) was added. The mixture was heated to 100°C and stirred overnight. After evaporation of the solvent, water (200 mL) was added and the material
- 25 was extracted with EtOAc (3x200 mL). The combined organic layers were washed with saturated aqueous NaCl (250 mL), dried over Na_2SO_4 , and concentrated to yield the crude residue, which was further purified by column chromatography (hexanes: EtOAc =4:1) to yield Compound 4 (16.2 g) as a light yellow oil. LC-MS: $[\text{M}+\text{Na}]^+$:392, $[\text{2M}+\text{Na}]^+$:761.



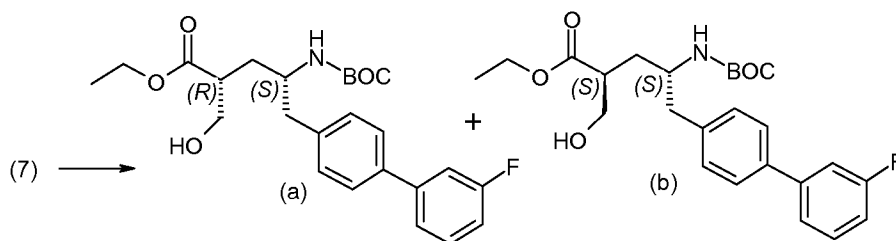
A mixture of Compound 4 (16.2 g, 43.8 mmol) and *t*-butoxy-*N,N,N',N'*-tetramethylmethanediamine (22.9 g, 131 mmol) was heated to 80°C under nitrogen. After stirring for 3 hours at 80°C, the mixture was diluted with EtOAc (300 mL), washed with
 5 water (2x150 mL) and saturated aqueous NaCl (2x150 mL), dried over MgSO₄, filtered, and evaporated to yield crude Compound 5 (18.6 g) as a light yellow oil. LC-MS: [M+H]⁺:425, [2M+H]⁺:849.

To a solution of crude Compound 5 (18.6 g, 43.8 mmol) in THF (200 mL) was added 1 M HCl (48 mL) at 0°C under nitrogen. After stirring for 1 hour at room
 10 temperature, the mixture was diluted with EtOAc (100 mL) and adjusted with saturated aqueous NaHCO₃ to pH 7. The aqueous layer was extracted with EtOAc (2x150 mL) and the combined organic layers were washed with water (2x150 mL) and saturated aqueous NaCl (150 mL), dried over MgSO₄, filtered, and evaporated to yield crude Compound 6 (17.4 g) as a yellow oil. LC-MS: [M+Na]⁺:420, [2M+Na]⁺:817.



To a solution of Compound 6 (17.4 g, 43.8 mmol) in anhydrous THF (300 mL) was added anhydrous EtOH (30 mL) and AcOH (52.6 g, 867 mmol) at -5°C under nitrogen. The mixture was stirred at -5°C for 0.5 hour, then NaBH₃CN (6.9 g, 110 mmol) was added in small portions over 1 hour. After stirring for one additional hour at -5°C, the mixture
 20 was adjusted with saturated aqueous NaHCO₃ to pH 7. The aqueous layer was extracted with EtOAc (2x200 mL) and the combined organic layers were washed with water (2x150 mL) and saturated aqueous NaCl (150 mL), dried over MgSO₄, filtered, and concentrated to yield the crude residue, which was further purified by chromatography (hexanes:EtOAc=6:1) to yield Compound 7 (6.7 g) as a light yellow solid. LC-MS:

$[M+Na]^+$:422, $[2M+Na]^+$:821.

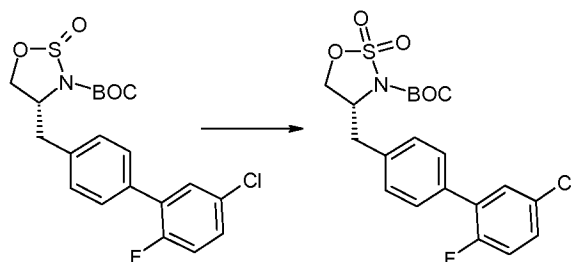


To a solution of Compound 7 (6.7 g, 16.7 mmol) in anhydrous EtOH (500 mL) was added anhydrous K_2CO_3 (4.6 g, 33.3 mmol) at $0^\circ C$ under nitrogen. After stirring for 1 hour at $0^\circ C$, the mixture was warmed to room temperature and stirred for 16 hours. After filtration, the filtrate was concentrated and the residue was diluted with water (150 mL), DCM (200 mL) and saturated aqueous NaCl (50 mL). The layers were separated and the aqueous layer was extracted with DCM (2x150 mL). The combined organic layers were washed with saturated aqueous NaCl (2x200 mL), dried over $MgSO_4$, and concentrated to yield the crude residue which was further purified by column chromatography (hexanes:EtOAc=5:1) to yield title compounds a and b (5.2 g) as light yellow solids.

Compound a: LC-MS: $[M+Na]^+$ =468, $[2M+Na]^+$ =913; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.39-7.34 (m, 3H), 7.27-7.23 (m, 2H), 7.01 (m, 1H), 4.42 (s, 1H), 4.20-4.13 (m, 2H), 3.90 (s, 1H), 3.78-3.74 (m, 2H), 2.84-2.82 (m, 2H), 2.70 (s, 1H), 2.22 (s, 1H), 2.02-1.95 (m, 1H), 1.59-1.50 (m, 1H), 1.39 (s, 9H), 1.27-1.23 (m, 3H).

Compound b: LC-MS: $[M+Na]^+$ =468, $[2M+Na]^+$ =913; ^1H NMR (300 MHz, $CDCl_3$): δ 7.50-7.48 (m, 2H), 7.39-7.34 (m, 3H), 7.25-7.23 (m, 2H), 7.01 (m, 1H), 4.42 (s, 1H), 4.19-4.13 (m, 2H), 3.90 (s, 1H), 3.79-3.75 (m, 2H), 2.83-2.81 (m, 2H), 2.70 (m, 1H), 2.21 (s, 1H), 1.79-1.74 (m, 2H), 1.37 (s, 9H), 1.29-1.23 (m, 3H).

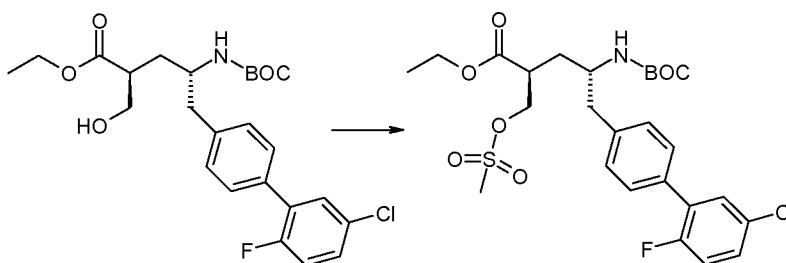
Preparation 24: (*R*)-*t*-Butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide



(*4R*)-*t*-Butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2-oxide (3.0 g, 7.0 mmol) was dissolved in MeCN (40 mL)

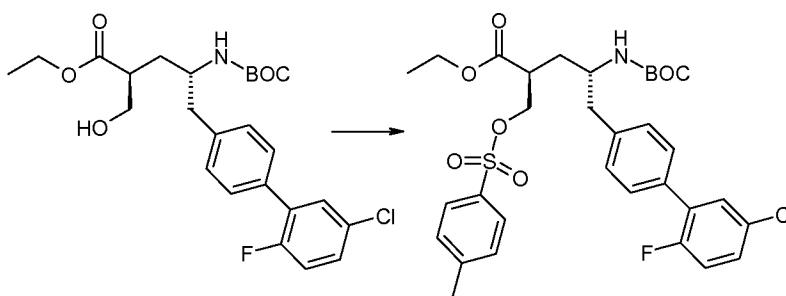
to yield a clear solution. The solution was cooled to 0°C and ruthenium(iii) chloride monohydrate (16 mg, 70 μmol) and sodium periodate (2.3 g, 10.6 mmol) were added. Water (20 mL) was added and the mixture was vigorously stirred at 0°C for 1 hour, yielding a thick slurry (analysis showed 10% conversion). The mixture was then stirred at 5°C overnight (almost complete conversion was observed). Additional water (20 mL) was added and the mixture was stirred at room temperature for 1 hour. The mixture was filtered and dried to yield the crude residue (3 g; purity 95%). The crude material was stirred in DCM (50 mL) for 2 hours. The mixture was filtered and the filtrate was concentrated to dryness to yield the title compound (2 g) as an off-white solid.

10 Preparation 25: (2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic Acid Ethyl Ester



(2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (250 mg, 521 μmol) was combined with DCM (2 mL), mesyl chloride (48.7 μL, 625 μmol), and Et₃N (145 μL, 1.0 mmol) slowly. The mixture was stirred for 10 minutes and purified by normal phase column chromatography (0-100% EtOAc/hexanes) to yield the title compound (240 mg).

15 Preparation 26: (2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic Acid Ethyl Ester

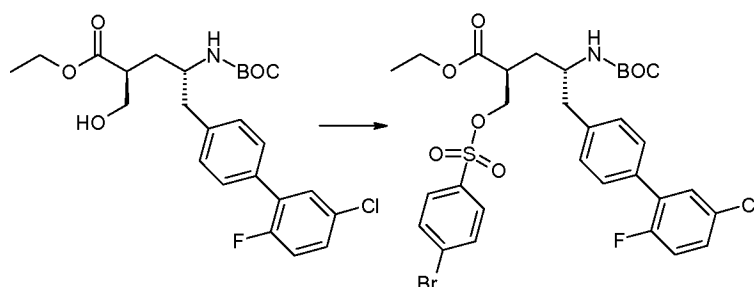


20 (2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (250 mg, 521 μmol) was combined with DCM (2 mL), *p*-toluenesulfonyl chloride (109 mg, 573 μmol), and Et₃N (145 μL, 1.0 mmol) slowly.

The mixture was stirred for 10 minutes and purified by normal phase column chromatography (0-100% EtOAc/hexanes) to yield the title compound (267 mg).

Preparation 27: (2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-
4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-
4-yl)pentanoic Acid Ethyl Ester

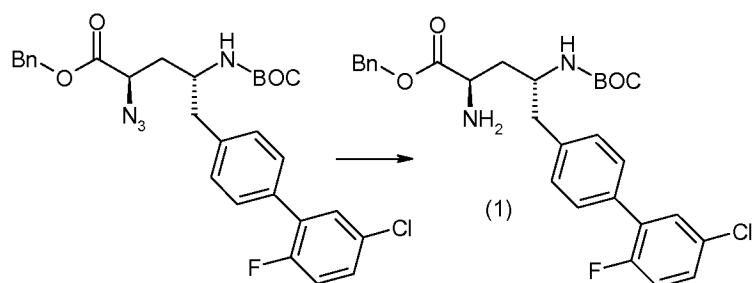
5



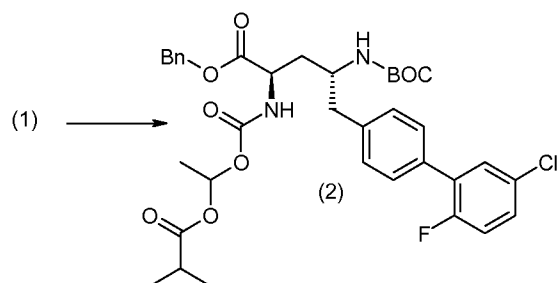
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (2.0 g, 4.2 mmol) was dissolved in dry DCM (10 mL) and 4-bromobenzenesulfonyl chloride (1.4 g, 5.4 mmol), and Et₃N (1.2 L, 8.3 mmol) was slowly added. The mixture was stirred for 90 minutes at room temperature, at which time LCMS indicated the mass of the desired compound. The crude solution was purified by normal phase column chromatography (0-100% EtOAc/hexanes) to yield the title compound (2.2 g).

Preparation 28: (2*R*,4*R*)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-
2-(1-isobutyryloxy-ethoxycarbonylamino)pentanoic Acid Benzyl Ester

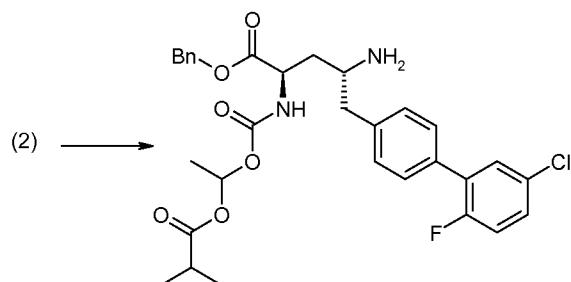
15



A mixture of (2*R*,4*R*)-2-azido-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid benzyl ester (2.6 g, 4.7 mmol), PPh₃ (1.5 g, 5.6 mmol) and THF/H₂O (50 mL/10 mL) was stirred at room temperature for two days. The solvent was concentrated *in vacuo* and purified by flash chromatography (DCM:MeOH = 40:1) to yield compound 1 (1.3 g) as a colorless oil. LC-MS: *m/z* = 527[(M⁺+1)].

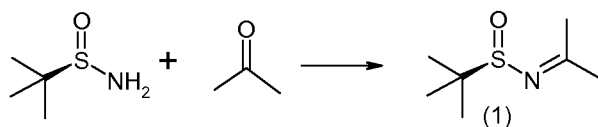


To a mixture of Compound 1 (763 mg, 1.5 mmol), DIPEA (374 mg, 2.9 mmol), DMAP (177 mg, 1.5 mmol) and THF (6 mL) was added a solution of 1-((4-nitrophenoxy) carbonyloxy)ethyl isobutyrate (645 mg, 2.2 mmol) in THF (2 mL) at 25°C. The resulting mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and purified by flash chromatography (PE:EtOAc = 4:1) to yield Compound 2 (555 mg) as a white solid. LC-MS: $m/z = 707[(M^+ + Na)]$.



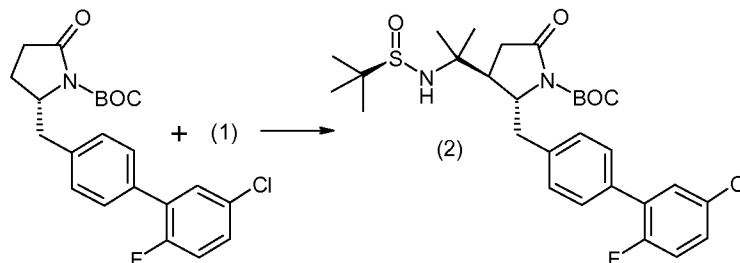
A suspension of Compound 2 (160 mg, 234 μ mol) and ZnBr₂ (263 mg, 1.2 mmol) in DCM (1.2 mL) was stirred at 25°C for 12 hours, then concentrated and purified by preparative HPLC (50-70% MeCN in water with 0.1% TFA) to yield the title compound (102 mg) as a white solid. LC-MS: $m/z = 585[(M^+ + 1)]$. ¹H NMR (300 MHz, CD₃OD) δ 7.32-7.49 (m, 11H), 7.17-7.23 (m, 1H), 6.76-6.79 (m, 1H), 5.10-5.24 (m, 2H), 4.39-4.53 (m, 1H), 3.59-3.64 (m, 1H), 2.91-3.20 (m, 2H), 2.45-2.57 (m, 1H), 2.18-2.28 (m, 1H), 1.99-2.13 (m, 1H), 1.45-1.47 (m, 3H), 1.10-1.15 (m, 6H).

Preparation 29: (2S,4S)-4-Amino-2-(1-amino-1-methylethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic Acid Ethyl Ester

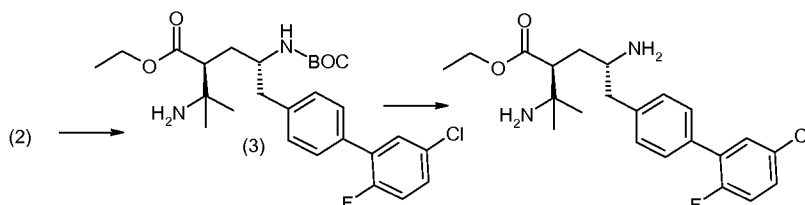


To a solution of 2-methylpropane-2-sulfinic acid amide (6.6 g, 54 mmol) in THF (400 mL) was added acetone (15.8 g, 273 mmol) and titanium ethoxide (62 g, 273 mmol) at room temperature. The mixture was refluxed for 24 hours and cooled to room

temperature. Saturated aqueous NaHCO_3 was added and the resulting solution was stirred for 5 minutes before being filtered. The solids were washed with EtOAc (50 mL), and the combined filtrates were transferred to a separatory funnel, where the aqueous portion was separated and extracted with EtOAc (2x50 mL). The combined organic phases were dried, filtered, and concentrated to yield Compound 1 (8 g) as a colorless oil. ^1H NMR (300 MHz, CDCl_3) δ 2.31 (s, 3H), 2.16 (s, 3H), 1.20 (s, 9H).



To a solution of (*S*)-2-(5'-chloro-2'-fluorobiphenyl-4-ylmethyl)-5-oxopyrrolidine-1-carboxylic acid *t*-butyl ester (1.1 g, 2.7 mmol) in anhydrous THF (20 mL) was added dropwise NaHMDS (1.8 mL, 3.5 mmol) at -78°C under nitrogen. After stirring at -78°C for 1.5 hours, Compound 1 (570 mg, 3.5 mmol) was added dropwise. After stirring at this temperature for 2 hours, the reaction was quenched with saturated aqueous NH_4Cl (20 mL), warmed to room temperature, and extracted with EtOAc (2x50 mL). The combined organic layers were washed with saturated aqueous NaCl (100 mL), dried over Na_2SO_4 , filtered and concentrated to give the crude product which was purified by chromatography (PE:EtOAc=2:1) to yield Compound 2 (500 mg) as a colorless oil. LC-MS: $[\text{M}+\text{Na}]^+$: 587.



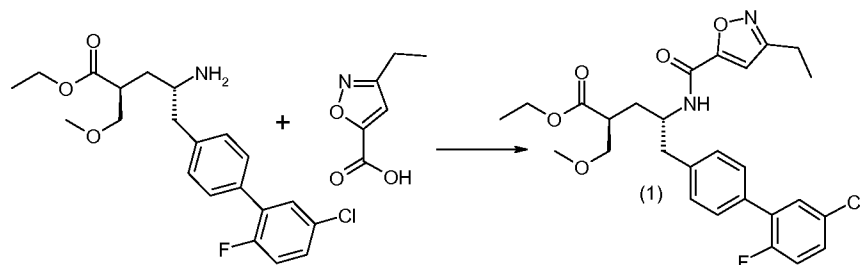
A mixture of Compound 2 (500 mg, 890 μmol) and K_2CO_3 (366 mg, 2.6 mmol) in EtOH (5 mL) was stirred at room temperature for 2 hours. The mixture was filtered, the filtrate was acidified with HCl (1N) to pH 5 and extracted with EtOAc (3x20 mL). The organic phase was dried over Na_2SO_4 , filtered, and concentrated to afford a residue, which was purified by column chromatography (PE:EtOAc=2:1) to yield Compound 3 (450 mg) as a colorless oil. LC-MS: $[\text{M}+\text{H}]^+$: 611.

A solution of Compound 3 (450 mg, 74 μmol) in 3.0 M HCl in dioxane (6 mL) was stirred at room temperature for 3 hours. The mixture was concentrated, and the residue

was purified by washing with Et₂O (7 mL) to yield the title compound (0.2 g) as a white solid. LC-MS: [M+H]⁺: 407. ¹H NMR (300 MHz, CD₃OD) δ 7.57~7.37 (m, 6H), 7.25~7.18 (m, 1H), 4.20 (m, 2H), 3.48 (m, 1H), 3.10~2.98 (m, 3H), 2.14~2.02 (m, 2H), 1.45~1.40 (m, 6H), 1.24~1.18 (m, 3H).

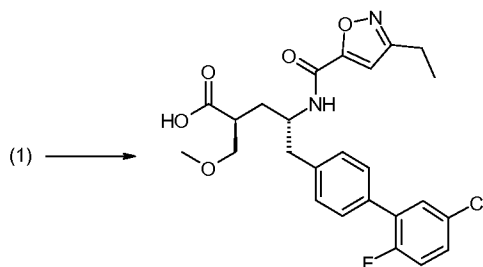
5

EXAMPLE 1: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethylisoxazole-5-carbonyl)amino]-2-methoxymethylpentanoic Acid



To a stirred solution of 3-ethylisoxazole-5-carboxylic acid (17 mg, 50 μmol) in HATU (23 mg, 60 μmol) and DMF, was added (2S,4S)-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethylpentanoic acid ethyl ester (384 mg, 60 μmol), followed by DIPEA (19 mg, 150 μmol). The mixture was stirred overnight to yield Compound 1, which was used directly in the next step.

10



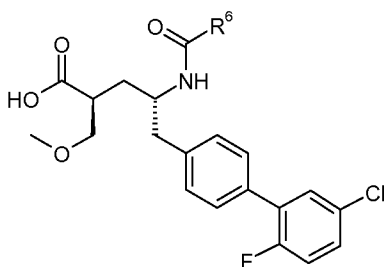
Crude Compound 1 was dissolved in THF and 10N NaOH (65 μL, 650 μmol) and stirred at 50°C overnight. The reaction was quenched with AcOH and the solution was purified by preparative HPLC to yield the title compound (6.6 mg; purity 100%). MS *m/z* [M+H]⁺ calc'd for C₂₅H₂₆ClFN₂O₅, 489.15; found 489.2.

15

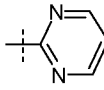
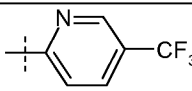
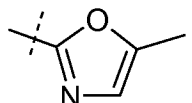
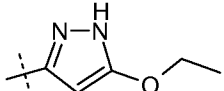
EXAMPLE 2

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

20



Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
1		C ₂₂ H ₂₂ ClFN ₄ O ₄	461.13	461.2
2		C ₂₃ H ₂₁ ClF ₄ N ₄ O ₄	529.12	529.2
3		C ₂₆ H ₂₆ ClF ₂ N ₃ O ₄	518.16	519.2
4		C ₂₅ H ₂₅ ClFN ₃ O ₅	502.15	502.2
5		C ₂₃ H ₂₂ ClFN ₂ O ₆	477.12	476
6		C ₂₄ H ₂₄ ClFN ₂ O ₆	491.13	491.2
7		C ₂₃ H ₂₂ ClFN ₂ O ₅	461.12	461.2
8		C ₂₃ H ₂₂ ClFN ₂ O ₅	461.12	461.2
9		C ₂₆ H ₂₆ ClFN ₂ O ₅	501.15	501.2
10		C ₂₃ H ₂₂ ClFN ₂ O ₆	477.12	476
11		C ₂₂ H ₂₁ ClFN ₃ O ₆	478.11	477
12		C ₂₅ H ₂₃ Cl ₂ FN ₂ O ₄	505.10	506.2

Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
13		C ₂₄ H ₂₃ ClFN ₃ O ₄	472.14	472.2
14		C ₂₆ H ₂₃ ClF ₄ N ₂ O ₄	539.13	537
15		C ₂₄ H ₂₄ ClFN ₂ O ₅	475.14	475
16		C ₂₅ H ₂₇ ClFN ₃ O ₅	504.16	504

1. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid
2. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-trifluoromethyl-1*H*-[1,2,4]triazole-3-carbonyl)amino]pentanoic acid
3. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-cyclopropyl-4-fluoro-2*H*-pyrazole-3-carbonyl)amino]-2-methoxymethylpentanoic acid
4. (2*S*,4*S*)-4-[(5-Acetyl-2*H*-pyrazole-3-carbonyl)-amino]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethylpentanoic acid
5. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)-amino]-2-methoxymethylpentanoic acid
6. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3-methoxyisoxazole-5-carbonyl)-amino]-2-methoxymethylpentanoic acid
7. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(oxazole-2-carbonyl)amino]pentanoic acid
8. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(oxazole-4-carbonyl)amino]pentanoic acid
9. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(2-cyclopropyloxazole-4-carbonyl)amino]-2-methoxymethylpentanoic acid
10. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(2-oxo-2,3-dihydro-oxazole-5-carbonyl)amino]pentanoic acid
11. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid
12. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-chloro-pyridine-2-carbonyl)-

amino]-2-methoxymethylpentanoic acid

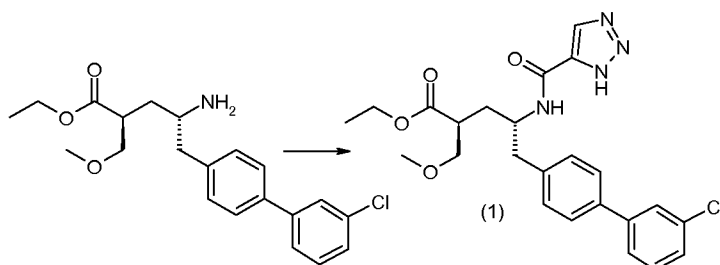
13. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(pyrimidine-2-carbonyl)amino]pentanoic acid

14. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-trifluoromethylpyridine-2-carbonyl)amino]pentanoic acid

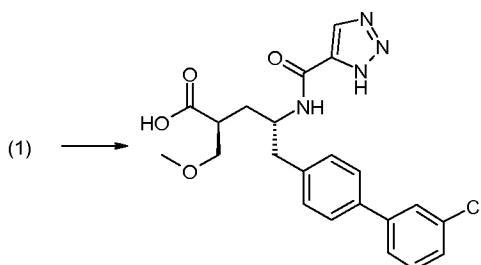
15. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid

16. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-ethoxy-1*H*-pyrazole-3-carbonyl)amino]-2-methoxymethylpentanoic acid

10 EXAMPLE 3: (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-methoxymethyl-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



To a stirred solution of 3*H*-[1,2,3]triazole-4-carboxylic acid (20 mg, 50 μ mol) in HATU (23 mg, 60 μ mol) and DMF (1 mL), was added (2*S*,4*S*)-4-amino-5-(3'-chlorobiphenyl-4-yl)-2-methoxymethyl-pentanoic acid ethyl ester (75 mg, 60 μ mol), followed by DIPEA (19 mg, 150 μ mol). The resulting mixture was stirred for 15 minutes to yield Compound 1, which was used directly in the next step.

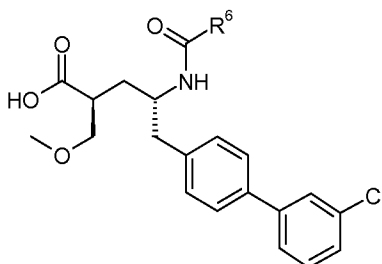


Compound 1 was dissolved in THF and 10*N* NaOH (50 μ L, 0.5 mmol) and stirred overnight at 50°C. The reaction was quenched with AcOH and the material was purified by preparative HPLC to yield the title compound (3.8 mg; purity 98%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}ClN_4O_4$, 443.14; found 443.2.

EXAMPLE 4

Following the procedures described herein, and substituting the appropriate starting

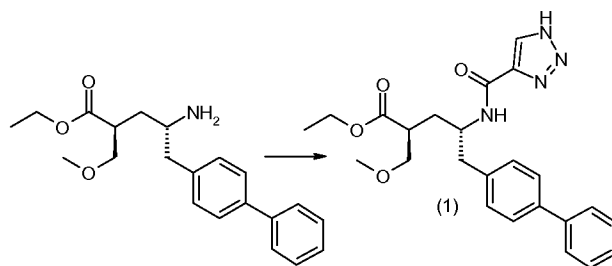
materials and reagents, these compounds were prepared, either as the parent compound or as a TFA salt:



Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
1		C ₂₃ H ₂₂ ClF ₃ N ₄ O ₄	511.13	511.2
2		C ₂₃ H ₂₃ ClN ₂ O ₆	459.12	458
3		C ₂₂ H ₂₂ ClN ₃ O ₆	460.12	459

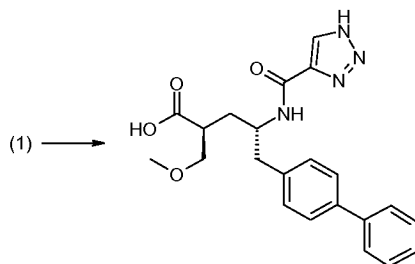
- 5 1. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-trifluoromethyl-1*H*-[1,2,4]triazole-3-carbonyl)amino]pentanoic acid
2. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-4-[(3-hydroxy-isoxazole-5-carbonyl)amino]-2-methoxymethylpentanoic acid
3. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-methoxymethyl-4-[(5-oxo-4,5-dihydro-
- 10 [1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid

EXAMPLE 5: (2*S*,4*S*)-5-Biphenyl-4-yl-2-methoxymethyl-4-[(1*H*-[1,2,3]-triazole-4-carbonyl)amino]pentanoic Acid



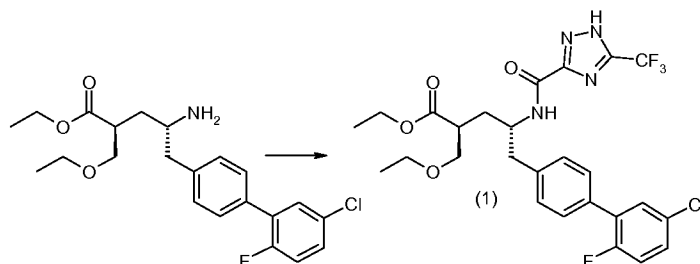
- (2*S*,4*S*)-4-Amino-5-biphenyl-4-yl-2-methoxymethylpentanoic acid ethyl ester (16 mg, 47 μmol) was dissolved in DMF (0.3 mL). 1*H*-1,2,3-Triazole-4-carboxylic acid (5.3 mg, 47 μmol) and HATU (18 mg, 47 μmol) were added followed by DIPEA (25 μL, 141

μmol). The mixture was stirred for 30 minutes and concentrated under reduced pressure to yield Compound 1, which was used in the next step without purification.

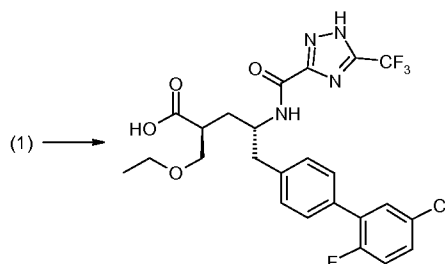


Compound 1 (21 mg, 47 μmol) was dissolved in THF and NaOH (188 μL, 188 μmol) and stirred for 2 hours at room temperature. AcOH was added to quench the reaction and the solution was purified by preparative HPLC to yield the title compound (6.5 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{24}N_4O_4$, 409.18; found 409.2.

EXAMPLE 6: (2S,4S)-5-(5'-(5-chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(5-trifluoromethyl-1H-[1,2,4]triazole-3-carbonyl)amino]pentanoic Acid



To a stirred solution of (2S,4S)-4-amino-5-(5-(5-chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethylpentanoic acid ethyl ester (398 mg, 65 μmol) in DMF (2 mL) and HATU (23 mg, 60 μmol), was added 5-methyl-1H-[1,2,4]triazole-3-carboxylic acid (22 mg, 60 μmol), followed by DIPEA (19 μL, 150 μmol). The mixture was stirred at room temperature overnight to yield Compound 1, which was used in the next step without purification.

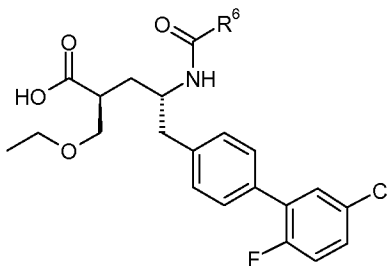


To Compound 1 (65 μmol, 1 eq.) was added THF (0.4 mL) and 1N NaOH (65 μL, 65 μmol, 10 eq.). The mixture was stirred at 50°C overnight. AcOH was added and the

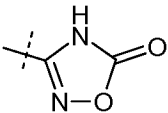
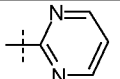
solution was purified by preparative HPLC to yield the title compound (4.7 mg; purity 99%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{23}ClF_4N_4O_4$, 543.13; found 543.2.

EXAMPLE 7

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

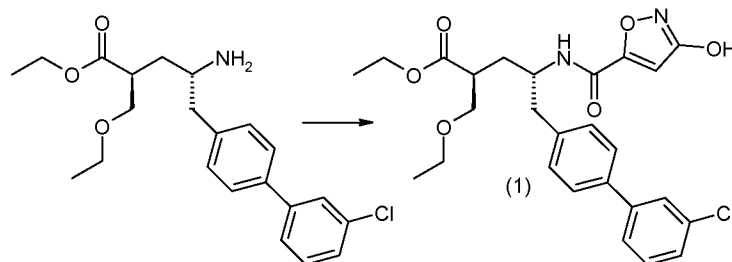


Ex.	R ⁶	Formula	MS m/z : $[M+H]^+$	
			calcd	found
1		$C_{23}H_{24}ClFN_4O_4$	475.15	475.2
2		$C_{27}H_{28}ClF_2N_3O_4$	532.17	533.2
3		$C_{26}H_{27}ClFN_3O_5$	516.16	517.2
4		$C_{24}H_{24}ClFN_2O_6$	491.13	490
5		$C_{26}H_{28}ClFN_2O_5$	503.17	503.2
6		$C_{24}H_{24}ClFN_2O_5$	475.14	475.2
7		$C_{24}H_{24}ClFN_2O_5$	475.14	475.2
8		$C_{27}H_{28}ClFN_2O_5$	515.17	515.2
9		$C_{24}H_{24}ClFN_2O_6$	491.13	491.2

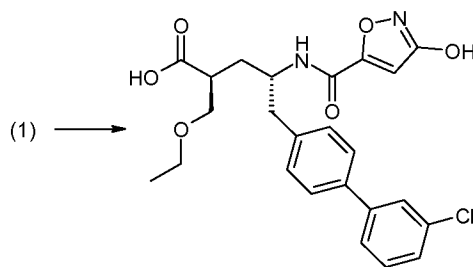
Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
10		C ₂₃ H ₂₃ ClFN ₃ O ₆	492.13	491
11		C ₂₅ H ₂₅ ClFN ₃ O ₄	486.15	486.2

1. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid
2. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-cyclopropyl-4-fluoro-2*H*-pyrazole-3-carbonyl)amino]-2-ethoxymethylpentanoic acid
- 5 3. (2*S*,4*S*)-4-[(5-Acetyl-2*H*-pyrazole-3-carbonyl)-amino]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethylpentanoic acid
4. (2*S*,4*S*)-5-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-2-ethoxymethyl-4-[(3-hydroxy-isoxazole-5-carbonyl)amino]pentanoic acid
- 10 5. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(3-ethyl-isoxazole-5-carbonyl)amino]pentanoic acid
6. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(oxazole-2-carbonyl)amino]pentanoic acid
7. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(oxazole-4-carbonyl)amino]pentanoic acid
- 15 8. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(2-cyclopropyloxazole-4-carbonyl)amino]-2-ethoxymethylpentanoic acid
9. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(2-oxo-2,3-dihydro-oxazole-5-carbonyl)amino]pentanoic acid
- 20 10. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid
11. (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-ethoxymethyl-4-[(pyrimidine-2-carbonyl)amino]pentanoic acid

EXAMPLE 8: (2S,4S)-5-(3'-Chlorobiphenyl-4-yl)-2-ethoxymethyl-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic Acid



To a stirred solution of (2S,4S)-4-amino-5-(3'-chlorobiphenyl-4-yl)-2-ethoxymethylpentanoic acid ethyl ester (40 mg, 103 μmol) in HATU (46.8 mg, 123 μmol), 3-hydroxy-isoxazole-5-carboxylic acid (13.2 mg, 133 μmol), and DMF (0.5 mL), was added DIPEA (53.8 μL , 308 μmol). The mixture was stirred for 1 hour, then concentrated under reduced pressure to yield crude Compound 1, which was used in the next step without purification.



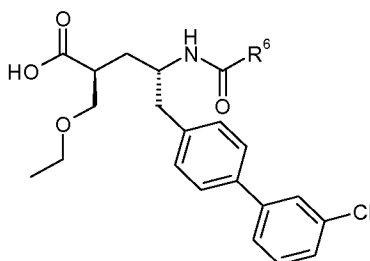
10

To Compound 1 (57 mg, 103 μmol) was added THF (0.8 mL) and 1N NaOH (412 μL , 412 μmol). A few drops of EtOH were added to the solution and it was stirred for 3 hours. The mixture was concentrated under reduced pressure. The residue was purified by reverse phase to yield the title compound (1 mg; purity 95%). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{25}\text{ClN}_2\text{O}_6$, 473.14; found 472.

15

EXAMPLE 9

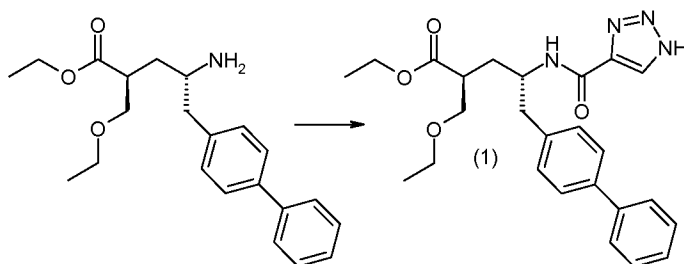
Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared, either as the parent compound or as a TFA salt:



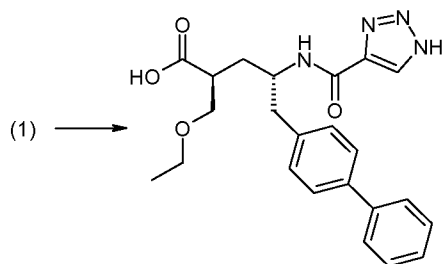
Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
1		C ₂₃ H ₂₅ ClN ₄ O ₄	457.16	456
2		C ₂₆ H ₂₈ ClN ₃ O ₅	498.17	497
3		C ₂₄ H ₂₄ ClF ₃ N ₄ O ₄	525.14	524
4		C ₂₅ H ₂₇ ClN ₂ O ₆	487.16	486
5		C ₂₃ H ₂₄ ClN ₃ O ₆	474.14	473

1. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-ethoxymethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid
- 5 2. (2*S*,4*S*)-4-[(5-Acetyl-1*H*-pyrazole-3-carbonyl)-amino]-5-(3'-chlorobiphenyl-4-yl)-2-ethoxymethylpentanoic acid
3. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-ethoxymethyl-4-[(5-trifluoromethyl-1*H*-[1,2,4]triazole-3-carbonyl)amino]pentanoic acid
4. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-ethoxymethyl-4-[(3-methoxy-isoxazole-5-carbonyl)amino]pentanoic acid
- 10 5. (2*S*,4*S*)-5-(3'-Chlorobiphenyl-4-yl)-2-ethoxymethyl-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid

EXAMPLE 10: (2*S*,4*S*)-5-Biphenyl-4-yl-2-ethoxymethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

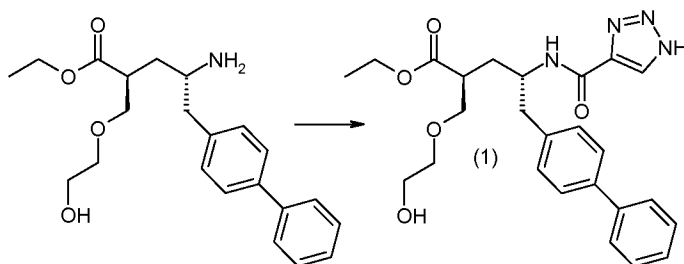


To a stirred solution of (2*S*,4*S*)-4-amino-5-biphenyl-4-yl-2-ethoxymethylpentanoic acid ethyl ester (17 mg, 47 μ mol) in DMF (0.3 mL), was added 1*H*-1,2,3-triazole-4-carboxylic acid (5.3 mg, 47 μ mol) and HATU (18 mg, 47 μ mol), followed by DIPEA (25 μ L, 141 μ mol). The mixture was stirred for 30 minutes, then concentrated under reduced pressure to yield crude Compound 1, which was used in the next step without purification.



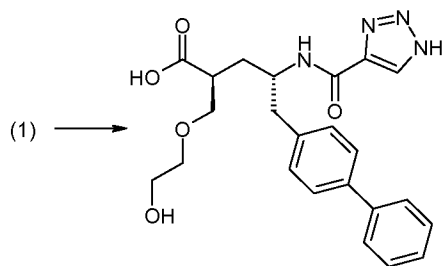
To Compound 1 (21 mg, 47 μ mol) was added THF (0.5 mL) and 1*N* NaOH (188 μ L, 188 μ mol) was added and stirred for 2 hours at room temperature. AcOH was added and the solution was purified by preparative HPLC to yield the title compound (4.5 mg; purity 94%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{26}N_4O_4$, 423.20; found 423.2.

EXAMPLE 11: (2*S*,4*S*)-5-Biphenyl-4-yl-2-(2-hydroxyethoxymethyl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



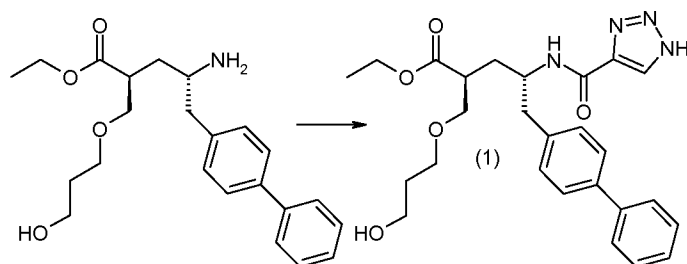
To a stirred solution of (2*S*,4*S*)-4-amino-5-biphenyl-4-yl-2-(2-hydroxyethoxymethyl)pentanoic acid ethyl ester (17 mg, 47 μ mol) in DMF (0.3 mL), was added 1*H*-1,2,3-triazole-4-carboxylic acid (5.3 mg, 47 μ mol) and HATU (18 mg, 47

μmol), followed by DIPEA (25 μL, 141 μmol). The mixture was stirred for 30 minutes, then concentrated under reduced pressure to yield crude Compound 1, which was used in the next step without purification.

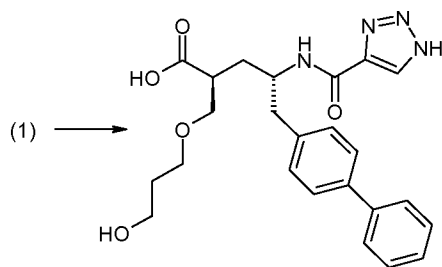


To Compound 1 (22 mg, 47 μmol) was added THF (0.5 mL) and 1N NaOH (188 μL, 188 μmol) was added and stirred for 2 hours at room temperature. AcOH was added and the solution was purified by preparative HPLC to yield the title compound (3.8 mg; purity 98%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{26}N_4O_5$, 439.19; found 439.2.

EXAMPLE 12: (2S,4S)-5-Biphenyl-4-yl-2-(3-hydroxypropoxymethyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



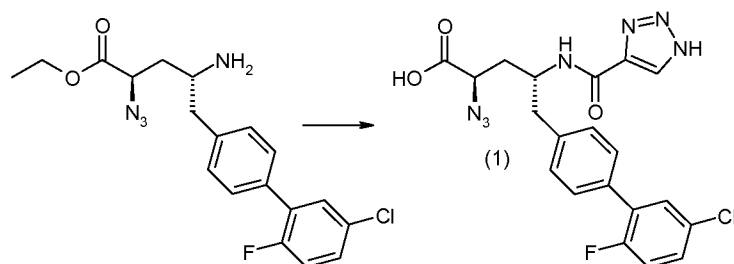
To a stirred solution of (2S,4S)-4-amino-5-biphenyl-4-yl-2-(3-hydroxypropoxymethyl)pentanoic acid ethyl ester (18 mg, 47 μmol) in DMF (0.3 mL), was added 1H-1,2,3-triazole-4-carboxylic acid (5.3 mg, 47 μmol) and HATU (18 mg, 47 μmol), followed by DIPEA (25 μL, 141 μmol). The mixture was stirred for 30 minutes, then concentrated under reduced pressure to yield crude Compound 1, which was used in the next step without purification.



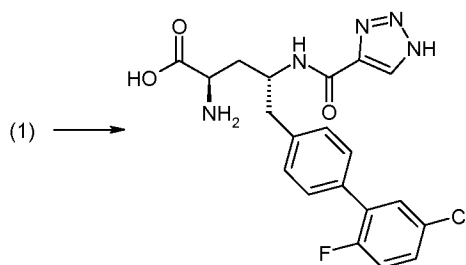
To Compound 1 (23 mg, 47 μmol) was added THF (0.5 mL) and 1N NaOH (188

μL , 188 μmol) was added and stirred for 2 hours at room temperature. AcOH was added and the solution was purified by preparative HPLC to yield the title compound (1.3 mg; purity 100%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{28}\text{N}_4\text{O}_5$, 453.21; found 453.2.

EXAMPLE 13: (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

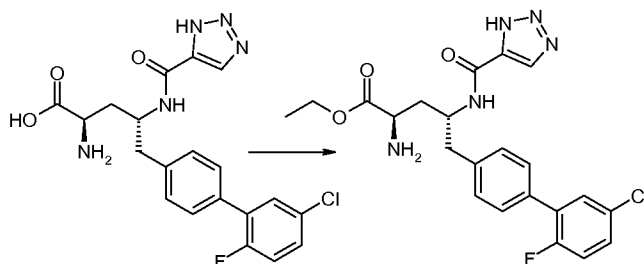


1*H*-1,2,3-triazole-4-carboxylic acid (15.9 mg, 141 μmol) and HATU (53.5 mg, 141 μmol) were dissolved in DMF (2 mL) and stirred for 15 minutes at room temperature. (2*R*,4*R*)-4-Amino-2-azido-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (50 mg, 128 μmol) and DIPEA (67 μL , 384 μmol) were added, and the mixture was stirred at room temperature for 15 minutes then concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL). An aqueous solution of 1*N* NaOH (1.3 mL, 1.3 mmol) was added, and the mixture was stirred at room temperature for 30 minutes then concentrated *in vacuo* and the residue was purified by reverse phase chromatography to yield Compound 1 (45 mg).



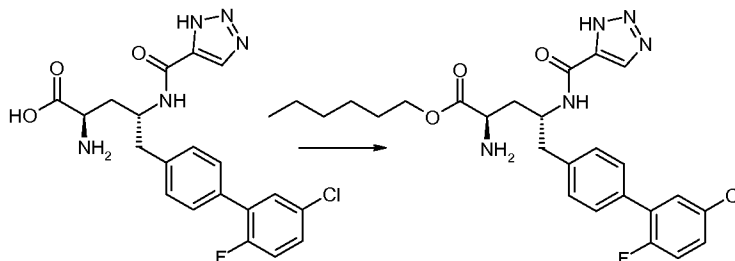
Compound 1 (45 mg, 98 μmol) and palladium hydroxide (2.1 mg, 15 μmol) were stirred at room temperature in dry MeOH (2 mL) and AcOH (2 mL). The reaction flask was placed under hydrogen and stirred at room temperature for 30 minutes. The hydrogen was removed *in vacuo* and the flask was purged with nitrogen. The mixture was filtered and the solution was concentrated *in vacuo*. The residue was purified by reverse phase chromatography in the absence of TFA to yield the title compound (27 mg; purity 96%). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{20}\text{H}_{19}\text{ClFN}_5\text{O}_3$, 432.12; found 432.2.

EXAMPLE 14a: (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester



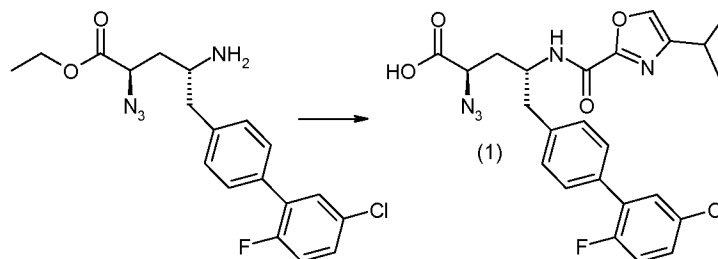
(2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (17 mg, 39 μ mol) was dissolved in EtOH (5 mL). A solution of 4N HCl in dioxane (148 μ L, 0.6 mmol) was added. The resulting mixture was stirred at room temperature for 2 days, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase chromatography to yield the title compound (10 mg; purity 99%) as a white powder TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}ClFN_5O_3$, 460.15; found 460.

EXAMPLE 14b: (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Hexyl Ester

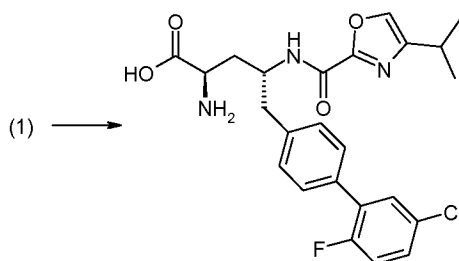


(2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (10 mg, 23 μ mol) was dissolved in 1-hexanol (500 mL; 237 mg, 2.3 mol). A solution of 4N HCl in dioxane (174 μ L, 0.7 mmol) was added. The resulting mixture was stirred overnight at 50°C then concentrated *in vacuo* and the residue was purified by reverse phase chromatography to yield the title compound (4.1 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{31}ClFN_5O_3$, 516.21; found 516.

EXAMPLE 15: (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-
4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid



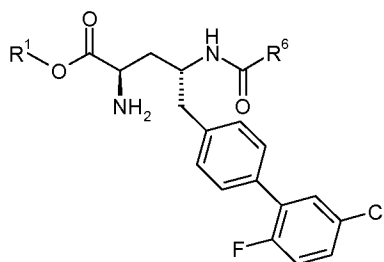
4-Isopropylloxazole-2-carboxylic acid (21.8 mg, 141 μ mol) and HATU (53.5 mg,
 5 141 μ mol) were dissolved in DMF (3.5 mL) and stirred for 15 minutes at room
 temperature. (2*R*,4*R*)-4-Amino-2-azido-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid
 ethyl ester (50 mg, 128 μ mol) and DIPEA (67 μ L, 384 μ mol) were added, and the mixture
 was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of
 the desired compound. The mixture was concentrated *in vacuo* and the residue was
 10 dissolved in EtOH (3 mL). An aqueous solution of 1N NaOH (1.3 mL, 1.3 mmol) was
 added, and the mixture was stirred at room temperature for 1 hour, at which time LCMS
 indicated the mass of the desired compound. The mixture was concentrated *in vacuo*. An
 aqueous solution of 1N HCl was added, and the crude residue was extracted with EtOAc.
 The organic layers were combined, dried over MgSO₄, filtered and evaporated to yield
 15 Compound 1, which was used in the next step without purification.



Compound 1 (65 mg, 130 μ mol) and palladium (10wt% on carbon, wet, 50 g, 65
 μ mol) were mixed in dry EtOAc (3 mL) and AcOH (3 mL). The reaction flask was placed
 under hydrogen and stirred at room temperature for 3 hours. The hydrogen was removed
 20 *in vacuo* and the flask was purged with nitrogen. The mixture was filtered and the solution
 was concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title
 compound (15 mg; purity 100%) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for
 C₂₄H₂₅ClFN₃O₄, 474.15, found 474.2.

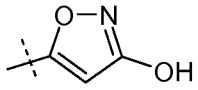
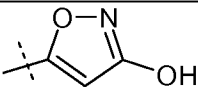
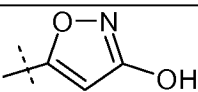
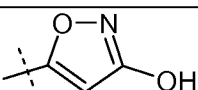
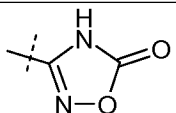
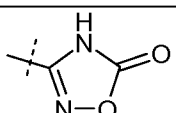
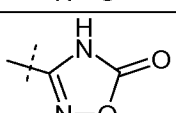
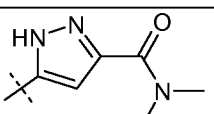
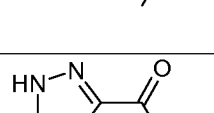
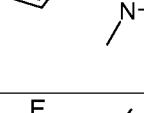
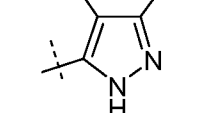
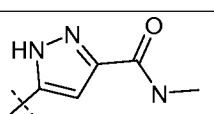
EXAMPLE 16

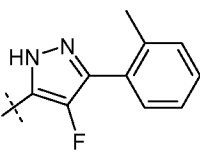
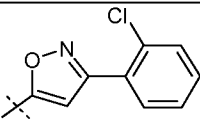
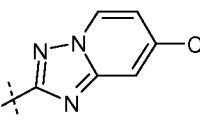
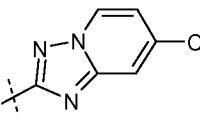
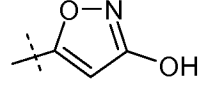
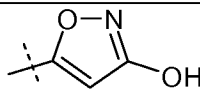
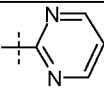
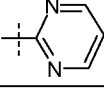
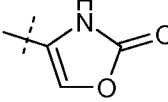
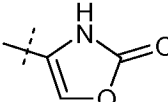
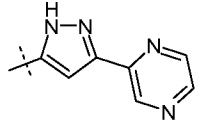
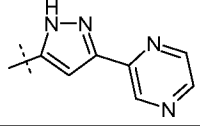
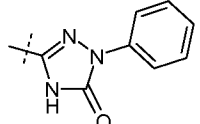
Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared, either as the parent compound or as a TFA salt:

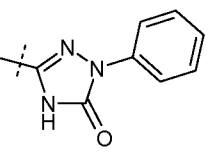


5

Ex.	R ¹	R ⁶	Formula	MS m/z: [M+H] ⁺	
				calcd	found
1	H		C ₂₃ H ₂₃ ClFN ₃ O ₄	460.14	460.2
2	H		C ₂₄ H ₂₅ ClFN ₃ O ₄	474.15	474.2
3	H		C ₂₂ H ₂₁ ClFN ₃ O ₄	446.12	446.2
4	H		C ₂₄ H ₂₃ ClFN ₃ O ₄	472.14	472.2
5	H		C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	476.2
6	H		C ₂₄ H ₂₅ ClFN ₃ O ₄	474.15	474.2
7	H		C ₂₃ H ₂₀ Cl ₂ FN ₃ O ₃	476.09	476.2
8	H		C ₂₁ H ₁₉ ClFN ₃ O ₃ S	448.08	448.2
9	H		C ₂₃ H ₂₂ ClFN ₄ O ₄	473.13	473.1
10	-CH ₂ CH ₃		C ₂₅ H ₂₆ ClFN ₄ O ₄	501.16	501

Ex.	R ¹	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
				calcd	found
11	-CH ₂ CH ₃		C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	475
12	-CH ₂ CH ₃		C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	475
13	-CH-(CH ₃) ₂		C ₂₄ H ₂₅ ClFN ₃ O ₅	490.15	490
14	-(CH ₂) ₃ -CH ₃		C ₂₅ H ₂₇ ClFN ₃ O ₅	504.16	504
15	H		C ₂₀ H ₁₈ ClFN ₄ O ₅	449.10	449.2
16	H		C ₂₀ H ₁₈ ClFN ₄ O ₅	449.10	449.1
17	-CH ₂ CH ₃		C ₂₂ H ₂₂ ClFN ₄ O ₅	477.13	477
18	H		C ₂₄ H ₂₅ ClFN ₅ O ₄	502.16	502.2
19	-CH ₂ CH ₃		C ₂₆ H ₂₉ ClFN ₅ O ₄	530.19	530.2
20	H		C ₂₂ H ₂₁ ClF ₂ N ₄ O ₃	463.13	463.2
21	H		C ₂₃ H ₂₃ ClFN ₅ O ₄	488.14	488.2
22	-CH ₂ CH ₃		C ₂₅ H ₂₇ ClFN ₅ O ₄	516.17	516

Ex.	R ¹	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
				calcd	found
23	H		C ₂₈ H ₂₅ ClF ₂ N ₄ O ₃	539.16	539.2
24	H		C ₂₇ H ₂₂ Cl ₂ FN ₃ O ₄	542.10	542.2
25	H		C ₂₄ H ₂₀ Cl ₂ FN ₅ O ₃	516.09	516.2
26	H		C ₂₄ H ₂₀ Cl ₂ FN ₅ O ₃	516.09	516.2
27	H		C ₂₁ H ₁₉ ClFN ₃ O ₅	448.10	448.0
28	H		C ₂₁ H ₁₉ ClFN ₃ O ₅	448.10	448.0
29	H		C ₂₂ H ₂₀ ClFN ₄ O ₃	443.12	443.0
30	-CH ₂ CH ₃		C ₂₄ H ₂₄ ClFN ₄ O ₃	471.15	471.1
31	H		C ₂₁ H ₁₉ ClFN ₃ O ₅	448.10	448.0
32	-CH ₂ CH ₃		C ₂₃ H ₂₃ ClFN ₃ O ₅	476.13	476.1
33	H		C ₂₅ H ₂₂ ClFN ₆ O ₃	509.14	509.1
34	-CH ₂ CH ₃		C ₂₇ H ₂₆ ClFN ₆ O ₃	537.17	537.1
35	H		C ₂₆ H ₂₃ ClFN ₅ O ₄	524.14	524.1

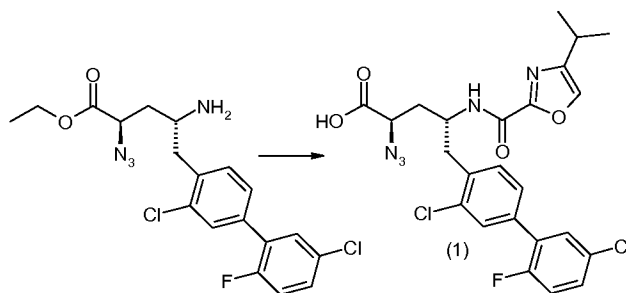
Ex.	R ¹	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
				calcd	found
36	-CH ₂ CH ₃		C ₂₈ H ₂₇ ClFN ₅ O ₄	552.17	552.1

1. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethylisoxazole-5-carbonyl)-amino]pentanoic acid
2. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-propylisoxazole-3-carbonyl)-amino]pentanoic acid
- 5 3. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-2-carbonyl)-amino]pentanoic acid
4. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-cyclopropyloxazole-4-carbonyl)amino]pentanoic acid
- 10 5. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-ethoxyoxazole-4-carbonyl)-amino]pentanoic acid
6. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-propyloxazole-4-carbonyl)-amino]pentanoic acid
7. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-chloropyridine-2-carbonyl)-amino]pentanoic acid
- 15 8. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(isothiazole-5-carbonyl)amino]-pentanoic acid
9. (2*R*,4*R*)-4-[(5-Acetyl-2H-pyrazole-3-carbonyl)amino]-2-amino-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)pentanoic acid
- 20 10. (2*R*,4*R*)-4-[(5-Acetyl-2H-pyrazole-3-carbonyl)amino]-2-amino-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)pentanoic acid ethyl ester
11. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic acid ethyl ester
12. (2*S*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic acid ethyl ester
- 25 13. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic acid isopropyl ester
14. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-

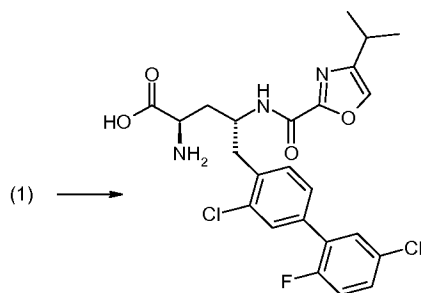
- carbonyl)amino]pentanoic acid butyl ester
15. (2*S*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid
 16. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-oxo-4,5-dihydro-
 - 5 [1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid
 17. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid ethyl ester
 18. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-dimethylcarbamoyl-2H-pyrazole-3-carbonyl)amino]pentanoic acid
 - 10 19. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-dimethylcarbamoyl-2H-pyrazole-3-carbonyl)amino]pentanoic acid ethyl ester
 20. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-fluoro-5-methyl-2H-pyrazole-3-carbonyl)amino]pentanoic acid
 21. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methylcarbamoyl-2H-
 - 15 pyrazole-3-carbonyl)amino]pentanoic acid
 22. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methylcarbamoyl-2H-pyrazole-3-carbonyl)amino]pentanoic acid ethyl ester
 23. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-fluoro-5-*o*-tolyl-2H-pyrazole-3-carbonyl)amino]pentanoic acid
 - 20 24. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-{[3-(2-chlorophenyl)-isoxazole-5-carbonyl]amino}pentanoic acid
 25. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(7-chloro-[1,2,4]triazolo[1,5-*a*]pyridine-2-carbonyl)amino]pentanoic acid
 26. (2*S*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(7-chloro-
 - 25 [1,2,4]triazolo[1,5-*a*]pyridine-2-carbonyl)amino]pentanoic acid
 27. (2*S*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic acid
 28. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-hydroxyisoxazole-5-carbonyl)amino]pentanoic acid
 - 30 29. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(pyrimidine-2-carbonyl)-amino]pentanoic acid
 30. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(pyrimidine-2-carbonyl)-amino]pentanoic acid ethyl ester

31. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-oxo-2,3-dihydro-oxazole-4-carbonyl)amino]pentanoic acid
32. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-oxo-2,3-dihydro-oxazole-4-carbonyl)amino]pentanoic acid ethyl ester
- 5 33. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-pyrazin-2-yl-2H-pyrazole-3-carbonyl)amino]pentanoic acid
34. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-pyrazin-2-yl-2H-pyrazole-3-carbonyl)amino]pentanoic acid ethyl ester
35. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-oxo-1-phenyl-4,5-
- 10 dihydro-1*H*-[1,2,4]triazole-3-carbonyl)amino]pentanoic acid
36. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-oxo-1-phenyl-4,5-dihydro-1*H*-[1,2,4]triazole-3-carbonyl)amino]pentanoic acid ethyl ester

15 EXAMPLE 17: (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid



4-Isopropylloxazole-2-carboxylic acid (10.4 mg, 67 μ mol) and HATU (25.6 mg, 67 μ mol) were dissolved in DMF (2 mL) and stirred for 15 minutes at room temperature. (2*R*,4*R*)-4-Amino-2-azido-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (26 mg, 61 μ mol) and DIPEA (32 μ L, 183 μ mol) were added, and the mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL). An aqueous solution of 1*N* NaOH (611 μ L, 611 μ mol) was added, and the mixture was stirred at room temperature for 30 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was diluted in an aqueous solution of 1*N* HCl and extracted twice with EtOAc. The organic layers were combined, dried over MgSO₄, filtered and evaporated, to yield crude Compound 1, which was directly in the next step.

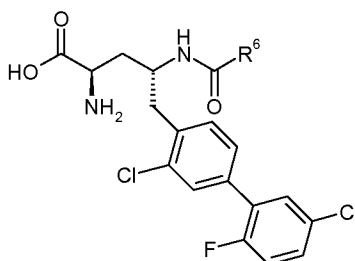


Compound 1 (30 mg, 56 μmol) and palladium (10wt% on carbon, wet 50 g; 5 mg, 5.6 μmol) were stirred at room temperature in dry EtOAc (2 mL) and AcOH (2 mL). The reaction flask was placed under hydrogen and stirred at room temperature for 30 minutes.

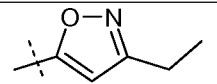
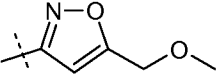
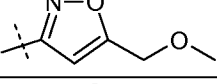
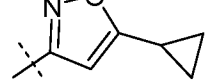
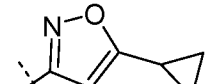
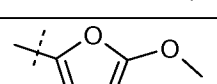
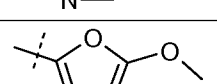
- 5 The hydrogen was removed *in vacuo* and the flask was purged with nitrogen. The mixture was filtered and the solution was concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title compound (1.4 mg; purity 80%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{FN}_3\text{O}_4$, 508.11; found 509.0.

EXAMPLE 18

- 10 Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared as a TFA salt:



Ex.	R^6	Formula	MS m/z : $[\text{M}+\text{H}]^+$	
			calcd	found
1		$\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{FN}_3\text{O}_4$	508.11	508.2
2		$\text{C}_{24}\text{H}_{24}\text{Cl}_2\text{FN}_3\text{O}_4$	508.11	508.2
3		$\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FN}_3\text{O}_4$	480.08	480.0
4		$\text{C}_{22}\text{H}_{20}\text{Cl}_2\text{FN}_3\text{O}_4$	480.08	480.0
5		$\text{C}_{23}\text{H}_{22}\text{Cl}_2\text{FN}_3\text{O}_4$	494.10	494.2

Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
6		C ₂₃ H ₂₂ Cl ₂ FN ₃ O ₄	494.10	494.2
7		C ₂₃ H ₂₂ Cl ₂ FN ₃ O ₅	510.09	510.2
8		C ₂₃ H ₂₂ Cl ₂ FN ₃ O ₅	510.09	510.2
9		C ₂₄ H ₂₂ Cl ₂ FN ₃ O ₄	506.10	506.2
10		C ₂₄ H ₂₂ Cl ₂ FN ₃ O ₄	506.10	506.2
11		C ₂₂ H ₂₀ Cl ₂ FN ₃ O ₅	496.08	496.0
12		C ₂₂ H ₂₀ Cl ₂ FN ₃ O ₅	496.08	496.0

1. (2*S*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylisoxazole-2-carbonyl)amino]pentanoic acid
2. (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(2-propylisoxazole-4-carbonyl)amino]pentanoic acid
- 5 3. (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid
4. (2*S*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid
- 10 5. (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethylisoxazole-5-carbonyl)amino]pentanoic acid
6. (2*S*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethylisoxazole-5-carbonyl)amino]pentanoic acid
7. (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(5-methoxymethylisoxazole-3-carbonyl)amino]pentanoic acid
- 15 8. (2*S*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)-4-[(5-methoxymethylisoxazole-3-carbonyl)amino]pentanoic acid
9. (2*R*,4*R*)-2-Amino-4-[(5-cyclopropyl-isoxazole-3-carbonyl)-amino]-5-(3,5'-

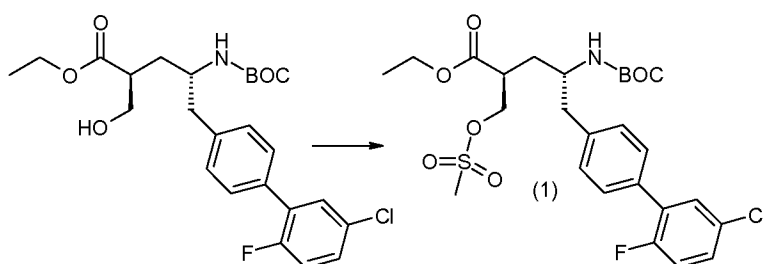
dichloro-2'-fluorobiphenyl-4-yl)pentanoic acid

10. (2*S*,4*R*)-2-Amino-4-[(5-cyclopropyl-isoxazole-3-carbonyl)-amino]-5-(3,5'-dichloro-2'-fluorobiphenyl-4-yl)pentanoic acid

11. (2*R*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluoro-biphenyl-4-yl)-4-[(5-methoxyoxazole-2-carbonyl)amino]pentanoic acid

12. (2*S*,4*R*)-2-Amino-5-(3,5'-dichloro-2'-fluoro-biphenyl-4-yl)-4-[(5-methoxyoxazole-2-carbonyl)amino]pentanoic acid

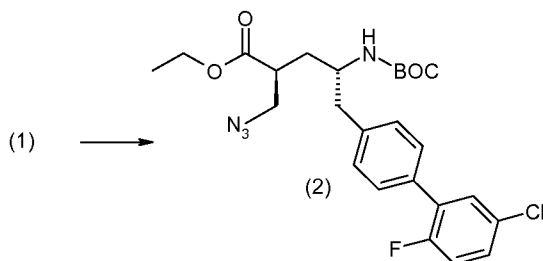
EXAMPLE 19: (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester



10

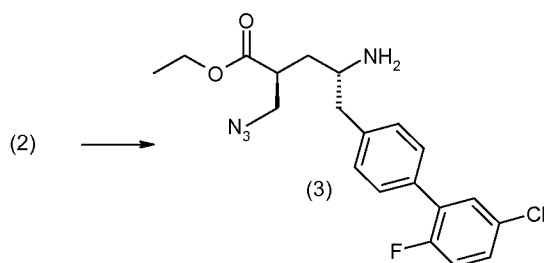
To a stirred solution of (2*S*,4*S*)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (525 mg, 1.1 mmol) in DCM (2 mL), was added methanesulfonyl chloride (102 μ L, 1.3 mmol), followed by the slow addition of Et₃N (305 μ L, 2.2 mmol). The mixture was stirred at room temperature for 30 minutes and was then purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (405 mg).

15

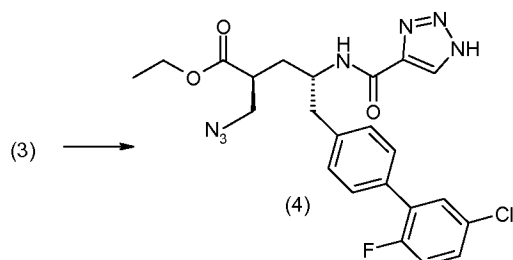


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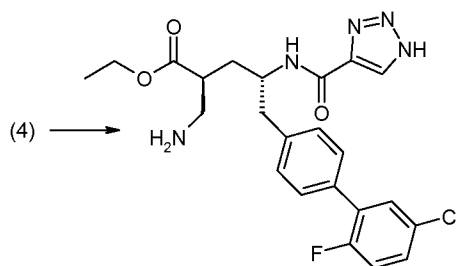
Compound 1 (325 mg, 582 μ mol) was dissolved in DMF (2 mL) and combined with sodium azide (41.6 mg, 641 μ mol), and the resulting mixture was stirred at room temperature for 3 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed (3x) with water, dried over Na₂SO₄, then concentrated under reduced pressure, and the residue purified by normal phase column chromatography (0-100% EtOAc/hexanes) to yield Compound 2 (290 mg).



Compound 2 (290 mg, 574 μ mol) was dissolved in MeCN (3 mL) and 4N HCl in dioxane (1 mL), and the mixture was stirred at room temperature for 10 minutes. The mixture was concentrated under reduced pressure to yield crude Compound 3 as an HCl salt.



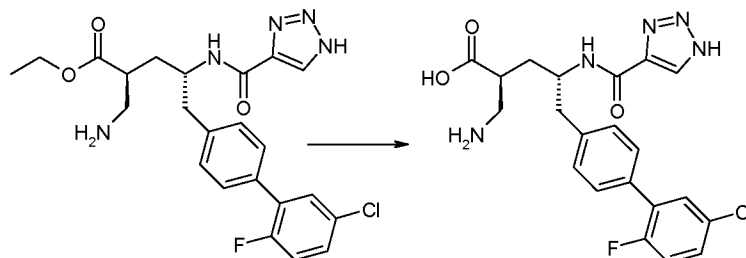
1H-1,2,3-triazole-5-carboxylic acid (55.9 mg, 494 μ mol) was combined with HATU (188 mg, 494 μ mol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1.5 eq.) was added and the mixture was stirred for 1 minute. Compound 3 (200 mg, 494 μ mol) was dissolved in DMF (1 mL) and DIPEA (259 μ L, 1.5 mmol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and the solvent was evaporated. The mixture was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 4 (100 mg).



Compound 4 (100 mg, 0.2 mmol) was combined with PdOH₂/C (21.3 mg, 40 μ mol) and EtOAc (1 mL) with 12N HCl (50 μ L). Oxygen was removed *in vacuo* and the flask placed under hydrogen (1 atm), then stirred at room temperature for 6 hours. The hydrogen was removed *in vacuo* and the flask was purged with nitrogen. The reaction was quenched with AcOH and purified by reverse phase chromatography to yield the title

compound (50 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}ClFN_5O_3$, 474.16; found 474.

EXAMPLE 20: (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



5

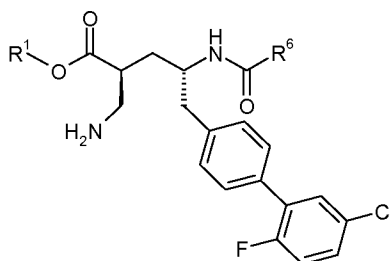
(2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester (40 mg, 84 μ mol) was dissolved in THF (1 mL), 1N LiOH (253 μ L, 253 μ mol) and 3 drops of MeOH and stirred at room temperature. The reaction was determined to be complete after 30 minutes and AcOH was added. The crude residue was purified (reverse phase chromatography) to yield the title compound (20 mg; purity 98%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{21}H_{21}ClFN_5O_3$, 446.13; found 446.

10

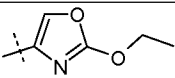
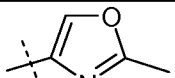
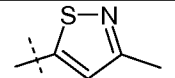
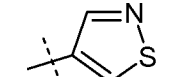
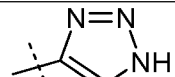
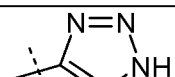
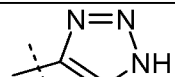
EXAMPLE 21

Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared as TFA salts:

15



Ex.	R^1	R^6	Formula	MS m/z : $[M+H]^+$	
				calcd	found
1	H		$C_{24}H_{25}ClFN_3O_4$	474.15	473
2	H		$C_{25}H_{25}ClFN_3O_4$	486.15	485
3	H		$C_{23}H_{23}ClFN_3O_4$	460.14	459

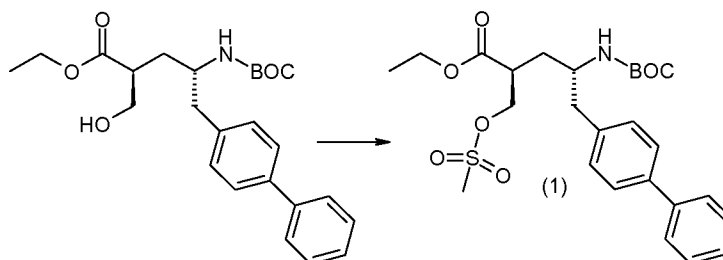
Ex.	R ¹	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
				calcd	found
4	H		C ₂₄ H ₂₅ ClFN ₃ O ₅	490.15	489
5	H		C ₂₃ H ₂₃ ClFN ₃ O ₄	460.14	459
6	H		C ₂₃ H ₂₃ ClFN ₃ O ₃ S	476.11	475
7	H		C ₂₂ H ₂₁ ClFN ₃ O ₃ S	462.10	462
8	⁻ CH(CH ₃) ₂		C ₂₄ H ₂₇ ClFN ₅ O ₃	488.18	489
9	-(CH ₂) ₃ - CH ₃		C ₂₅ H ₂₉ ClFN ₅ O ₃	502.19	503
10	-(CH ₂) ₅ - CH ₃		C ₂₇ H ₃₃ ClFN ₅ O ₃	530.23	531

1. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethyl-isoxazole-5-carbonyl)amino]pentanoic acid
2. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-cyclopropyl-oxazole-4-carbonyl)amino]pentanoic acid
3. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyl-oxazole-2-carbonyl)amino]pentanoic acid
4. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-ethoxy-oxazole-4-carbonyl)amino]pentanoic acid
5. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(2-methyloxazole-4-carbonyl)amino]pentanoic acid
6. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3-methylisothiazole-5-carbonyl)amino]pentanoic acid
7. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(isothiazole-4-carbonyl)amino]pentanoic acid
8. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid isopropyl ester
9. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-

4-carbonyl)amino]pentanoic acid butyl ester

10. (2*S*,4*S*)-2-Aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-

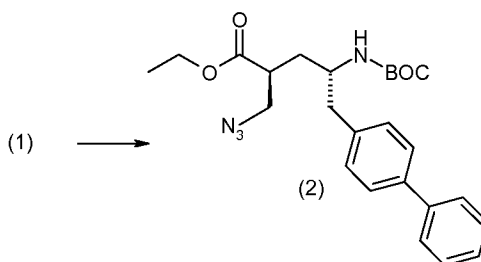
EXAMPLE 22: (2*S*,4*S*)-2-Aminomethyl-5-biphenyl-4-yl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



5

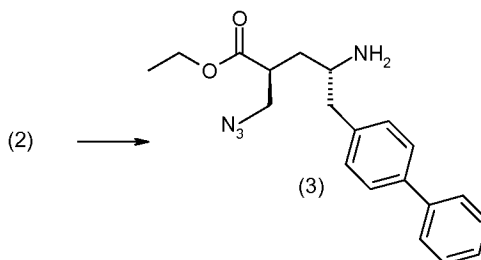
(2*S*,4*S*)-5-Biphenyl-4-yl-4-*t*-butoxycarbonylamino-2-hydroxymethylpentanoic acid ethyl ester (450 mg, 1.1 mmol) was dissolved in DCM (2 mL) and methanesulfonyl chloride (98 μ L, 1.3 mmol) was added, followed by Et₃N (293 μ L, 2.1 mmol). The mixture was stirred at room temperature for 30 minutes, and the solution was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (405 mg).

10



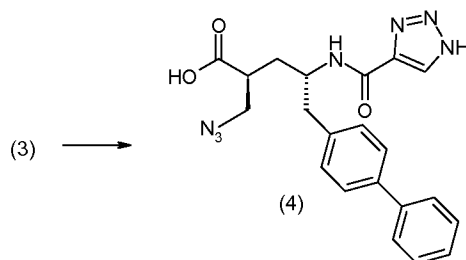
Compound 1 (200 mg, 396 μ mol) in DMF (2 mL) was combined with sodium azide (33 mg, 514 μ mol), and the resulting mixture was stirred at 50°C overnight. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed (3x) with water, dried over Na₂SO₄, then concentrated under reduced pressure and purified by normal phase chromatography (0-60% EtOAc/hexanes) to yield Compound 2 (115 mg).

15

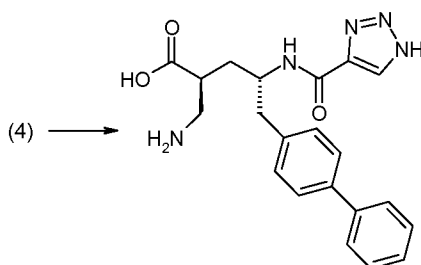


Compound 2 (93 mg, 206 μ mol) was dissolved in MeCN and 4*N* HCl in dioxane, and the mixture was stirred at room temperature for 10 minutes. The mixture was

concentrated under reduced pressure to yield crude Compound 3 as an HCl salt, which was used directly in the next step.

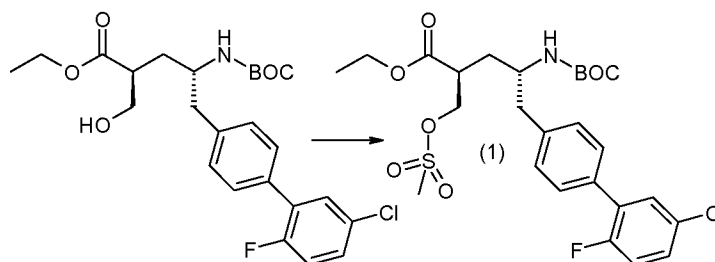


Compound 3 (30 mg, 199 μ mol) was combined with 3H-[1,2,3]triazole-4-carboxylic acid (22 mg, 199 μ mol), HATU (76 mg, 199 μ mol) and DIPEA (104 μ L, 596 μ mol) in DMF (1 mL) and stirred at room temperature for 20 minutes then concentrated *in vacuo* and the crude residue was purified by normal phase chromatography (0-100% EtOAc/hexanes). The intermediate (30 mg, 67 μ mol) was dissolved in THF (1 mL) and 10N NaOH (268 μ L, 268 μ mol) and stirred at room temperature for 1 hour. The mixture was acidified with AcOH and purified by preparative HPLC to yield Compound 4 (10 mg).

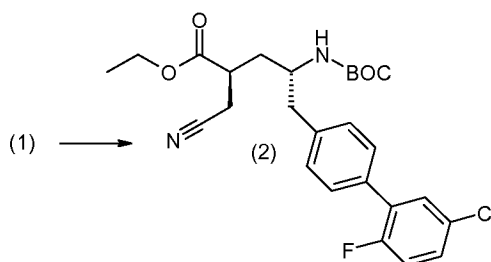


Compound 4 (50 mg, 119 μ mol) was combined with PdOH₂/C (17 mg, 119 μ mol) in MeOH. Oxygen was removed *in vacuo* and the solution was placed under hydrogen (1 atm), then stirred for 2 hours. The flask was purged with nitrogen. The reaction was quenched with AcOH, filtered, and purified by reverse phase chromatography to yield the title compound (10 mg; purity 95%) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for C₂₁H₂₃N₅O₃, 394.18; found 394.

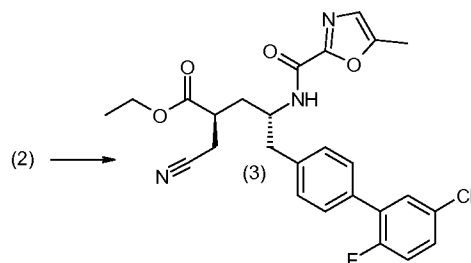
EXAMPLE 23: (2R,4S)-2-(2-Aminoethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic Acid



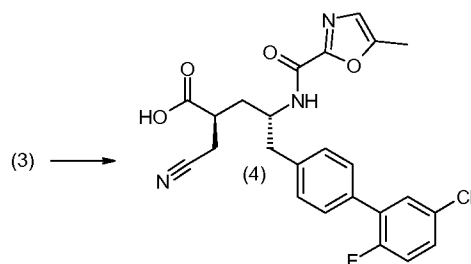
To a solution of (2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (530 mg, 1.1 mmol) in DCM (5.5 mL) was added Et₃N (308 μL, 2.2 mmol). The solution was cooled to 0°C and methanesulfonyl chloride (95 μL, 1.2 mmol) was added slowly over a period of 5 minutes. After 20 minutes of stirring at this temperature, LCMS indicated that the desired product had been formed. The solution was washed with ice-cold water (5 mL), ice-cold 1N HCl (5 mL), NaHCO₃ (5 mL), and saturated aqueous NaCl (5 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo* to yield Compound 1 (602 mg).



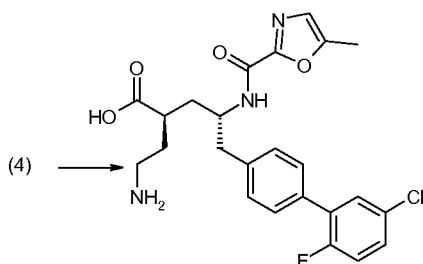
To a solution of Compound 1 (602 mg, 1.1 mmol) in DMF (6 mL) was added sodium cyanide (116 mg, 2.4 mmol) and 4-(dimethylamino)pyridine (13 mg, 0.1 mmol), and the resulting mixture was heated to 50°C and stirred overnight. EtOAc (20 mL) and water (20 mL) were added, and the layers were separated. The organic layer was washed with water (3x20 mL), dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by column chromatography (0-60% EtOAc/hexanes) to yield Compound 2 (421 mg).



To a solution of Compound 2 (84 mg, 0.2 mmol) in dioxane (4.3 mL) was added HCl (861 μ L, 3.4 mmol). The resulting mixture was stirred at room temperature for 3 hours, after which time LCMS indicated that the BOC group had been removed. The solution was concentrated *in vacuo*. The residue was dissolved in DMF (2 mL) and DIPEA (90 μ L, 0.5 mmol) and added to a solution of 5-methyloxazole-2-carboxylic acid (26 mg, 0.2 mmol), HATU (79 mg, 0.2 mmol) in DMF (4.3 mL), that had been stirred at room temperature for 15 minutes. The resulting solution was stirred at room temperature for 1 hour, until the reaction was complete. The solution was concentrated *in vacuo* and the residue purified by column chromatography (0-60% EtOAc/hexanes) to yield Compound 3 (554 mg).



To a solution of Compound 3 (55 mg, 0.111 mmol) in EtOH (1.1 mL) was added NaOH (890 μ L, 890 μ mol). The solution was stirred at room temperature for 1 hour, then concentrated *in vacuo* and purified by reverse phase column chromatography. The desired fractions were combined and lyophilized to yield Compound 4 (31 mg).



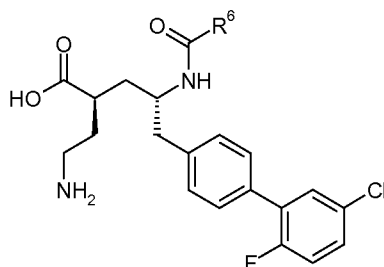
To a solution of Compound 4 (31 mg, 66 μ mol) in EtOAc (1.5 mL) and AcOH (38 μ L, 660 μ mol) was added PdOH₂/C (4.6 mg, 33 μ mol) and (BOC)₂O (15 μ L, 66 μ mol).

The resulting solution was sparged with hydrogen and then stirred at room temperature for 2 hours. The solution was concentrated *in vacuo* and the residue was purified by reverse phase column chromatography to yield the title compound (1.7 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{25}ClFN_3O_4$, 474.15; found 474.2.

5

EXAMPLE 24

Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared as a TFA salt:

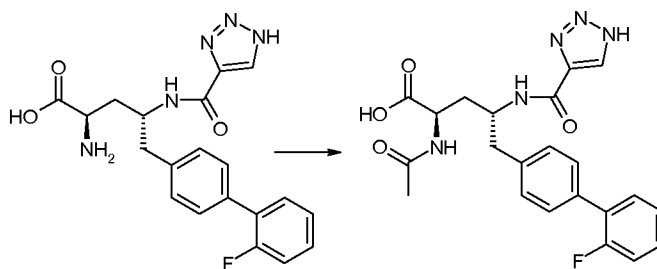


Ex.	R ⁶	Formula	MS m/z : $[M+H]^+$	
			calcd	found
1		$C_{26}H_{29}ClFN_3O_4$	502.18	502.2
2		$C_{22}H_{23}ClFN_5O_3$	460.15	460.2

- 10 1. $(2R,4S)$ -2-(2-Aminoethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylisoxazole-2-carbonyl)amino]pentanoic acid
2. $(2R,4S)$ -2-(2-Aminoethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid

EXAMPLE 25: $(2R,4R)$ -2-Acetylamino-5-(2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

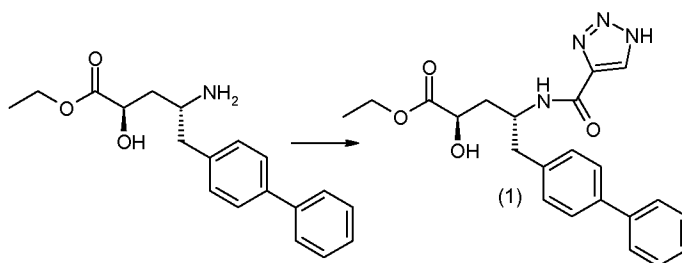
15



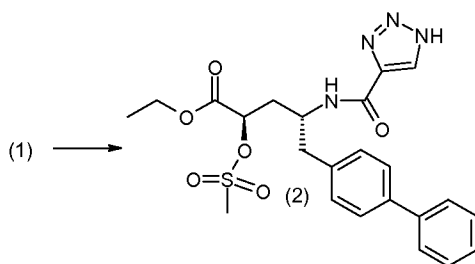
$(2R,4R)$ -2-Amino-5-(2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-

carbonyl)amino]pentanoic acid (9 mg, 23 μmol) was dissolved in DCM (2 mL). Acetyl chloride (1.8 μL , 25 μmol) and DIPEA (12 μL , 68 μmol) were added and the resulting mixture was stirred at room temperature for 15 minutes then concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL). An aqueous solution of 1N NaOH (227 μL , 227 μmol) was added and the mixture was stirred at room temperature for 30 minutes then concentrated *in vacuo* and the residue was purified by reverse phase column chromatography to yield the title compound (5 mg; purity 98%). MS m/z $[M+H]^+$ calc'd for $\text{C}_{22}\text{H}_{22}\text{FN}_5\text{O}_4$, 440.17; found 440.1.

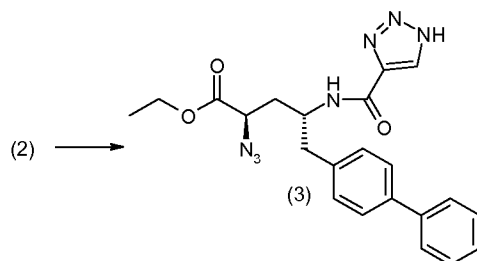
EXAMPLE 26: (2R,4R)-2-Acetyl-amino-5-biphenyl-4-yl-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



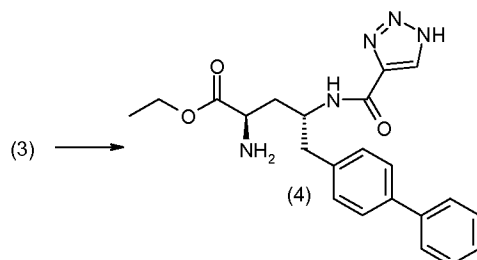
To a stirred solution of (2R,4R)-4-Amino-5-biphenyl-4-yl-2-hydroxypentanoic acid ethyl ester (200 mg, 638 μmol), HATU (291 mg, 766 μmol), 3H-[1,2,3]triazole-4-carboxylic acid (87 mg, 766 μmol), and DMF (3 mL), was added DIPEA (357 μL , 2.0 mmol), and the mixture was stirred at room temperature for 30 minutes. A saturated aqueous NH_4Cl was added and the mixture was extracted with EtOAc. The organics were combined, dried over Na_2SO_4 , and the solvent was evaporated. The crude residue was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (76 mg).



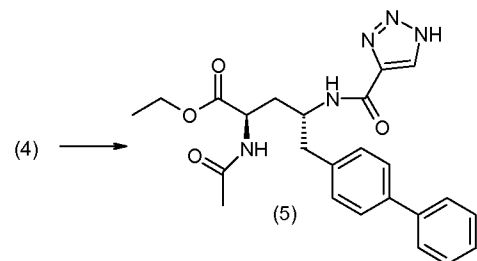
Compound 1 (111 mg, 272 μmol) was dissolved in DCM (3 mL). Methanesulfonyl chloride (46.4 μL , 599 μmol) was added at 0°C , followed by Et_3N (114 μL , 817 μmol). The mixture was stirred for 10 minutes, and then concentrated and was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 2 (60 mg).



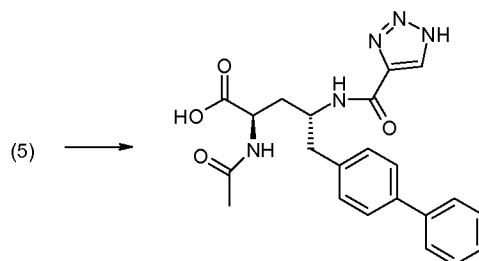
Compound 2 (60 mg, 123 μ mol) in DMF (2 mL) was combined with sodium azide (17.6 mg, 271 μ mol), and the resulting mixture was stirred overnight. The solution was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 3
5 (54 mg).



Compound 3 (54 mg, 125 μ mol) was combined with PdOH₂/C (17.5mg, 25 μ mol) in MeOH. The flask was purged *in vacuo* (3x), then purged with nitrogen, then placed under hydrogen (1 atm) and stirred at room temperature for 30 minutes. The reaction was
10 quenched with AcOH. The mixture was stirred for 10 minutes, filtered and concentrated *in vacuo* to yield Compound 4.



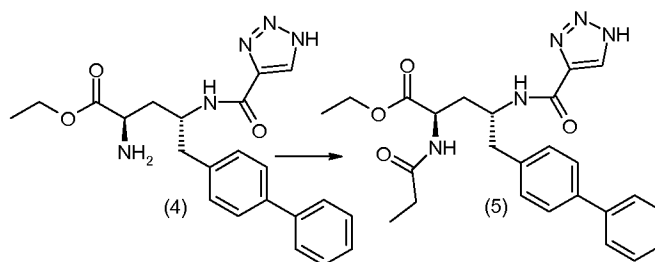
Compound 4 (10 mg, 25 μ mol) was combined with DCM (2 mL), methyl chloroformate (2.3 mg, 25 μ mol) and Et₃N (3.4 μ L, 25 μ mol l). The mixture was stirred
15 for 10 minutes and the solvent evaporated to yield Compound 5.



Compound 5 (11 mg, 24 μ mol) was dissolved in THF (1 mL) and 1N NaOH (119 μ L, 119 μ mol) and stirred at room temperature for 3 hours. To the mixture was added AcOH and the solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 98%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}N_5O_4$, 422.18; found 422.

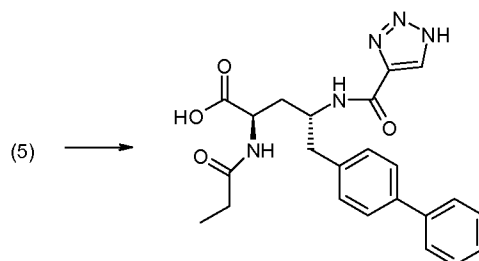
EXAMPLE 27: (2R,4R)-5-Biphenyl-4-yl-2-propionylamino-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 4 was prepared as described herein.



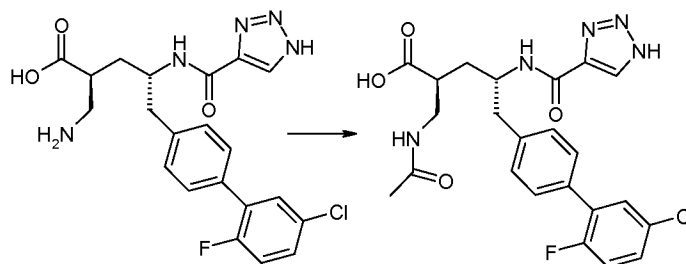
10

Compound 4 (10 mg, 25 μ mol) was combined with DCM (2 mL), propionyl chloride (2.3 mg, 25 μ mol) and Et_3N (3.4 μ L, 25 μ mol l). The mixture was stirred for 10 minutes and the solvent evaporated to yield Compound 5.



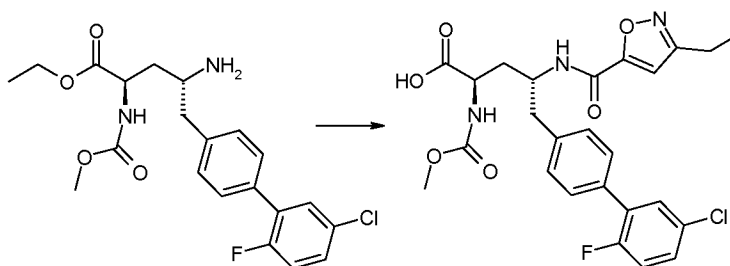
15 Compound 5 (11 mg, 24 μ mol) was dissolved in THF (1 mL) and 10N NaOH (119 μ L, 119 μ mol) and stirred for 3 hours. To the mixture was added AcOH and the solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}N_5O_4$, 436.19; found 436.

EXAMPLE 28: (2S,4S)-2-(Acetylaminomethyl)-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



To a stirred solution of (2S,4S)-2-aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (5 mg, 11 μ mol), DCM (0.3 mL), and acetyl chloride (3.5 mg, 45 μ mol), was added Et₃N (9.4 μ L, 67 μ mol), and the mixture was stirred for 5 minutes. The reaction was quenched with 1N NaOH (0.1 mL) and THF (0.5 mL) and the mixture stirred for 10 minutes. The solvent was evaporated and the residue was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₃H₂₃ClFN₅O₄, 488.14; found 488.

EXAMPLE 29: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3-ethyl-isoxazole-5-carbonyl)amino]-2-methoxycarbonylaminopentanoic Acid

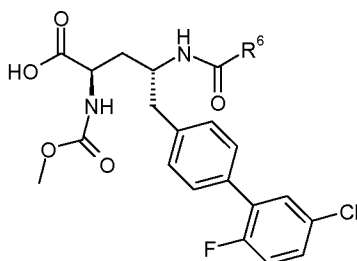


3-Ethylisoxazole-5-carboxylic acid (5.5 mg, 39 μ mol) and HATU (14.8 mg, 39 μ mol) were dissolved in DMF (3 mL) and stirred at room temperature for 15 minutes. (2R,4R)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylaminopentanoic acid ethyl ester (15 mg, 35 μ mol) and DIPEA (19 μ L, 106 μ mol) were added, and the resulting mixture was stirred at room temperature for 15 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was dissolved in EtOH (3 mL). An aqueous 1N NaOH solution (355 μ L, 355 μ mol) was added, and the resulting mixture was stirred at room temperature for 1 hour (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue purified by preparative HPLC to yield the title compound (3.7 mg; purity 100%). MS m/z [M+H]⁺ calc'd for C₂₅H₂₅ClFN₃O₆, 518.14;

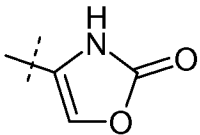
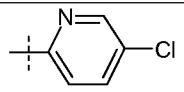
found 518.2.

EXAMPLE 30

Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared, either as the parent compound or
5 as a TFA salt:



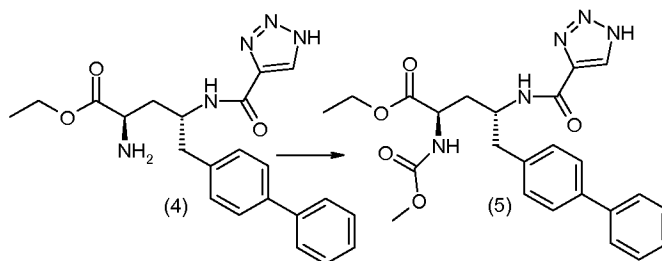
Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
1		C ₂₂ H ₂₁ ClFN ₅ O ₅	490.12	490.0
2		C ₂₅ H ₂₄ ClFN ₄ O ₆	531.14	531.2
3		C ₂₃ H ₂₁ ClFN ₃ O ₆	490.11	490.2
4		C ₂₄ H ₂₃ ClFN ₃ O ₆	504.13	504
5		C ₂₆ H ₂₅ ClFN ₃ O ₆	530.14	530.2
6		C ₂₅ H ₂₅ ClFN ₃ O ₆	518.14	518.2
7		C ₂₅ H ₂₅ ClFN ₃ O ₇	534.14	534.2
8		C ₂₆ H ₂₇ ClFN ₃ O ₇	548.15	548.2
9		C ₂₂ H ₂₀ ClFN ₄ O ₇	507.10	507.2
10		C ₂₃ H ₂₁ ClFN ₃ O ₇	506.11	506.2

Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
11		C ₂₃ H ₂₁ ClFN ₃ O ₇	506.11	506.2
12		C ₂₅ H ₂₂ Cl ₂ FN ₃ O ₅	534.09	534.2

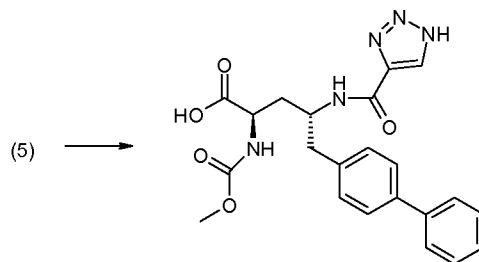
1. (2*R*,4*R*)-5-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-2-methoxycarbonylamino-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid
2. (2*R*,4*R*)-4-[(5-Acetyl-2*H*-pyrazole-3-carbonyl)-amino]-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)-2-methoxycarbonylaminopentanoic acid
- 5 3. (2*R*,4*R*)-5-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-2-methoxycarbonylamino-4-[(oxazole-2-carbonyl)amino]pentanoic acid
4. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylamino-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic acid
- 10 5. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(2-cyclopropyl-oxazole-4-carbonyl)amino]-2-methoxycarbonylaminopentanoic acid
6. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(2-ethyl-oxazole-4-carbonyl)amino]-2-methoxycarbonylaminopentanoic acid
7. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(2-ethoxy-oxazole-4-
- 15 carbonyl)amino]-2-methoxycarbonylaminopentanoic acid
8. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-ethoxy-4-methyl-oxazole-2-carbonyl)amino]-2-methoxycarbonylaminopentanoic acid
9. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylamino-4-[(5-oxo-4,5-dihydro-[1,2,4]oxadiazole-3-carbonyl)amino]pentanoic acid
- 20 10. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylamino-4-[(2-oxo-2,3-dihydro-oxazole-5-carbonyl)amino]pentanoic acid
11. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methoxycarbonylamino-4-[(2-oxo-2,3-dihydro-oxazole-4-carbonyl)amino]pentanoic acid
12. (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(5-chloro-pyridine-2-carbonyl)-
- 25 amino]-2-methoxycarbonylaminopentanoic acid

EXAMPLE 31: (2R,4R)-5-Biphenyl-4-yl-2-methoxycarbonylamino-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 4 was prepared as described herein.

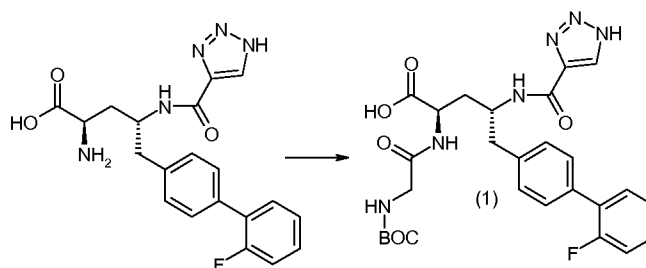


- 5 To a stirred solution of Compound 4 (10 mg, 25 μmol) in DCM (2 mL), was added methyl chloroformate (2.3 mg, 25 μmol) and Et_3N (3.4 μL , 25 μmol). The mixture was stirred for 10 minutes and the solvent evaporated to yield Compound 5.



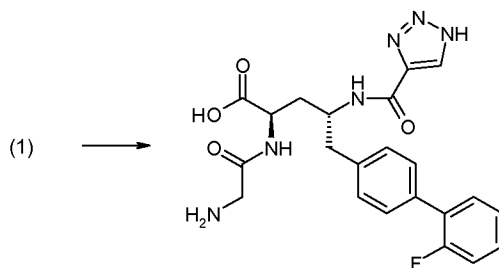
- A solution of Compound 5 (11 mg, 24 μmol) in THF (1 mL) and 1N NaOH (119 μL , 119 μmol) was stirred for 3 hours. To the mixture was added AcOH and the solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{23}\text{N}_5\text{O}_5$, 438.17; found 438.

Example 32: (2R,4R)-2-(2-Aminoacetyl-amino)-5-(2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



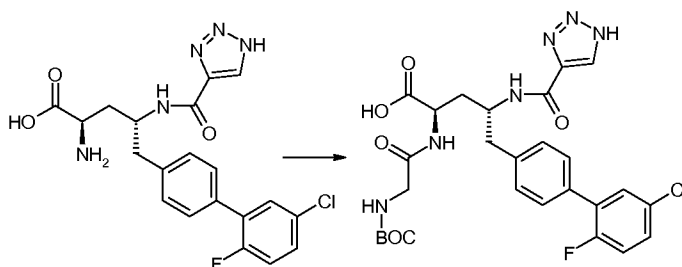
- 15 n -BOC-Glycine (9.7 mg, 55 μmol) and HATU (21.1 mg, 55 μmol) were dissolved in DMF (2 mL) and stirred for 15 minutes at room temperature. (2R,4R)-2-Amino-5-(2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (20 mg, 50 μmol) and DIPEA (22 μL , 126 μmol) were added and the resulting mixture was stirred at

room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL). An aqueous solution of 1N NaOH (503 μ L, 503 μ mol) was added and the resulting mixture was stirred at room temperature for 30 minutes (LC/MS showed the mass of the
 5 desired product) then concentrated *in vacuo* to yield Compound 1, which was used in the next step without purification.

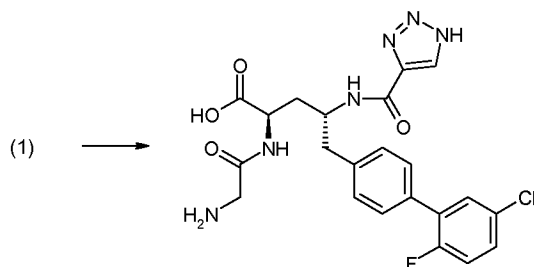


Compound 1 (14 mg, 25 μ mol) was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (63 μ L, 252 μ mol) was added and the mixture was stirred at room
 10 temperature for 10 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase column chromatography to yield the title compound (3 mg; purity 96%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}FN_6O_4$, 455.18; found 455.

15 EXAMPLE 33: (2R,4R)-2-(2-Aminoacetyl-amino)-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



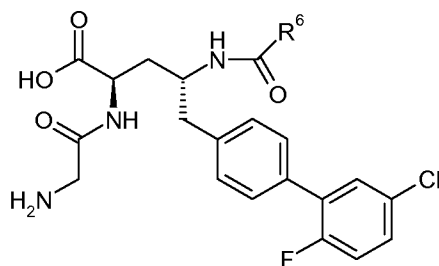
n-BOC-Glycine (3.3 mg, 19 μ mol) and HATU (7.1 mg, 19 μ mol) were dissolved in DMF (2 mL) and stirred for 15 minutes at room temperature. (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (7.3
 20 mg, 17 μ mol) and DIPEA (8.9 μ L, 51 μ mol) were added and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* to yield Compound 1, which was used in the next step without purification.



Compound 1 (10 mg, 17 μ mol) was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (4.2 μ L, 17 μ mol) was added and the mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by reverse phase column chromatography to yield the title compound (2.5 mg; purity 98%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{22}ClFN_6O_4$, 489.14; found 489.

EXAMPLE 34

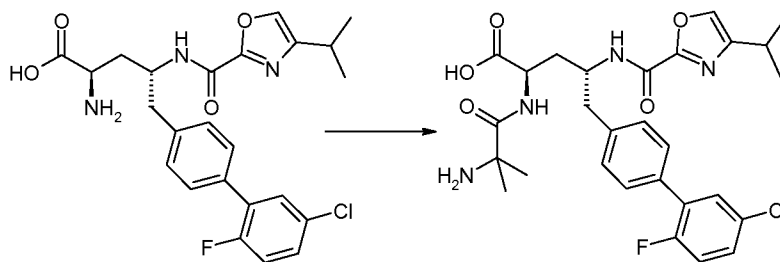
Following the procedures described herein, and substituting the appropriate starting materials and reagents, this compound was prepared as a TFA salt:



Ex.	R ⁶	Formula	MS m/z : $[M+H]^+$	
			calcd	found
1		$C_{26}H_{28}ClFN_4O_5$	531.17	531.2

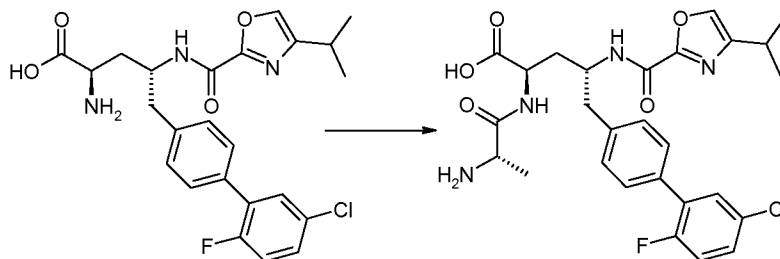
1. (2*R*,4*R*)-2-(2-Aminoacetyl-amino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylisoxazole-2-carbonyl)amino]pentanoic acid

EXAMPLE 35: (2R,4R)-2-(2-Amino-2-methylpropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid



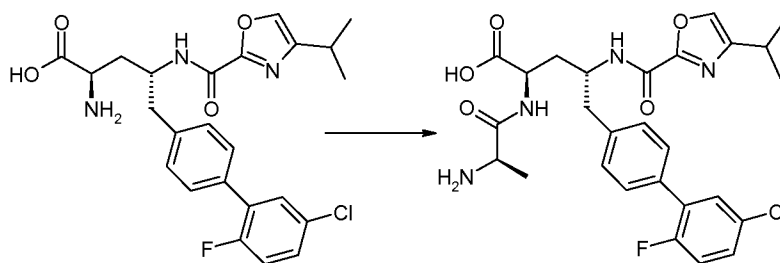
2-*t*-Butoxycarbonylamino-2-methylpropionic acid (4.5 mg, 22 μ mol) and HATU (8.4 mg, 22 μ mol) were dissolved in DMF (2 mL) and stirred for 15 min at room temperature. (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic acid (10 mg, 21 μ mol) and DIPEA (11 μ L, 63 μ mol) were added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). An excess of a solution of 4N HCl in dioxane was added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (2.1 mg; purity 96%) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for C₂₈H₃₂ClFN₄O₅, 559.20; found 559.2.

EXAMPLE 36: (2R,4R)-2-((S)-2-Aminopropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid (compound 36-1) and (2R,4R)-2-((R)-2-Aminopropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropyl-oxazole-2-carbonyl)-amino]pentanoic Acid (compound 36-2)



(*S*)-2-*t*-Butoxycarbonylamino-2-methylpropionic acid (4.2 mg, 22 μ mol) and HATU (8.4 mg, 22 μ mol) were dissolved in DMF (2 mL) and stirred for 15 min at room temperature.

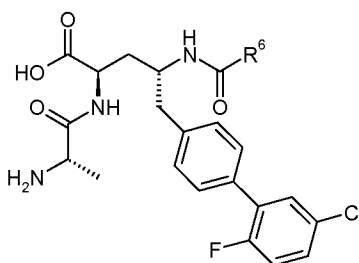
(2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropyl-oxazole-2-carbonyl)amino]pentanoic acid (10 mg, 21 μ mol) and DIPEA (11 μ L, 63 μ mol) were added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). An excess of a solution of 4*N* HCl in dioxane was added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title Compound 36-1 (2.4 mg; purity 100%) as a TFA salt. MS *m/z* $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_4O_5$, 545.19; found 545.2.



This procedure was repeated using (*R*)-2-*t*-butoxycarbonylaminopropionic acid (4.5 mg, 22 μ mol) to yield the title Compound 36-2 (2.2 mg; purity 100%) as a TFA salt. MS *m/z* $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_4O_5$, 545.19; found 545.2.

EXAMPLE 37

Following the procedures described herein, and substituting the appropriate starting materials and reagents, this compound was prepared as a TFA salt:

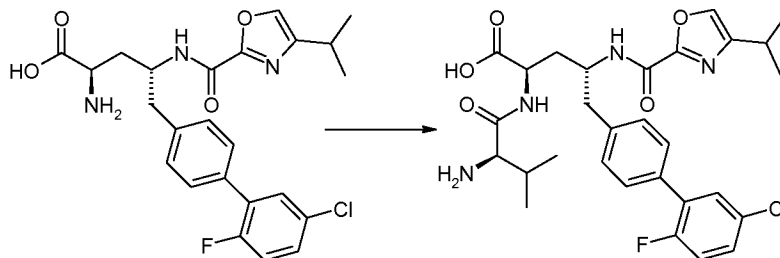


Ex.	R ⁶	Formula	MS <i>m/z</i> : $[M+H]^+$	
			calcd	found
1		$C_{23}H_{24}ClFN_6O_4$	503.15	503.2

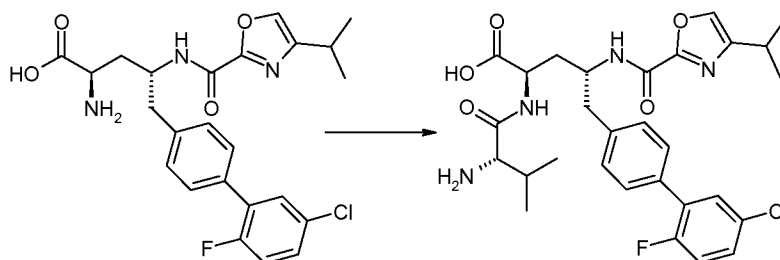
1. (2*R*,4*R*)-2-((*S*)-2-Aminopropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-

[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid

EXAMPLE 38: (2R,4R)-2-((R)-2-Amino-3-methylbutyrylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid (compound 38-1) and (2R,4R)-2-((S)-2-Amino-3-methylbutyrylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)-amino]pentanoic Acid (compound 38-2)



(*R*)-2-*t*-Butoxycarbonylamino-3-methylbutyric acid (4.8 mg, 22 μ mol) and HATU (8.4 mg, 22 μ mol) were dissolved in DMF (2 mL) and stirred for 15 min at room temperature. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic acid (10 mg, 21 μ mol) and DIPEA (11 μ L, 63 μ mol) were added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). An excess of a solution of 4N HCl in dioxane was added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title Compound 38-1 (1.7 mg; purity 92%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{29}H_{34}ClFN_4O_5$, 573.22; found 573.2.

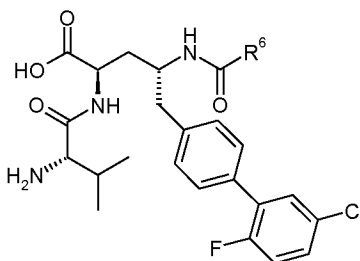


20

This procedure was repeated using (*S*)-2-*t*-butoxycarbonylamino-3-methylbutyric acid (4.8 mg, 22 μ mol) to yield the title Compound 38-2 (1.1 mg; purity 81%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{29}H_{34}ClFN_4O_5$, 573.22; found 573.2. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_4O_5$, 545.19; found 545.2.

EXAMPLE 39

Following the procedures described herein, and substituting the appropriate starting materials and reagents, this compound was prepared as a TFA salt:

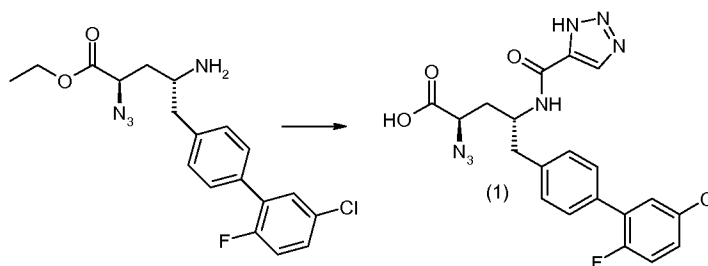


Ex.	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
			calcd	found
1		C ₂₅ H ₂₈ ClFN ₆ O ₄	531.18	531.2

5

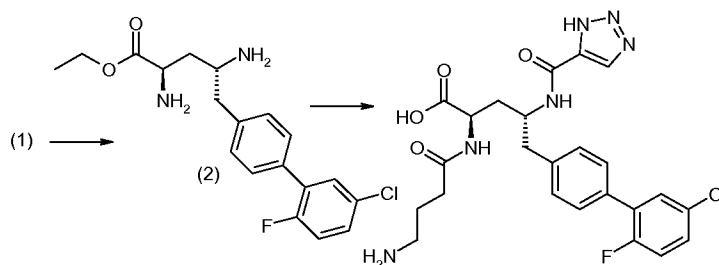
1. (2*R*,4*R*)-2-((*S*)-2-Amino-3-methylbutyrylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid

EXAMPLE 40: (2*R*,4*R*)-2-(4-Aminobutyrylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



10

- 1H-1,2,3-triazole-4-carboxylic acid (135 mg, 1.2 mmol) and HATU (453 mg, 1.2 mmol) were dissolved in DMF (4 mL) and stirred for 15 minutes at room temperature. (2*R*,4*R*)-4-Amino-2-azido-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (423 mg, 1.2 mmol) and DIPEA (567 μ L, 3.3 mmol) were added, and the mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the crude residue was purified by normal phase column chromatography (20-100% EtOAc/hexanes) to yield Compound 1 (324 mg).

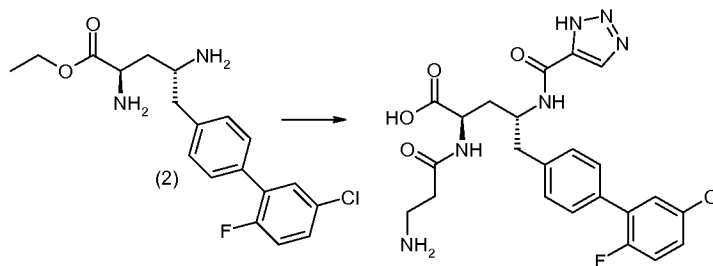


Compound 1 (203 mg, 443 μ mol) and palladium hydroxide (12.5 mg, 89 μ mol) were stirred in dry MeOH (3 mL) and AcOH (3 mL). The hydrogen was removed *in vacuo* and the flask was purged with nitrogen and the mixture stirred at room temperature for 1
5 hour. LC/MS showed the desired mass. The mixture was filtered and the solution was purified by preparative HPLC to yield Compound 2 (105 mg).

4-*t*-Butoxycarbonylaminobutyric acid (6.4 mg, 31 μ mol) and HATU (10.8 mg, 28 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. Compound 2 (12.3 mg, 28 μ mol) and DIPEA (15 μ L, 85 μ mol) were added, and the
10 mixture was stirred at room temperature for 15 minutes (LC/MS showed the desired product) then concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (107 mL, 427 μ mol) was added, and the mixture was stirred for 15 minutes at room temperature. LC/MS showed the desired mass. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to yield the title
15 compound (8 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{26}ClFN_6O_4$, 517.17; found 517.2.

EXAMPLE 41: (2*R*,4*R*)-2-(3-Aminopropionylamino)-5-(5'-chloro-2'-fluoro-biphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 2 was prepared as described herein.

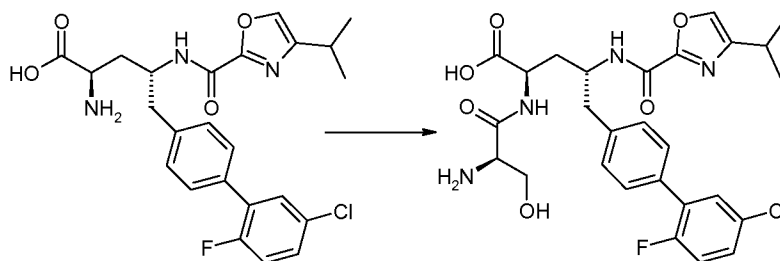


20

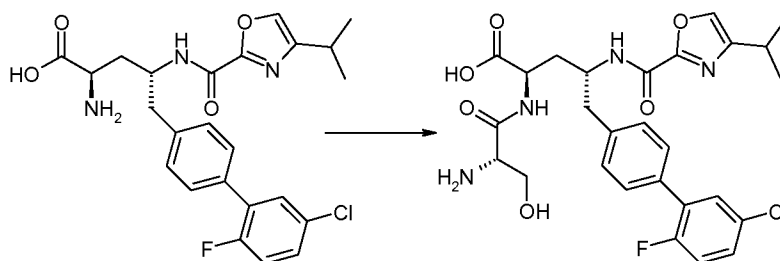
3-*t*-Butoxycarbonylaminopropionic acid (5.9 mg, 31 μ mol) and HATU (10.8 mg, 28 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. Compound 2 (12.3 mg, 28 μ mol) and DIPEA (15 μ L, 85 μ mol) were added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed the desired

product) then concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (107 mL, 427 μ mol) was added, and the mixture was stirred for 15 minutes at room temperature. LC/MS showed the desired mass. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (8.2 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{24}ClFN_6O_4$, 503.15; found 503.2.

EXAMPLE 42: (2R,4R)-2-((R)-2-Amino-3-hydroxypropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)-amino]pentanoic Acid (compound 42-1) and (2R,4R)-2-((S)-2-Amino-3-hydroxypropionylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic Acid (compound 42-2)

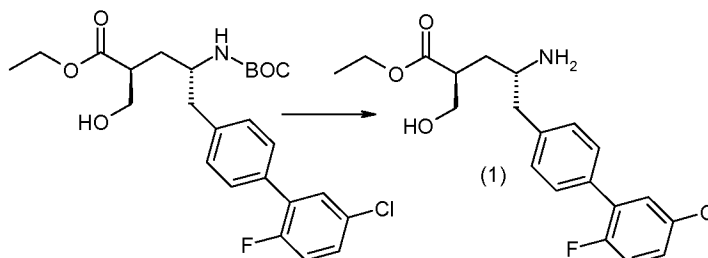


(*R*)-2-*t*-Butoxycarbonylamino-3-hydroxypropionic acid (4.5 mg, 22 μ mol) and HATU (8.4 mg, 22 μ mol) were dissolved in DMF (2 mL) and stirred at room temperature for 15 minutes. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(4-isopropylloxazole-2-carbonyl)amino]pentanoic acid (10 mg, 21 μ mol) and DIPEA (11 μ L, 63 μ mol) were added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). An excess of a solution of 4N HCl in dioxane was added, and the resulting mixture was stirred at room temperature for 15 minutes, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title Compound 42-1 (1 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_4O_6$, 561.18; found 561.2.

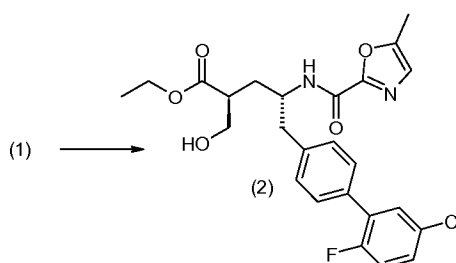


This procedure was repeated using (*S*)-2-*t*-butoxycarbonylamino-3-hydroxypropionic acid (4.5 mg, 22 μ mol) to yield the title Compound 42-2 (1.3 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_4O_6$, 561.18; found 561.2.

5 EXAMPLE 43: (2*S*,4*S*)-2-[(2-Aminoacetyl)amino]methyl]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-2-carbonyl)amino]pentanoic Acid

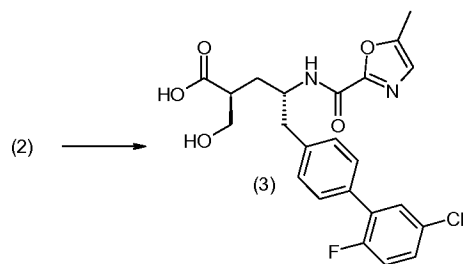


(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (1.65 g, 3.4 mmol) was dissolved in MeCN (6 mL) and 4N HCl in dioxane (3 mL), and stirred for 10 minutes. The mixture was concentrated under reduced pressure to yield Compound 1 (1.26 g) as and HCl salt, which was used without further purification.

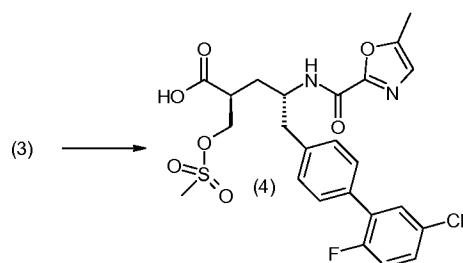


5-methyloxazole-2-carboxylic acid (422 mg, 3.3 mmol) was combined with HATU (1261 mg, 3.3 mmol) in DMF (3 mL) and stirred for 10 minutes. DIPEA (869 μ L) was added and the mixture was stirred for 1 minute. Compound 1 (1.26 g, 3.3 mmol) was dissolved in DMF (1 mL) and DIPEA (869 μ L) was added, followed by addition of the activated 5-methyloxazole-2-carboxylic acid solution. The resulting mixture was stirred for 30 minutes and concentrated *in vacuo* to yield Compound 2, which was used without

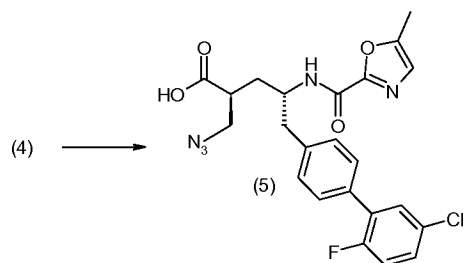
further purification.



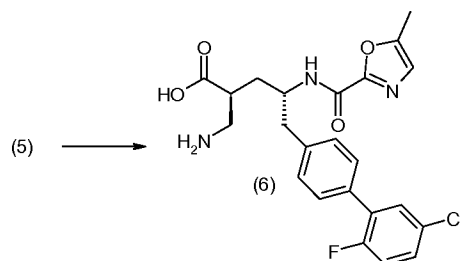
Compound 2 (1.6 g, 3.3 mmol) was dissolved in THF (10 mL) and 5N NaOH (3.3 mL, 16.6 mmol) and stirred for 2 hours at 50°C. AcOH was added and the solution was
 5 purified by reverse phase chromatography to yield Compound 3 (589 mg).



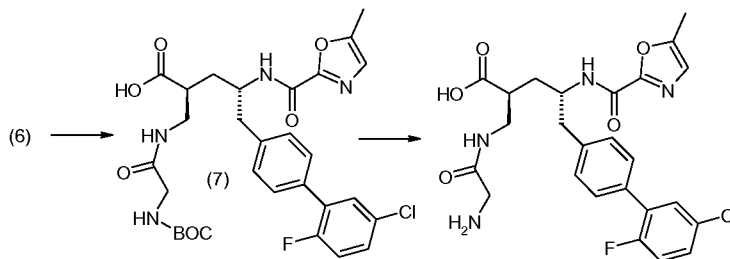
To a stirred solution of Compound 3 (390 mg, 846 μ mol) in DCM (10 mL), was added methanesulfonyl chloride (79 μ L, 1.0 mmol) and Et₃N (259 μ L, 1.9 mmol). The resulting mixture was stirred for 5 minutes and concentrated *in vacuo* to yield Compound
 10 4, which was used without further purification.



Compound 4 (200 mg, 371 μ mol) in DMF (1 mL) was combined with sodium azide (72.4 mg, 1.1 mmol) and the mixture was stirred at 50°C for 2 hours. The reaction was quenched with water and extracted with EtOAc. The organic layer was washed with water
 15 (3x) and then concentrated *in vacuo*. The residue was then purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 5.



Compound 5 (100 mg, 206 μmol) was combined with palladium on carbon (11 mg, 21 μmol), AcOH (0.3 mL) and EtOAc (1 mL). The reaction flask was purged with nitrogen and hydrogen (1 atm) added. The mixture was stirred for 2 hours. Hydrogen was removed *in vacuo* and nitrogen added. To the mixture was added AcOH (2 mL), the mixture was filtered and the solution was purified by reverse phase chromatography to yield Compound 6 (40 mg).

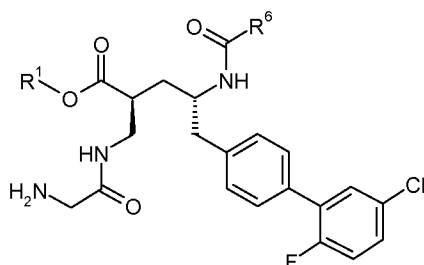


t-Butoxycarbonylamino acetic acid (3.1 mg, 17 μmol) was combined with HATU (6.6 mg, 17 μmol), DMF (0.5 mL) and DIPEA (9.1 μL , 52 μmol), and stirred for 5 minutes. This was then added to a solution of Compound 6 (8.0 mg, 17 μmol) in DMF (0.5 mL) and DIPEA (3eq.). The mixture was stirred for 10 minutes and the reaction was quenched with a saturated NaHCO_3 solution (1 mL) and EtOAc (3 mL). The organic layer was extracted and dried over MgSO_4 , filtered and concentrated under pressure to yield Compound 7.

Compound 7 (8 mg, 13 μmol) was dissolved in MeCN (0.5 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and the solvent removed under reduced pressure. The residue was then purified by reverse phase chromatography to yield the title compound (2.5 mg; purity 95%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{26}\text{ClFN}_4\text{O}_5$, 517.16; found 517.

EXAMPLE 44

Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared as a TFA salt:

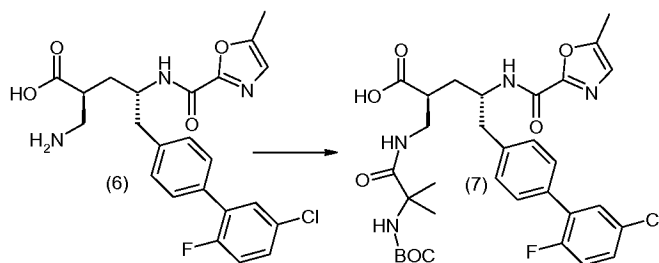


Ex.	R ¹	R ⁶	Formula	MS <i>m/z</i> : [M+H] ⁺	
				calcd	found
1	H		C ₂₃ H ₂₄ ClFN ₆ O ₄	503.15	502
2	-CH ₂ CH ₃		C ₂₅ H ₂₈ ClFN ₆ O ₄	531.18	531

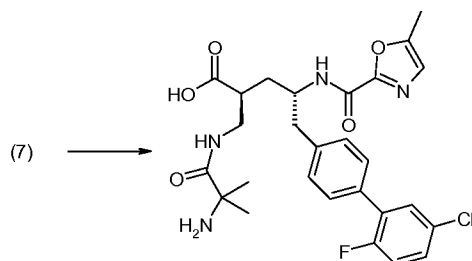
1. (2*S*,4*S*)-2-[(2-Aminoacetyl)amino]methyl]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid
- 5 2. (2*S*,4*S*)-2-[(2-Aminoacetyl)amino]methyl]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester

EXAMPLE 45 (2*S*,4*S*)-2-[(2-Amino-2-methylpropionylamino)methyl]-
5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(5-methyloxazole-
2-carbonyl)-amino]pentanoic Acid

10 Compound 6 was prepared as described herein.

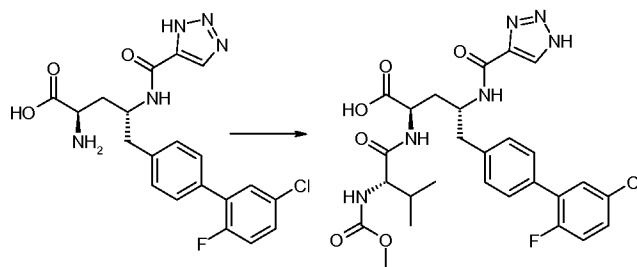


2-*t*-Butoxycarbonylamino-2-methylpropionic acid (3.5 mg, 17 μmol) was combined with HATU (6.6 mg, 17 μmol), DMF (0.5 mL) and DIPEA (9.1 μL, 52 μmol), and stirred for 5 minutes. This was then added to a solution of Compound 6 (8.0 mg, 17 μmol) in DMF (0.5 mL) and DIPEA (3eq.). The mixture was stirred for 10 minutes and the reaction was quenched with a saturated aqueous NaHCO₃ solution (1 mL) and EtOAc (3 mL). The organic layer was separated and dried over MgSO₄ followed by evaporation under pressure to yield Compound 7.



Compound 7 (8.4 mg, 13 μmol) was dissolved in MeCN (0.5 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and the solvent removed under reduced pressure. The residue was then purified (reverse phase chromatography) to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{27}\text{H}_{30}\text{ClFN}_4\text{O}_5$, 545.19; found 545.

EXAMPLE 46: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((S)-2-methoxycarbonylamino-3-methylbutyrylamino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



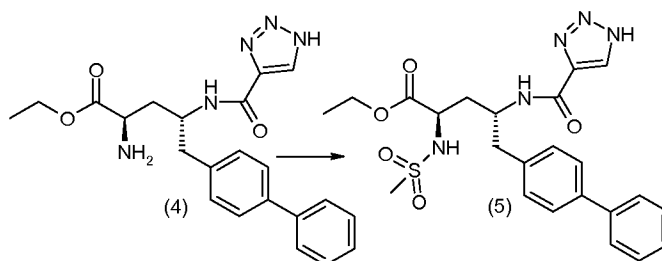
10

(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoic acid (6.7 mg, 38 μmol) and HATU (13.9 mg, 36 μmol) were dissolved in DMF (4 mL) and stirred at room temperature for 15 minutes. (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (15 mg, 35 μmol) and DIPEA (15 μL , 87 μmol) were then added, and the resulting mixture was stirred at room temperature for 15 minutes. LC/MS showed reaction completion (2 isomers were observed). The solution was concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (6 mg; purity 100%) as a white powder TFA salt. The 1:1 ratio of isomers were not isolated. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{27}\text{H}_{30}\text{ClFN}_6\text{O}_6$, 589.19; found 589.19.

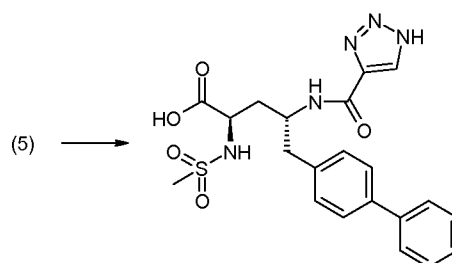
20

EXAMPLE 47: (2R,4R)-5-Biphenyl-4-yl-2-methanesulfonylamino-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 4 was prepared as described herein.



Compound 4 (10 mg, 25 μmol) was combined with DCM (2 mL), methanesulfonyl chloride (2.8 mg, 25 μmol) and Et_3N (3.4 μL , 25 μmol l). The mixture was stirred for 10 minutes and the solvent evaporated to yield Compound 5.

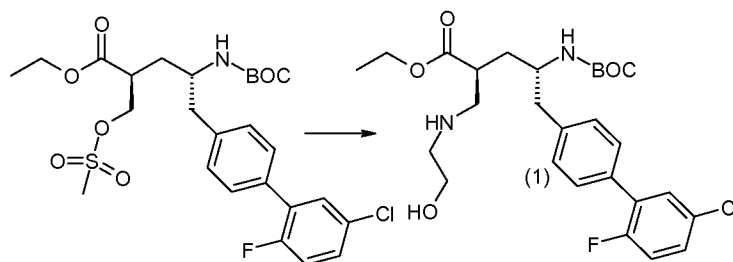


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Compound 5 (11.5 mg, 24 μmol) was dissolved in THF (1 mL) and 1N NaOH (119 μL , 119 μmol) and stirred for 3 hours. The reaction was quenched with AcOH and the solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{21}\text{H}_{23}\text{N}_5\text{O}_5\text{S}$, 458.14; found 458.

10

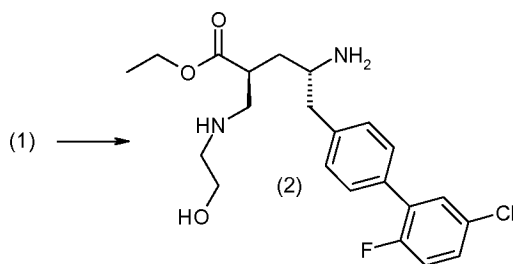
EXAMPLE 48: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2-hydroxyethylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (isomer a) and (isomer b) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2-hydroxyethylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (compound c)



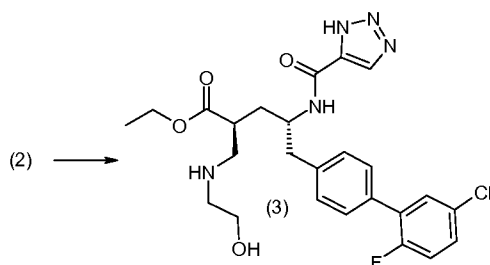
15

(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic acid ethyl ester (28 mg, 50 μmol) was combined with EtOH (2 mL), followed by Na_2CO_3 (16.0 mg, 151 μmol) and 2-aminoethanol (9.2 mg, 151 μmol) and stirred at 70°C overnight. EtOAc and water were added, the organic layer was

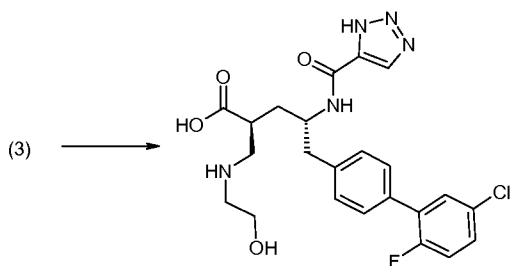
separated and concentrated under reduced pressure to yield Compound 1.



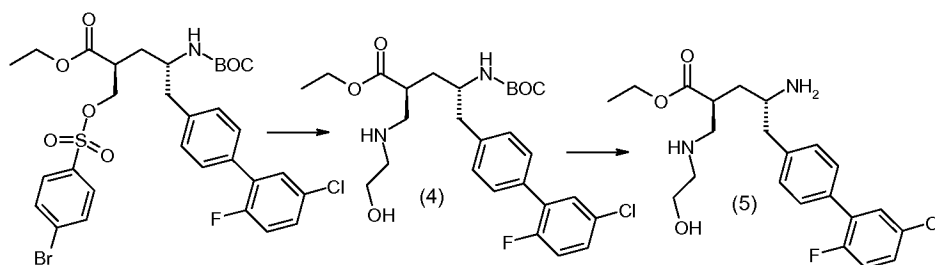
Compound 1 (25.7 mg, 49 μ mol) was dissolved in MeCN (0.5 mL) and dry 4N HCl in dioxane (0.1 mL). The mixture was stirred for 10 minutes and was then concentrated under reduced pressure. The residue was purified by reverse phase chromatography to yield Compound 2 (8 mg).



3H-1,2,3-triazole-5-carboxylic acid (1.1 mg, 10.0 μ mol) was combined with HATU (3.0 mg, 7.8 μ mol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1.0 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (4.7 mg, 11 μ mol) was dissolved in DMF (1 mL) and DIPEA (5.8 μ L, 33 mmol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes to yield crude Compound 3.

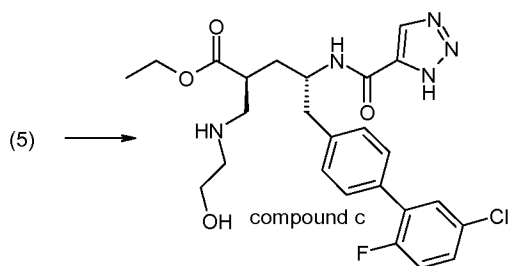


To the crude solution of Compound 3 (5.7 mg, 11 μ mol) was added 1N LiOH (55.1 μ L, 55 μ mol) and THF (0.5 mL). The mixture was stirred for 40 minutes and AcOH (1 mL) was added. The solution was purified by reverse phase chromatography to yield isomer a (MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}ClFN_5O_4$, 490.16; found 490) and isomer b (MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}ClFN_5O_4$, 490.16; found 490).



(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and 2-amino-ethanol (44 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H_2O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/ H_2O gradient) to yield Compound 4 (20 mg).

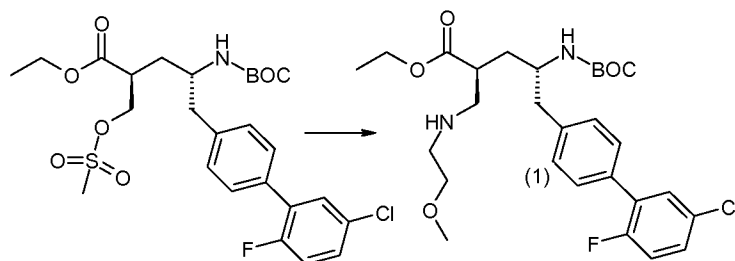
Compound 4 (26 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 5 as an HCl salt, which was used in the next step without purification.



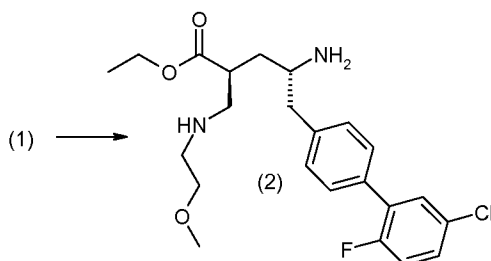
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 5 (9 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield the title compound c as a TFA salt (1 mg). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{29}\text{ClFN}_5\text{O}_4$, 518.19; found 518.

EXAMPLE 49: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2-methoxyethylamino)-methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (isomer a) and (isomer b) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2-methoxyethylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)-
amino]pentanoic Acid Ethyl Ester (compound c)

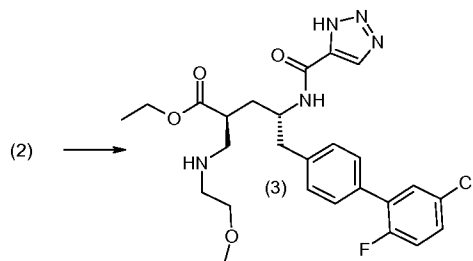
5



(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic acid ethyl ester (28 mg, 50 μ mol) was combined with EtOH (2 mL), followed by Na₂CO₃ (16.0 mg, 151 μ mol) and 2-methoxyethylamine (11.3
 10 mg, 151 μ mol) and stirred at room temperature overnight. EtOAc and water was added, the organic layer was separated and concentrated under reduced pressure to yield Compound 1.

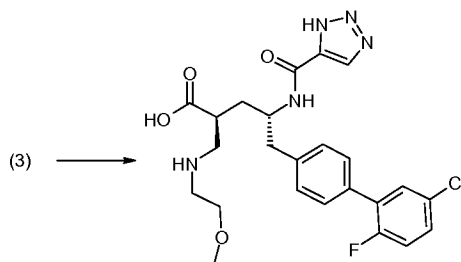


Compound 1 (26.4 mg, 49 μ mol) was dissolved in MeCN (0.5 mL) and dry 4N HCl
 15 in dioxane (0.1 mL). The mixture was stirred for 10 minutes and was then concentrated under reduced pressure. The residue was purified by reverse phase chromatography to yield Compound 2 (10 mg).



3H-1,2,3-triazole-5-carboxylic acid (1.1 mg, 10.0 μ mol) was combined with HATU

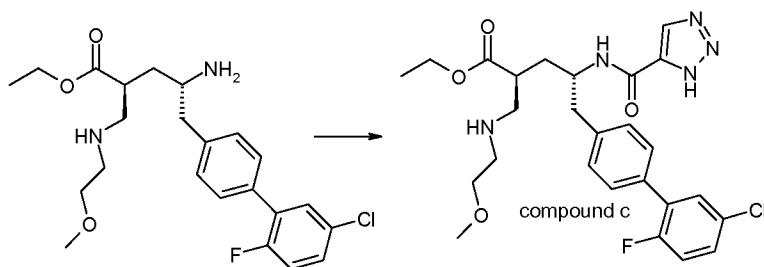
(3.0 mg, 7.8 μmol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1.0 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (4.9 mg, 11 μmol) was dissolved in DMF (1 mL) and DIPEA (5.8 μL , 33 mmol) was added, followed by addition of the activate acid solution. The mixture was stirred for 30 minutes to yield Compound 3.



5

To a solution of crude Compound 3 (5.9 mg, 11 μmol) was added 1N LiOH (55.1 μL , 55 μmol) and THF (0.5 mL). The mixture was stirred for 40 minutes and AcOH (1.0 mL) was added. The solution was purified by reverse phase chromatography to yield isomer a (MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{27}\text{ClFN}_5\text{O}_4$, 504.17; found 504) and isomer b (MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{27}\text{ClFN}_5\text{O}_4$, 504.17; found 504).

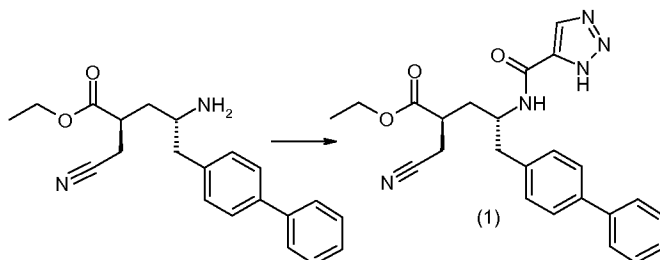
10



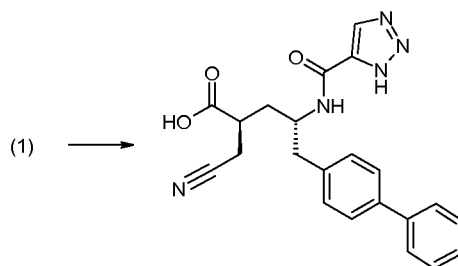
1H-1,2,3-triazole-4-carboxylic acid (2.6 mg, 23 μmol) and HATU (9.6 mg, 25 μmol) were combined in DMF (3.0 mL) and stirred at room temperature for 15 minutes. (2S,4S)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-[(2-methoxyethylamino)methyl]-pentanoic acid ethyl ester (10 mg, 23 μmol) and DIPEA (12 μL , 69 μmol) were added and the resulting solution was stirred at room temperature for 15 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield the title compound c as a TFA salt (1.2 mg). MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{26}\text{H}_{31}\text{ClFN}_5\text{O}_4$, 532.21; found 532.

15

EXAMPLE 50: (2*S*,4*S*)-5-Biphenyl-4-yl-2-cyanomethyl-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



(2*S*,4*S*)-4-Amino-5-biphenyl-4-yl-2-cyanomethylpentanoic acid ethyl ester (70 mg, 199 μ mol) was combined with DMF (1 mL), HATU (76 mg, 199 μ mol), DIPEA (104 μ L, 596 μ mol), and 3*H*-[1,2,3]triazole-4-carboxylic acid (22 mg, 199 μ mol) and the mixture was stirred at room temperature for 20 minutes. The solvent was evaporated and the crude mixture was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (60 mg).

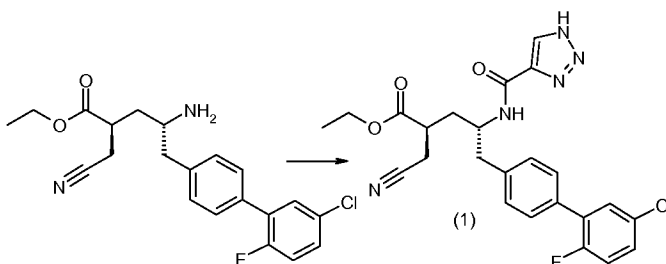


10

Compound 1 (28.9 mg, 67 μ mol) was dissolved in THF (1 mL) and 1*N* NaOH (268 μ L, 268 μ mol) and stirred at room temperature for 1 hour. The mixture was acidified with AcOH (1 mL) and purified by preparative HPLC to yield the title compound (19 mg; purity 90%) as a TFA salt. MS *m/z* $[M+H]^+$ calc'd for C₂₂H₂₁N₅O₃, 404.16; found 404.

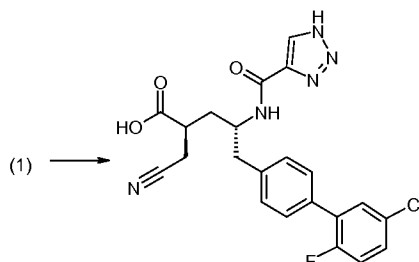
15

EXAMPLE 51: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



(2*S*,4*S*)-4-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethylpentanoic acid ethyl ester (55 mg, 141 μ mol) was combined with 3*H*-[1,2,3]triazole-4-carboxylic acid

(19.2 mg, 170 μ mol), HATU (64.5 mg, 170 μ mol) and DIPEA (79 μ L, 453 μ mol) in DMF (2 mL) and was stirred at room temperature for 30 minutes then concentrated *in vacuo* and the crude residue was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 55 mg).



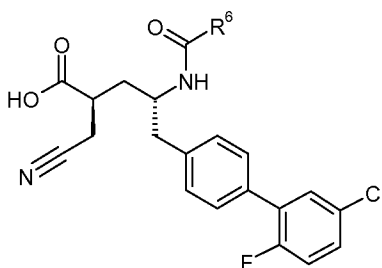
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Compound 1 (48.4 mg, 0.1 mmol) was dissolved in THF (2 mL) and 2N NaOH (250 μ L, 0.5 mmol) and stirred for 1 hour, then concentrated under reduced pressure. The crude residue was dissolved in AcOH (2 mL) was purified by reverse phase chromatography to yield the title compound (15 mg; purity 95%) as a TFA salt. MS *m/z*

10 $[M+H]^+$ calc'd for $C_{22}H_{19}ClFN_3O_3$, 456.12; found 455.

EXAMPLE 52

Following the procedures described herein, and substituting the appropriate starting materials and reagents, these compounds were prepared as the parent compound:



Ex.	R ⁶	Formula	MS <i>m/z</i> : $[M+H]^+$	
			calcd	found
1		$C_{24}H_{21}ClFN_3O_3S$	486.1	486.2
2		$C_{24}H_{21}ClFN_3O_3S$	486.1	486.2
3		$C_{23}H_{19}ClFN_3O_3S$	472.08	472.2

15

1. (*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(3-methylisothiazole-5-

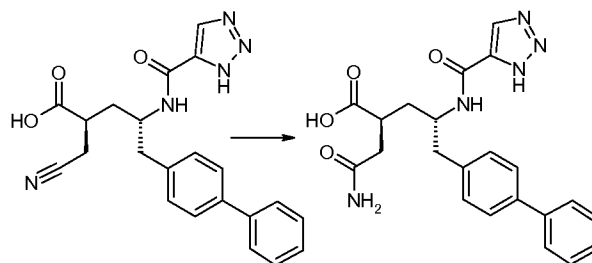
carbonyl)amino]pentanoic acid (diastereomer 1)

2. (*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(3-methylisothiazole-5-carbonyl)amino]pentanoic acid (diastereomer 2)

3. (*2S,4S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(isothiazole-4-

5 carbonyl)amino]pentanoic acid

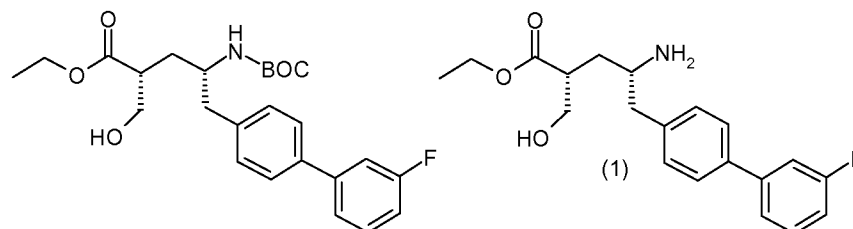
EXAMPLE 53: (*2S,4S*)-5-Biphenyl-4-yl-2-carbamoylmethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



(*2S,4S*)-5-Biphenyl-4-yl-2-cyanomethyl-4-[(3H-[1,2,3]triazole-4-

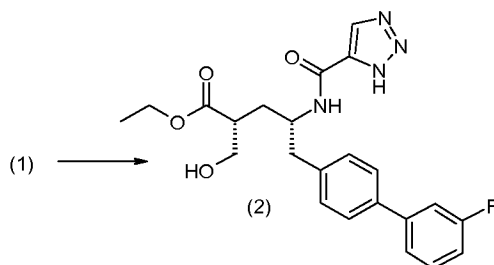
10 carbonyl)amino]pentanoic acid (5 mg, 12 μ mol) was combined with DMSO (0.5 mL), H_2O_2 (54.4 μ L, 533 μ mol) and K_2CO_3 (15.4 mg, 112 μ mol), and stirred overnight,. The reaction was quenched with 1 drop of concentrated HCl. AcOH was added and the mixture was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}N_5O_4$, 422.18; found 422.

15 EXAMPLE 54: (*2R,4S*)-2-Carbamoylmethyl-5-(3'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

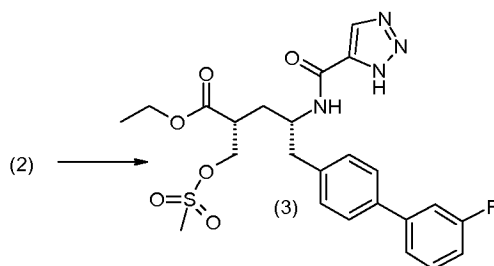


(*2R,4S*)-4-*t*-butoxycarbonylamino-5-(3'-fluorobiphenyl-4-yl)-2-

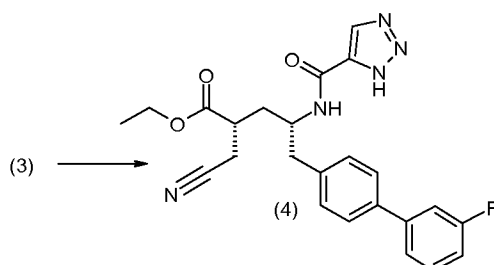
20 hydroxymethylpentanoic acid ethyl ester (985 mg, 2.2 mmol) was dissolved in MeCN (10 mL) and 4N HCl in dioxane (5 mL) and stirred for 15 minutes, then concentrated under reduced pressure to yield Compound 1.



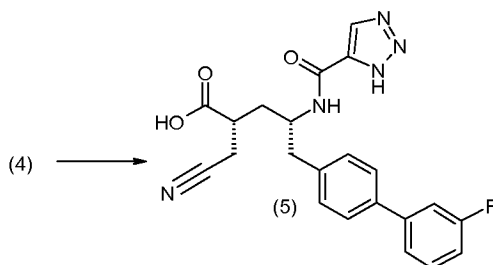
Compound 1 (500 mg, 1.4 mmol) was combined with HATU (656 mg, 1.7 mmol), 3H-[1,2,3]triazole-4-carboxylic acid (195 mg, 1.7 mmol) and DMF (3 mL). DIPEA (803 μ L, 4.6 mmol) was added and the mixture was stirred for 30 minutes. Saturated aqueous
 5 NH_4Cl (10 mL) and EtOAc (40 mL) were added. The organic layer was separated and dried over MgSO_4 . The solvent was evaporated and the residue purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 2 (650 mg).



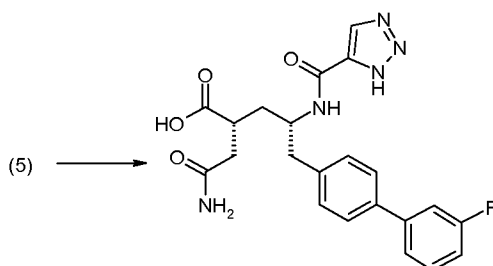
Compound 2 (650 mg, 1.5 mmol) was dissolved in DCM (3 mL). Methanesulfonyl
 10 chloride (173 μ L, 2.2 mmol) was added at 0°C , followed by the slow addition of Et_3N (425 μ L, 3.0 mmol). The mixture was stirred for 10 minutes and the solution was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 3 (690 mg).



Compound 3 (390 mg, 752 μ mol) was dissolved in DMF (2 mL). Sodium cyanide
 15 (47.9 mg, 978 μ mol) and DMAP (3 mg) was added and the mixture was stirred at 50°C overnight. EtOAc (5 mL) and water (2 mL) were added, the organics were separated and washed (3x) with water, then concentrated under reduced pressure. The crude residue was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 4 (90 mg).



Compound 4 (90 mg, 0.2 mmol) was dissolved in THF (1 mL) and 2N NaOH (160 μ L, 0.8 mmol). The mixture was stirred for 2 hours. AcOH (2 mL) was added and the solution was purified by reverse phase chromatography to yield Compound 5 (35 mg).



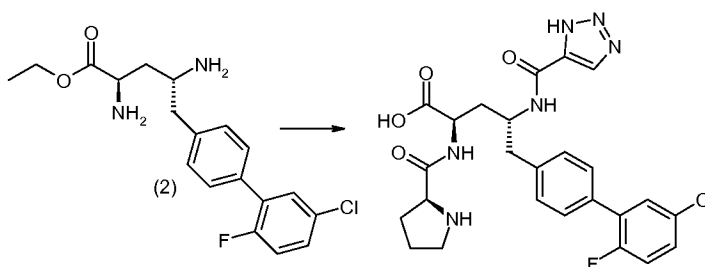
5

Compound 5 (8 mg, 19 μ mol) was combined with DMSO (0.5 mL), H_2O_2 (83 μ L, 816 μ mol) and K_2CO_3 (23.6 mg, 171 μ mol), and stirred overnight,. The reaction was quenched with 1 drop of concentrated HCl. AcOH was added and the mixture was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA

10 salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{22}\text{H}_{22}\text{FN}_5\text{O}_4$, 440.17; found 441.

EXAMPLE 55: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(S)-pyrrolidine-2-carbonyl]amino]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 2 was prepared as described herein.



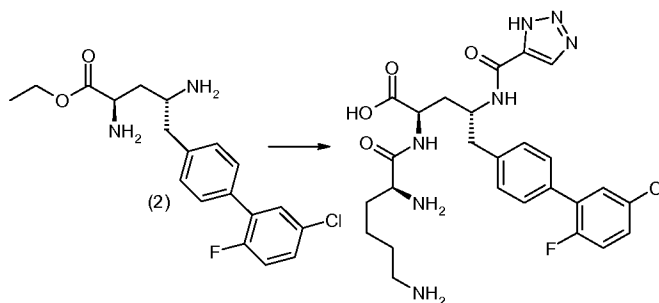
15

(S)-Pyrrolidine-2-carboxylic acid (3.6 mg, 31 μ mol) and HATU (11.4 mg, 30 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. Compound 2 (12.3 mg, 28 μ mol) and DIPEA (15 μ L, 85 μ mol) were added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed the desired

product) then concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (4 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{26}ClFN_6O_4$, 529.17; found 530.0.

EXAMPLE 56: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-
2-((S)-2,6-diaminohexanoylamino)-4-[(3H-[1,2,3]triazole-
4-carbonyl)amino]pentanoic Acid

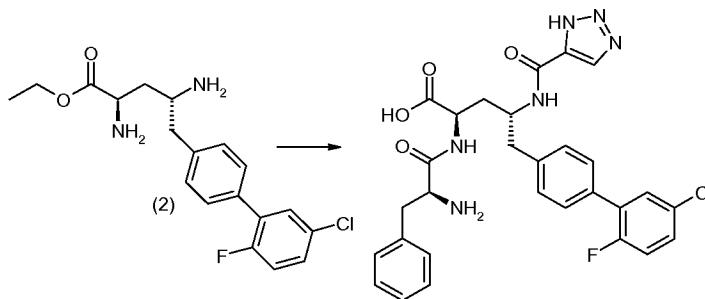
Compound 2 was prepared as described herein.



(S)-2,6-Bis-*t*-butoxycarbonylamino hexanoic acid (10.9 mg, 31 μ mol) and HATU (11.4 mg, 30 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. Compound 2 (12.3 mg, 28 μ mol) and DIPEA (15 μ L, 85 μ mol) were added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed the desired product) then concentrated *in vacuo* and the residue was dissolved in MeCN (3 mL). A solution of 4N HCl in dioxane (107 mL, 427 μ mol) was added, and the mixture was stirred for 15 minutes at room temperature. LC/MS showed the desired mass. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (7.8 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{31}ClFN_7O_4$, 560.21; found 560.2.

EXAMPLE 57: (2R,4R)-2-((S)-2-Amino-3-phenylpropionylamino)-
5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid

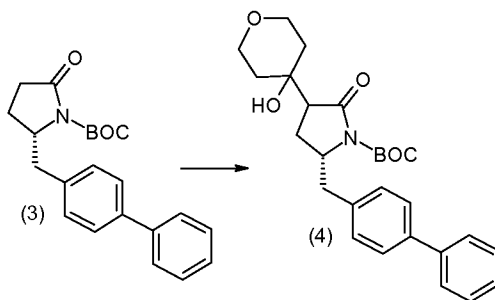
Compound 2 was prepared as described herein.



(*S*)-2-*t*-Butoxycarbonylamino-3-phenylpropionic acid (8.3 mg, 31 μ mol) and HATU (11.4 mg, 30 μ mol) were dissolved in DMF (3 mL) and stirred for 15 minutes at room temperature. Compound 2 (12.3 mg, 28 μ mol) and DIPEA (15 μ L, 85 μ mol) were added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed the
 5 desired product) then concentrated *in vacuo* and the residue was dissolved in MeCN (3 mL). A solution of 4N HCl in dioxane (107 mL, 427 μ mol) was added, and the mixture was stirred for 15 minutes at room temperature. LC/MS showed the desired mass. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (5.5 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for
 10 $C_{29}H_{28}ClFN_6O_4$, 579.18; found 579.2.

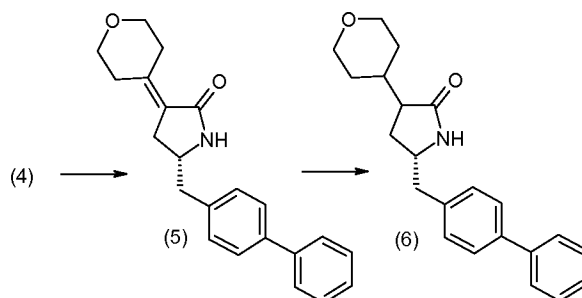
EXAMPLE 58: (*S*)-5-Biphenyl-4-yl-2-(tetrahydropyran-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 3 was prepared as described herein.



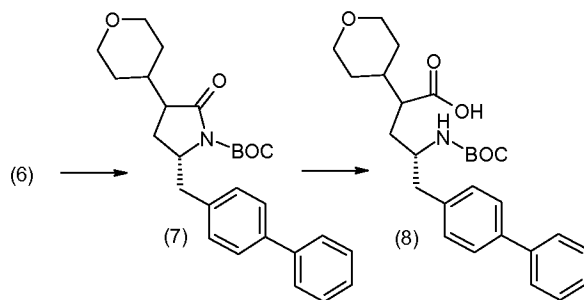
Compound 3 (80 mg, 230 μ mol, 1.0 eq.) was dissolved in dry THF (1.5 mL). The
 15 resulting solution was cooled to -78°C , then LDA (1.8 M, 157 μ L, 290 μ mol, 1.3 eq.) was added dropwise and the resulting solution was stirred at -78°C for 20 minutes. A solution of tetrahydropyran-4-one (25 mg, 280 μ mol, 1.2 eq.) in THF (100 μ L) was added dropwise, and the resulting mixture was stirred at -78°C for 30 minutes. LC/MS analysis
 20 revealed a mixture of starting material and desired product. LDA (1.8M, 100 μ L, 180 μ mol, 0.8 eq.) was added and the mixture was stirred for 20 minutes at -78°C , then tetrahydropyran-4-one (20 mg, 220 μ mol, 1.0 eq.) was added and the mixture was stirred for an additional 20 minutes at -78°C and when the reaction was complete (as determined by LC/MS analysis), the mixture was warmed to -40°C and the reaction was quenched with
 25 10% citric acid (10 mL), then extracted with EtOAc (2x10 mL). The aqueous phase was discarded and the combined organics were dried over Na_2SO_4 , filtered and concentrated *in vacuo*, then purified by flash chromatography (0-60% EtOAc/hexanes, 40 minutes) to yield Compound 4 (100 mg). LCMS (ESI): calc. $C_{27}H_{33}NO_5$ = 451; obs. $M+H^+$ = 452.2.

Retention time: 6.05 min.



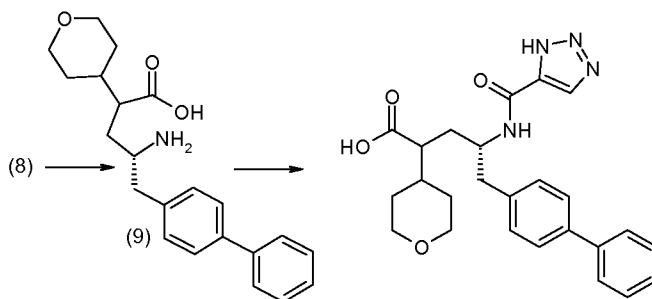
Compound 4 (100 mg, 220 μmol , 1.0 eq.) was dissolved in 50% (v/v) sulfuric acid/ H_2O (10 mL) and heated to 105°C for 30 minutes. LC/MS analysis after 30 minutes revealed ~50% of the desired product. The mixture was heated at 105°C for 1.5 hours, cooled to room temperature, and poured onto ice. The pH was adjusted to ~6 with 4M NaOH and the resulting mixture was extracted with DCM (3x75 mL). The aqueous phase was discarded and the combined organics were washed with saturated aqueous NaCl (50 mL). The aqueous phase was discarded and the organic phase was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*, then purified by flash chromatography 0-60% EtOAc/hexanes, 40 minutes) to yield Compound 5 (100 mg; quantitative). LCMS (ESI): calc. $\text{C}_{22}\text{H}_{23}\text{NO}_2 = 333$; obs. $\text{M}+\text{H}^+ = 334.3$. Retention time: 5.23 min.

Compound 5 (100 mg, 220 μmol , 1.0 eq.) was dissolved in MeOH (10 mL). Palladium on carbon (20 mg, 10% w/w) and AcOH (100 μL) were added and the mixture was stirred under 1 atm. of hydrogen overnight. LC/MS analysis revealed a mixture of starting material and desired product. The mixture was filtered through Celite[®]. The Celite[®] was then washed with MeOH (2x20 mL) and the combined solutions were concentrated and re-dissolved in MeOH (10 mL). Palladium on carbon (10 mg, 10% w/w) was added and the mixture was hydrogenated on a Parr apparatus at 40 psi hydrogen. LC/MS analysis revealed a mixture of starting material and desired product. AcOH (300 μL) was added and the hydrogen pressure was increased to 60 psi and when the reaction was complete (as determined by LC/MS analysis), the mixture was filtered through Celite[®], and the Celite[®] was then washed with MeOH (2x20 mL). The combined organics were concentrated *in vacuo* to yield Compound 6 (40 mg). LCMS (ESI): calc. $\text{C}_{22}\text{H}_{25}\text{NO}_2 = 335$; obs. $\text{M}+\text{H}^+ = 336.2$. Retention time: 5.23 min.



Compound 6 (40 mg, 120 μ mol, 1 eq.) and (BOC)₂O (57 mg, 280 μ mol, 2.3 eq.) were dissolved in dry THF (2 mL) and cooled to -40°C for ten minutes. NaHMDS (1.0 M, 260 μ L, 2.2 eq.) was added and the mixture was stirred for 20 minutes at -40°C and when the reaction was complete (as determined by LC/MS analysis), the mixture was warmed to room temperature and the reaction was quenched with a few drops of water, then concentrated *in vacuo* to yield Compound 7, which was used directly in the next step. LCMS (ESI): calc. C₂₇H₃₃NO₄ = 435; obs. M+H = 436.1. Retention time: 6.87 min.

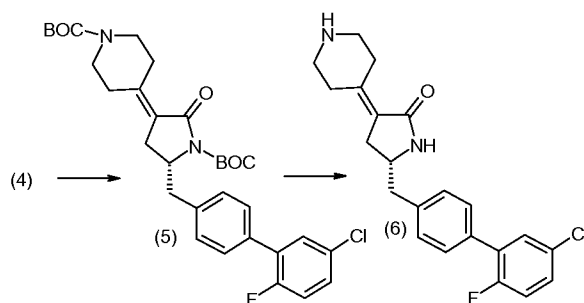
Compound 7 was dissolved in a mixture of THF (2 mL) and 4N NaOH (0.5 mL) and stirred at room temperature for three days and when the reaction was complete (as determined by LC/MS analysis), the mixture was acidified with 5% HCl (5 mL) and extracted with EtOAc (2x10 mL). The aqueous phase was discarded and the combined organics were dried over Na₂SO₄ and purified by preparative HPLC to yield Compound 8 (17 mg). LCMS (ESI): calc. C₂₇H₃₅NO₅ = 453; obs. M+H⁺ = 454.3. Retention time: 5.36 min.



Compound 8 (17 mg, 46 μ mol, 1.0 eq.) was dissolved in 4M HCl/*p*-dioxane (2 mL) and stirred at room temperature for one hour and when the reaction was complete (as determined by LC/MS analysis), the mixture was concentrated to dryness to yield Compound 9 (17 mg; quantitative) as a TFA salt. LCMS (ESI): calc. C₂₂H₂₇NO₃ = 353; obs. M+H⁺ = 354.4. Retention time: 3.79 min.

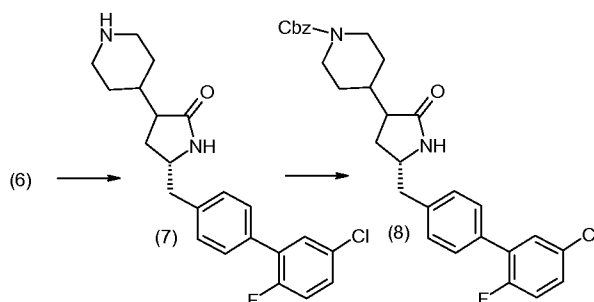
Compound 9 (17 mg, 46 μ mol, 1.0 eq.) was dissolved in a solution of DIPEA (29 μ L, 170 μ mol, 4.0 eq.) in DMF (350 μ L). A solution of 1H-1,2,3-triazole-4-carboxylic

and evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 4 (250 mg). LC-MS (ESI): calc. $C_{32}H_{40}ClFN_2O_6 = 603.1$; obs. m/z 603.2 $[M+H]^+$. Retention time 7.39 min.



5 To a solution of Compound 4 (260 mg, 215 μ mol) and Et_3N (338 μ L, 2.3 mmol) in DCM (710 μ L) was added methylsilyl chloride (193 μ L, 2.3 mmol) dropwise at room temperature under a stream of nitrogen. The mixture was stirred at room temperature for 5 minutes, then the reaction was quenched with 2% aqueous HCl and extracted with EtOAc (3x30 mL), washed with saturated aqueous NaCl (20 mL), and dried over $MgSO_4$. The
10 mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (0-30% hexanes/EtOAc gradient over 55 minutes). The fractions containing the desired product were combined and evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 5 (210 mg). LC-MS (ESI): calc. $C_{32}H_{38}ClFN_2O_5 = 585.1$; obs. m/z 585.2 $[M+H]^+$. Retention time 7.86 min.

15 Compound 5 (210 mg, 360 μ mol) was dissolved in 4N HCl/dioxane (8 mL, 32 mmol) and stirred for 20 minutes at room temperature. The solvent was evaporated and the residue was dried *in vacuo* at room temperature overnight to yield Compound 6 as the HCl salt (150 mg). LC-MS (ESI): calc. $C_{22}H_{22}ClFN_2O = 384.9$; obs. m/z 385.2 $[M+H]^+$. Retention time 2.71 min.

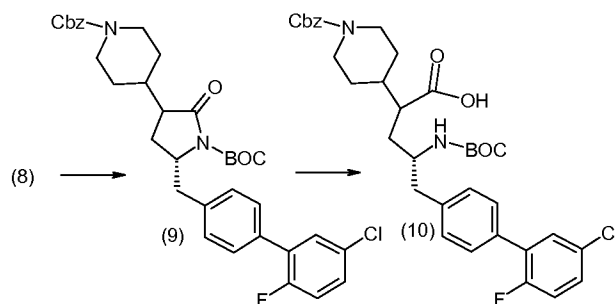


20

To a solution of Compound 6 (150 mg, 328 μ mol) in a mixture of isopropanol/MeOH (27 mL/3 mL), was added AcOH (19 μ L, 328 μ mol) and palladium on carbon (10%, 90 mg). The mixture was subjected to hydrogenation (H_2 , Parr apparatus, 60

psi) at room temperature for 2 hours. The mixture was filtered through Celite[®] and evaporated. The residue was dried *in vacuo* at room temperature for 4 hours to yield Compound 7 (146 mg). LC-MS (ESI): calc. $C_{22}H_{24}ClFN_2O = 386.9$; obs. m/z 387.1 $[M+H]^+$. Retention time 4.34 min.

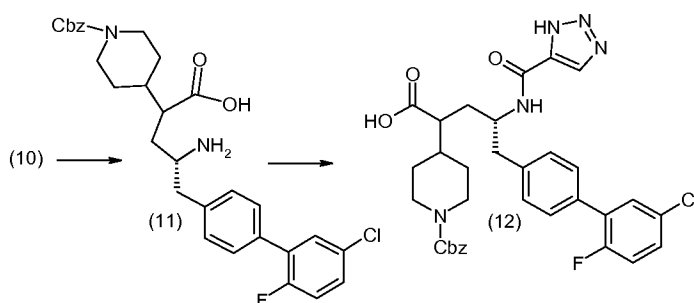
- 5 A solution of Compound 7 (146 mg, 318 μ mol) and Et_3N (90 μ L, 637 μ mol) in DCM (1.5 mL) was cooled to 4°C, followed by the dropwise addition of benzyl chloroformate (45 μ L, 318 μ mol). The mixture was stirred at 4°C for 20 minutes, then the reaction was quenched with 5% aqueous $NaHCO_3$ (10 mL). The mixture was extracted with DCM (2x10 mL), and the organic layer was washed with saturated aqueous $NaCl$ (20 mL) and dried over $MgSO_4$. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (0-50% hexanes/ $EtOAc$ gradient over 45 minutes). The fractions containing the desired product were combined and evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 8 (120 mg). LC-MS (ESI): calc. $C_{30}H_{30}ClFN_2O_3 = 521.0$; obs. m/z 521.1 $[M+H]^+$. Retention time 6.70 min.



- A solution of Compound 8 (120 mg, 230 μ mol), Boc_2O (125 mg, 576 μ mol) in THF (1.1 mL) was cooled to -40°C, followed by the dropwise addition of a 1M THF solution of $NaHMDS$ (576 μ L, 576 μ mol). The mixture was stirred at -40°C for 10 minutes, before being warmed to room temperature and the reaction was quenched with 5% aqueous $NaHCO_3$ (10 mL). The mixture was extracted with $EtOAc$ (2x25 mL), washed with saturated aqueous $NaCl$ (20 mL), and dried over $MgSO_4$. The mixture was filtered and the filtrate was evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 9 (156 mg). LC-MS (ESI): calc. $C_{35}H_{38}ClFN_2O_5 = 621.1$; obs. m/z 621.3 $[M+H]^+$. Retention time 7.93 min.

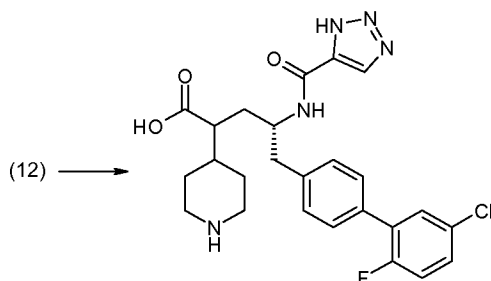
To a solution of Compound 9 (150 mg, 230 μ mol) in a mixture of THF/water (2.5 mL/0.5 mL) was added $NaOH$ (40 mg, 1 mmol) and H_2O_2 (60 μ L, 530 μ mol) at room temperature. The mixture was stirred at room temperature overnight, followed by the

- addition of 5% aqueous HCl to take the pH of the solution to 3. The mixture was extracted with EtOAc (2x20 mL), washed with saturated aqueous NaCl (10 mL), and dried over MgSO₄. The mixture was filtered and the filtrate was evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 10 (133 mg). LC-MS (ESI):
- 5 calc. C₃₅H₄₀ClFN₂O₆ = 639.2; obs. m/z 639.3 [M+H]⁺. Retention time 7.01 min.



- Compound 10 (133 mg, 210 μmol) was dissolved in 4N HCl/dioxane (5 mL, 20 mmol) and stirred for 20 minutes at room temperature. The solvent was evaporated and the residue was dried *in vacuo* at room temperature overnight to yield Compound 11 as the
- 10 hydrochloric salt (140 mg). LC-MS (ESI): calc. C₃₀H₃₂ClFN₂O₄ = 539.1; obs. m/z 539.2 [M+H]⁺. Retention time 5.14 min.

- To a solution of 3H-[1,2,3]triazole-4-carboxylic acid (77 mg, 688 μmol) and HATU (130 mg, 344 μmol) in DMF (1.5 mL) was added DIPEA (160 μL, 920 μmol). The mixture was stirred at room temperature for 20 minutes, followed by the addition of
- 15 Compound 11 (140 mg, 210 μmol). The mixture was stirred at room temperature for 20 minutes, then the reaction was quenched with 10% aqueous citric acid (15 mL) to pH 4. The mixture was extracted with EtOAc (3x20 mL), washed with saturated aqueous NaCl (10 mL) and dried over MgSO₄. The mixture was filtered and the filtrate was evaporated. The residue was purified by flash chromatography (10-100% hexanes/EtOAc gradient over
- 20 45 minutes). The fractions containing the desired product were combined and evaporated. The residue was dried *in vacuo* at room temperature overnight to yield Compound 12 (70 mg). LC-MS (ESI): calc. C₃₃H₃₃ClFN₅O₅ = 634.1; obs. m/z 634.2[M+H]⁺. Retention time 5.96 min.

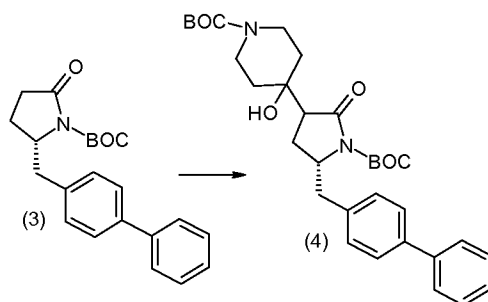


To a solution of Compound 12 (70 mg, 110 μmol) in dioxane (1 mL) was added 6N aqueous HCl (2 mL, 12 mmol) under a stream of nitrogen. The mixture was stirred at 100°C for 20 minutes, then cooled to room temperature. The solvent was evaporated and the residue was purified (preparative LCMS). The fractions containing desired compound were combined and lyophilized to yield the title compound (29 mg, 53%; purity by LC-MS 95.7%) as a TFA salt. LC-MS (ESI): calc. $\text{C}_{25}\text{H}_{27}\text{ClFN}_5\text{O}_3 = 500.0$; obs. m/z 500.2 $[\text{M}+\text{H}]^+$. Retention time 1.75 min.

EXAMPLE 60: (S)-2-(1-Acetylpiperidin-4-yl)-5-biphenyl-4-yl-4-

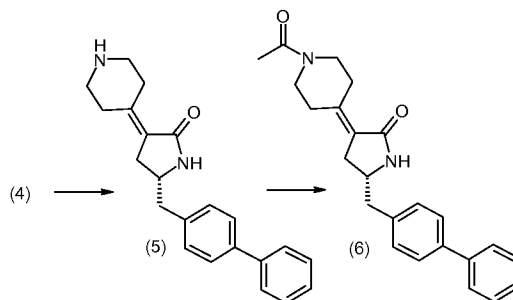
[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 3 was prepared as described herein.



Compound 3 (450 mg, 1280 μmol , 1.0 eq.) was dissolved in dry THF (4.2 mL). The resulting solution was cooled to -78°C, then LDA (1.8 M, 990 μL , 1790 μmol , 1.4 eq.) was added dropwise and the resulting solution was stirred at -78°C for 30 minutes. A solution of N-*t*-butoxycarbonyl-4-piperidone (356 mg, 1790 μmol , 1.4 eq.) in THF (500 μL) was added dropwise. The resulting mixture was stirred at -78°C for 20 minutes. LC/MS analysis revealed a mixture of starting material and desired product. LDA (1.8 M, 400 μL , 720 μmol , 0.6 eq.) was added and the mixture was stirred for 20 minutes at -78°C, then a solution of N-*t*-butoxycarbonyl-4-piperidone (190 mg, 960 μmol , 0.7 eq.) in THF (200 μL) was added and the resulting mixture stirred at -78°C for one hour and when the reaction was complete (as determined by LC/MS analysis), the mixture was then warmed to -50°C and the reaction was quenched with 10% citric acid (10 mL) then extracted with

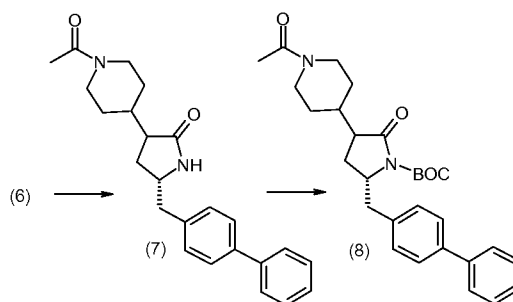
EtOAc (2x25 mL). The aqueous phase was discarded and the combined organics were dried over Na_2SO_4 , concentrated *in vacuo*, and purified by flash chromatography (0-80% EtOAc/hexanes) to yield Compound 4 (600 mg). LCMS (ESI): calc. $\text{C}_{32}\text{H}_{42}\text{N}_2\text{O}_6 = 550$; obs. $[\text{M}+\text{H}]^+ = 551.2$. Retention time: 7.06 min.



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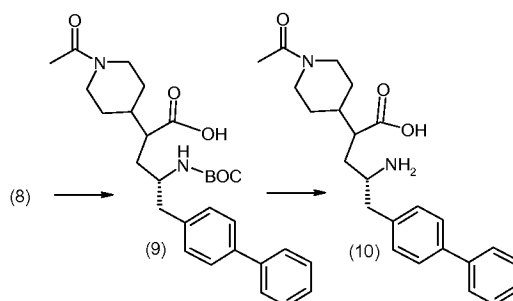
Compound 4 (300 mg, 544 μmol , 1.0 eq.) was dissolved in a mixture of MeCN (2 mL) and 50% (v/v) aqueous H_2SO_4 (16 mL) and heated to 130°C for two hours and when the reaction was complete (as determined by LC/MS analysis), the mixture was cooled to room temperature, poured onto ice, and the pH was adjusted to ~ 7 with 4M NaOH and the resulting mixture was extracted with DCM (3x50 mL) and chloroform (3x50 mL). The aqueous phase was discarded and the combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo* to yield Compound 5 (60 mg). LCMS (ESI): calc. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O} = 332$; obs. $[\text{M}+\text{H}]^+ = 333.3$. Retention time: 3.98 min.

Compound 5 (60 mg, 180 μmol , 1 eq.) was dissolved in DCM (3 mL). Et_3N (50 μL , 360 μmol 2.0 eq.) was added, followed by acetic anhydride (28 μL , 270 μmol , 1.5 eq.). The mixture was stirred for 20 minutes at room temperature and when the reaction was complete (as determined by LC/MS analysis), the mixture was diluted with DCM (10 mL) and saturated aqueous NaHCO_3 (2 mL). The phases were separated and the aqueous phase was extracted with DCM (10 mL). The aqueous phase was then discarded and the combined organics were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*, and purified by preparative HPLC (30-60% $\text{H}_2\text{O}/\text{MeCN}$ with 0.1% TFA, 30 mL/minute, 30 minutes) to yield Compound 6 (28 mg). LCMS (ESI): calc. $\text{C}_{24}\text{H}_{26}\text{N}_2\text{O}_2 = 374$; obs. $[\text{M}+\text{H}]^+ = 375.2$. Retention time: 4.85 min.



Compound 6 (28 mg, 150 μ mol, 1.0 eq.) was dissolved in MeOH (5 mL). Palladium on carbon (10 mg, 10% w/w) and AcOH (25 μ L) were added and the mixture was stirred under 1 atm. of hydrogen overnight and when the reaction was complete (as determined by LC/MS analysis), the mixture filtered through Celite[®] with MeOH (20 mL) and concentrated to yield crude Compound 7 (32 mg; quantitative). LCMS (ESI): calc. $C_{24}H_{28}N_2O_2 = 376$; obs. $[M+H]^+ = 377.4$. Retention time: 4.78 min.

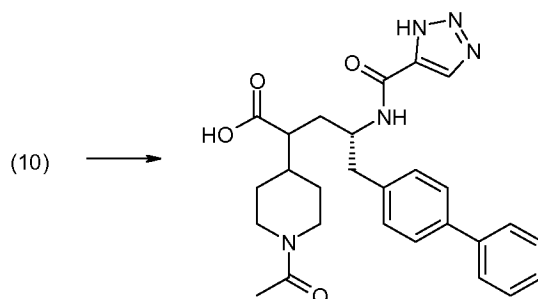
Compound 7 (32 mg, 85 μ mol, 1.0 eq.) was dissolved in dry THF (2 mL) at -40°C , followed by $(\text{BOC})_2\text{O}$ (37 mg, 170 μ mol, 2.0 eq.). The mixture was stirred for ten minutes then NaHMDS (1.0M, 170 μ L, 170 μ mol, 2.0 eq.) was added and the mixture was stirred at -40°C for 20 minutes and when the reaction was complete (as determined by LC/MS analysis), the mixture was warmed to room temperature, the reaction quenched with water (50 μ L), and the mixture concentrated to dryness to yield crude Compound 8, which was used directly in the next step. LCMS (ESI): calc. $C_{29}H_{36}N_2O_4 = 476$; obs. $[M+H]^+ = 477.3$. Retention time: 6.15 min.



Compound 8 was dissolved in a mixture of THF (2 mL) and 4N NaOH (2 mL) and stirred at room temperature for two hours. Additional THF (1 mL) was added and the mixture was stirred at room temperature overnight and when the reaction was complete (as determined by LC/MS analysis), the pH was adjusted to 4 with 5% aqueous HCl and the mixture extracted with EtOAc (2x20 mL). The aqueous phase was discarded and the combined organics were extracted with saturated aqueous NaCl (5 mL). The aqueous phase was discarded and the organic phase was dried over Na_2SO_4 , filtered, and

concentrated to dryness to yield Compound 9 (32 mg), which was used without purification in the next step. LCMS (ESI): calc. $C_{29}H_{38}N_2O_5 = 494$; obs. $[M+H]^+ = 495.1$. Retention time: 5.39 min.

Compound 9 (32 mg, 85 μ mol, 1.0 eq.) was dissolved in 4N HCl in *p*-dioxane (1.2 mL) and stirred at room temperature for 20 minutes and when the reaction was complete (as determined by LC/MS analysis), the solution was concentrated to dryness to yield Compound 10 as the hydrochloride salt (32 mg). LCMS (ESI): calc. $C_{24}H_{30}N_2O_3 = 394$; obs. $M+H = 395.2$. Retention time: 3.64 min.

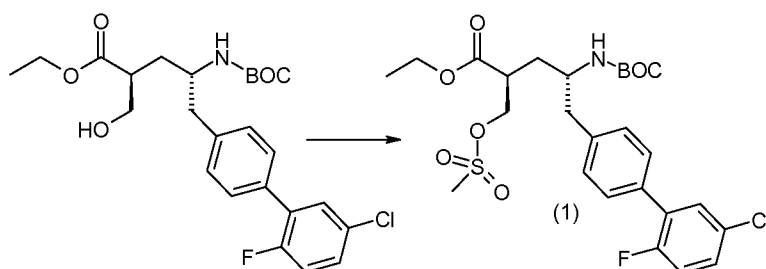


Compound 10 (32 mg, 75 μ mol, 1.0 eq.) was dissolved in DMF (500 μ L). 1H-1, 2, 3-triazole-4-carboxylic acid (25 mg, 221 μ mol, 3.0 eq.) was dissolved in DMF (500 μ L), followed by the addition of DIPEA (51 μ L, 297 μ mol, 4.0 eq.) and HATU (42 mg, 111 μ mol, 1.5 eq.). The solutions were stirred at room temperature for 20 minutes, then combined and stirred at room temperature for an additional 20 minutes and when the reaction was complete (as determined by LC/MS analysis), the mixture was diluted with water (0.5 mL), the pH adjusted to 4 with 10% citric acid, then washed with EtOAc (2x20 mL). The aqueous phase was discarded and the combined organics were extracted with saturated aqueous NaCl (10 mL). The aqueous phase was discarded and the organic phase was dried over Na_2SO_4 , filtered, and concentrated *in vacuo*, and purified by preparative HPLC to yield the title compound (11 mg; purity 99.6%). LCMS (ESI): calc. $C_{27}H_{31}N_5O_4 = 489$; obs. $M+H = 490.2$. Retention time: 4.23 min.

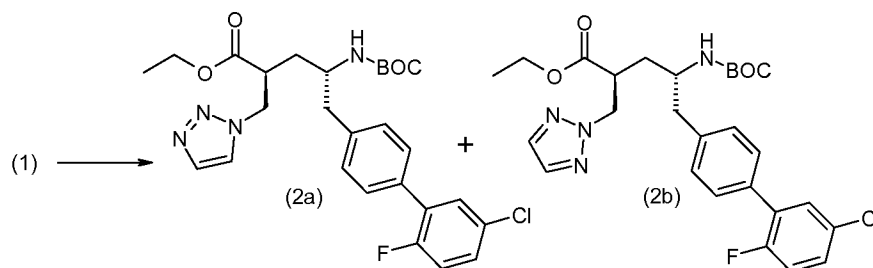
LC/MS Method: flow rate: 1.5 mL/min; Buffer A: 0.1% TFA/ H_2O ; Buffer B 0.1% TFA/MeCN; gradient elution from 5%-100% B over 9.6 min, then 100% B for 1.0 minute, detection at 254 nm.

EXAMPLE 61: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]-2-[1,2,3]triazol-1-ylmethylpentanoic
Acid (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-4-[(3*H*[1,2,3]triazole-4-carbonyl)amino]-2-[1,2,3]triazol-2-
ylmethylpentanoic Acid (Compound b)

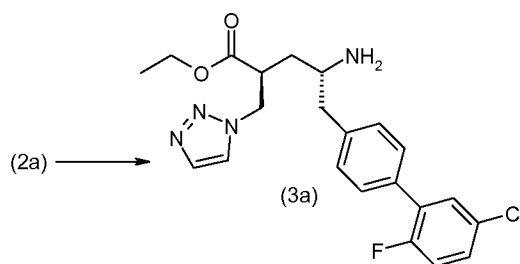
5



(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (200 mg, 417 μ mol) was dissolved in DCM (5 mL). Methanesulfonyl chloride (39 μ L, 0.5 mmol) and Et₃N (116 μ L, 833 μ mol) were added. The mixture was stirred for 10 minutes and the solution was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 1 (198 mg).

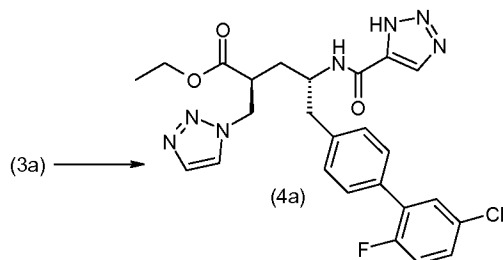


Compound 1 (25 mg, 45 μ mol) was combined with K₂CO₃ (12.4 mg, 90 μ mol), 1,2,3-triazole (4.3 mg, 63 μ mol), and DMF (0.5 mL), and the mixture was stirred overnight. The mixture was concentrated under reduced pressure and the residue was purified by normal phase chromatography (0-100% EtOAc/hexanes), to yield Compounds 2a (8 mg) and 2b (7 mg).

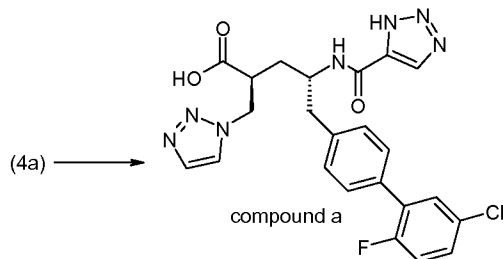


Compound 2a (8 mg, 15 μ mol) was dissolved in MeCN (0.3 mL) and 4N HCl in

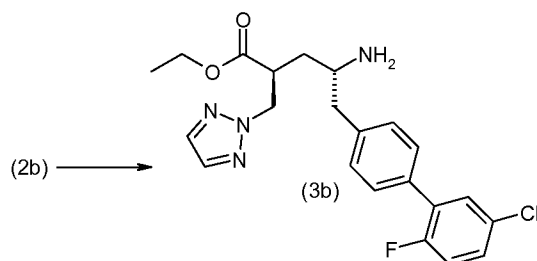
dioxane (0.3 mL). The mixture was stirred for 10 minutes and concentrated under reduced pressure to yield Compound 3a as an HCl salt.



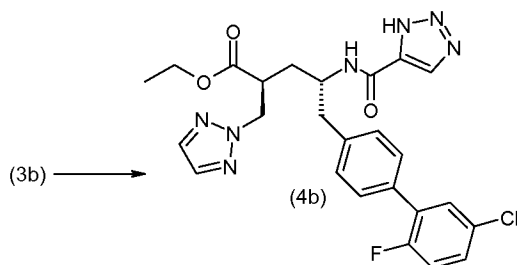
Compound 3a (7.0 mg, 16 μ mol) was combined with DMF (0.5 mL), 1H-1,2,3-triazole-5-carboxylic acid (2.0 mg, 18 μ mol), HATU (6.8 mg, 18 μ mol) and DIPEA (8.5 μ L, 49 μ mol). The mixture was stirred for 30 minutes after which time LCMS showed the desired product formation. The solution was concentrated *in vacuo* to yield Compound 4a which was used directly in the next step.



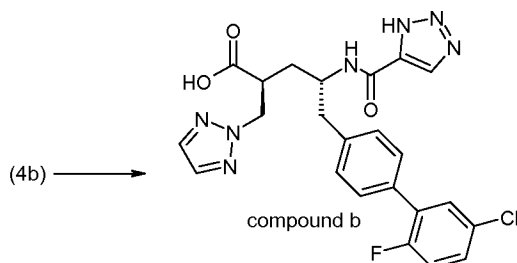
Compound 4a (8.0 mg, 15 μ mol) was dissolved in THF (0.5 mL) and 1N NaOH (76 μ L, 76 μ mol) and stirred for 2 hours. AcOH (1 mL) was added and the mixture was purified by reverse phase chromatography to yield the title compound (Compound a; 2 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{21}ClFN_7O_3$, 498.14; found 498.



Compound 2b (7 mg, 13 μ mol) was dissolved in MeCN (0.3 mL) and 4N HCl in dioxane (0.3 mL). The mixture was stirred for 10 minutes and concentrated under reduced pressure to yield Compound 3b as an HCl salt.



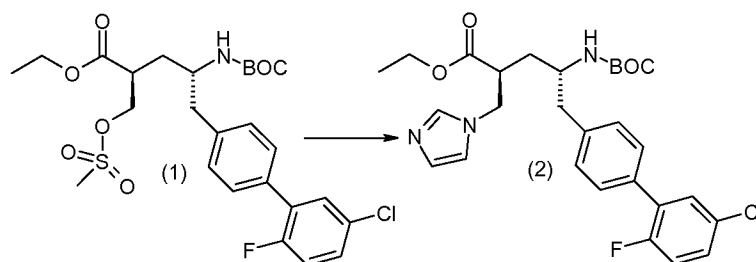
Compound 3b (7.0 mg, 16 μ mol) was combined with DMF (0.5 mL), 1H-1,2,3-triazole-5-carboxylic acid (2.0 mg, 18 μ mol), HATU (6.8 mg, 18 μ mol) and DIPEA (8.5 μ L, 49 μ mol). The mixture was stirred for 30 minutes after which time LCMS showed the
 5 desired product formation. The solution was concentrated *in vacuo* to yield Compound 4b which was used directly in the next step.



Compound 4b (8.0 mg, 15 μ mol) was dissolved in THF (0.5 mL) and 10N NaOH (76 μ L, 76 μ mol) and stirred for 2 hours. AcOH (1 mL) was added and the mixture was
 10 purified by reverse phase chromatography to yield the title compound (Compound b; 2 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{21}ClFN_7O_3$, 498.14; found 498.

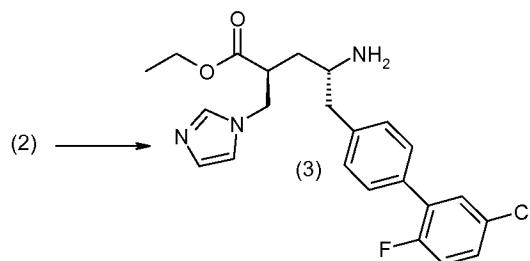
EXAMPLE 62: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-imidazol-1-ylmethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

Compound 1 was prepared as described herein.

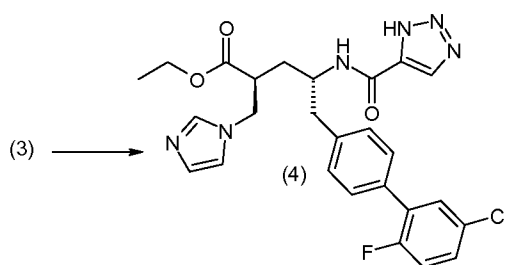


15

Compound 1 (25 mg, 45 μ mol) was combined with K_2CO_3 (12.4 mg, 90 μ mol), imidazole (4.0 mg, 58 μ mol), and DMF (0.5 mL), and the mixture was stirred overnight. The solution was concentrated under reduced pressure and the residue was purified by normal phase chromatography (0-100% EtOAc/hexanes) to yield Compound 2 (15 mg).

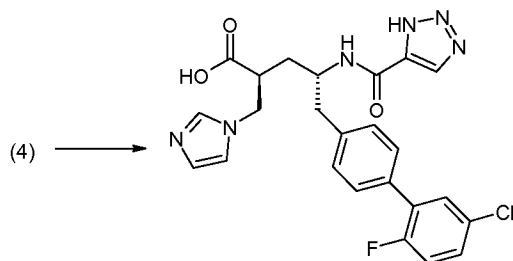


Compound 2 (15 mg, 28 μmol) was dissolved in MeCN (0.3 mL) and 4N HCl in dioxane (0.3 mL). The mixture was stirred for 10 minutes and concentrated under reduced pressure to yield Compound 3 as an HCl salt.



5

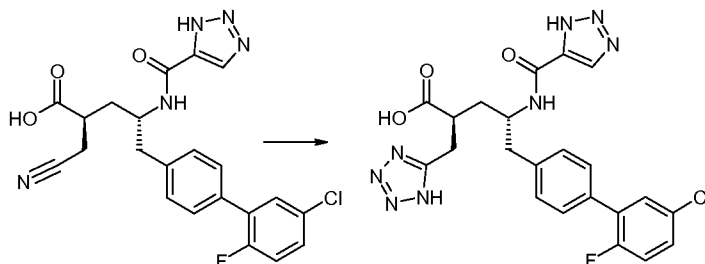
Compound 3 (7.0 mg, 16 μmol) was combined with DMF (0.5 mL), 1H-1,2,3-triazole-5-carboxylic acid (2.0 mg, 18 μmol), HATU (6.8 mg, 18 μmol) and DIPEA (8.5 μL , 49 μmol). The mixture was stirred for 30 minutes after which time LCMS showed the desired product formation, Compound 4, which was used directly in the next step.



10

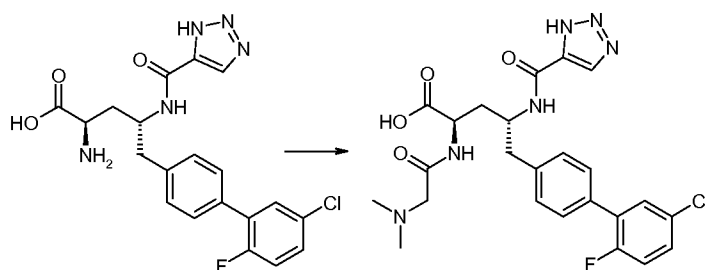
Compound 4 (8.0 mg, 15 μmol) was dissolved in THF (0.5 mL) and NaOH (76 μL , 76 μmol) and stirred for 2 hours. AcOH (1 mL) was added and the mixture was purified by reverse phase chromatography to yield the title compound (4 mg) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{22}\text{ClFN}_6\text{O}_3$, 497.14; found 497.

EXAMPLE 63: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(1H-tetrazol-5-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



A solution of (2S,4S)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (10.5 mg, 22 μ mol), sodium azide (2.8 mg, 43 μ mol) and zinc bromide (4.9 mg, 22 μ mol) in water (0.2 mL) and isopropanol (0.1 mL) was heated at 100°C overnight. The solution was cooled to room temperature and 3M HCl (60 μ L) and EtOAc (1 mL) were added. The organic layer was isolated and the aqueous layer was extracted with EtOAc (2x1 mL). The combined organic layers were washed with saturated aqueous NaCl and concentrated *in vacuo*. The residue (12 mg, 22 μ mol) was dissolved in EtOH (22 μ L) and 10N NaOH (176 μ L, 176 μ mol) was added. The resulting solution was stirred for 2 hours, then concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title compound (2.2 mg). MS *m/z* [M+H]⁺ calc'd for C₂₂H₂₀ClFN₈O₃, 499.13; found 499.2.

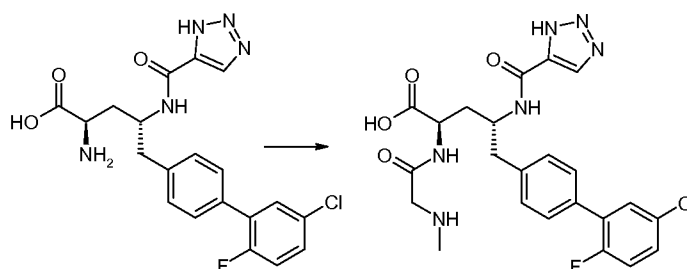
EXAMPLE 64: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-dimethylaminoacetyl)amino-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



Dimethylamino acetic acid (3.9 mg, 38 μ mol) and HATU (14.5 mg, 38 μ mol) were dissolved in DMF (4 mL) and stirred at room temperature for 15 minutes. (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (15 mg, 35 μ mol) and DIPEA (18 μ L, 104 μ mol) were then added and the resulting mixture was stirred at room temperature for 15 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was purified by

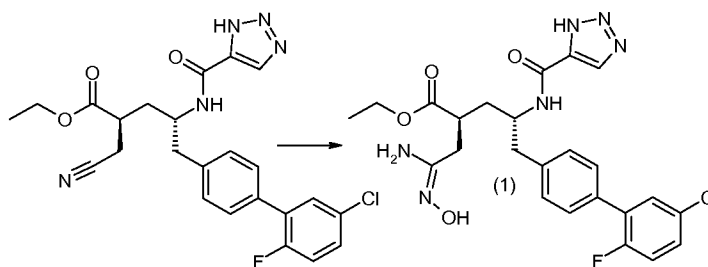
preparative HPLC to yield the title compound (14.5 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{26}ClFN_6O_4$, 517.17; found 517.2.

EXAMPLE 65: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-methylaminoacetyl-amino)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



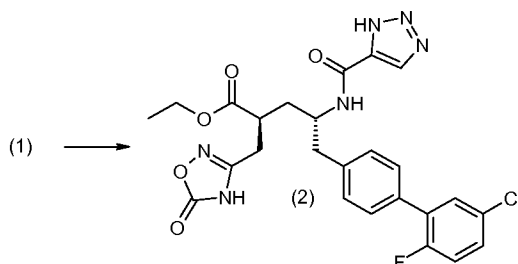
(*t*-Butoxycarbonylmethylamino) acetic acid (7.2 mg, 38 μ mol) and HATU (14.5 mg, 38 μ mol) were dissolved in DMF (4 mL) and stirred at room temperature for 15 minutes. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (15 mg, 35 μ mol) and DIPEA (18 μ L, 104 μ mol) were then added and the resulting mixture was stirred at room temperature for 15 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (130 μ L, 521 μ mol) was added, and the mixture was stirred at room temperature for 10 min. LC/MS showed the mass of the desired product. The solvent was removed *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (10.4 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{24}ClFN_6O_4$, 503.15; found 503.2.

EXAMPLE 66: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(5-oxo-4,5-dihydro-[1,2,4]oxadiazol-3-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

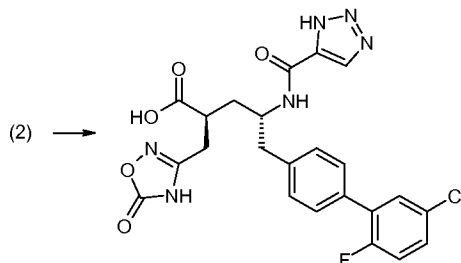


To a solution of (2*S*,4*S*)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-cyanomethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester (11 mg, 22 μ mol) in DMSO (25 μ L) was added hydroxylamine (1.3 μ L, 22 μ mol) and $NaHCO_3$ (1.8 mg, 22

μmol), and the resulting suspension was heated at 70°C to yield a yellow solution. The solution was removed from the heat and diluted with water (0.2 mL), and the resulting suspension was extracted with EtOAc. The organic layers were washed with saturated aqueous NaCl, dried over Na₂SO₄, filtered, and concentrated *in vacuo* to yield Compound 1, which was used without further purification.

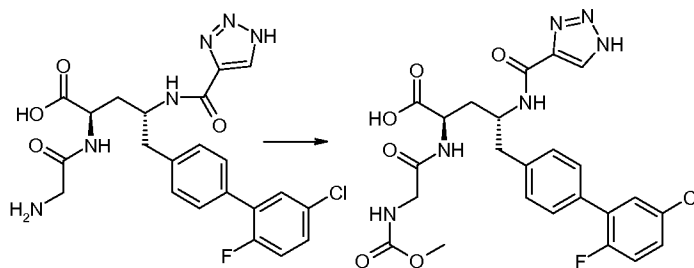


A solution of Compound 1 (11 mg, 22 μmol), DIPEA (9.6 μL, 55 μmol) and TFA (1.7 μL, 22 μmol) in chloroform (0.6 mL) was cooled to 0°C. A solution of diphosgene (3.2 μL, 26 μmol) in chloroform (0.3 mL) was added dropwise. The resulting solution was stirred at 0°C for 1h, and then at 110°C for 30 min in a microwave. After this time, the solution was concentrated *in vacuo* to yield Compound 2, which was used without further purification.



NaOH (176 μL, 176 μmol) was added to a solution of Compound 2 (12 mg, 22 μmol) in EtOH (220 μL), and the resulting mixture was stirred at room temperature overnight. The solution was then concentrated and the residue was purified by preparative HPLC to yield the title compound (0.5 mg; purity 100%). MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₀ClFN₆O₅, 515.12; found 515.2.

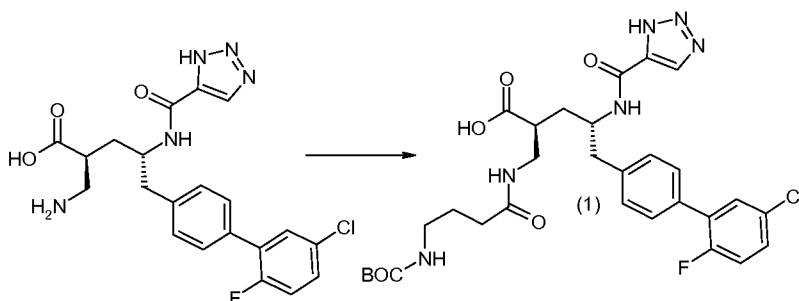
EXAMPLE 67: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-methoxycarbonylaminoacetyl-amino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



5 (2R,4R)-2-(2-Aminoacetyl-amino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (6.4 mg, 13 μ mol) was dissolved in DCM (2 mL). Methyl chloroformate (1.1 μ L, 14 μ mol) was added, followed by DIPEA (6.9 μ L, 39 μ mol). The resulting mixture was stirred at room temperature for 10 minutes (LC/MS indicated no starting material) then concentrated *in vacuo* and the crude residue was

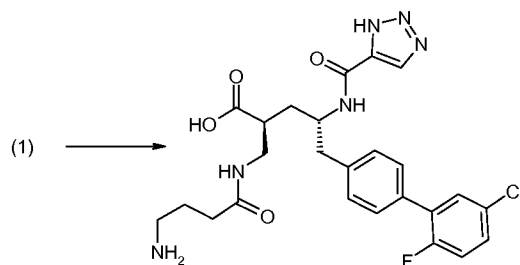
10 purified by reverse phase chromatography to yield the title compound (0.6 mg; purity 99%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{24}ClFN_6O_6$, 547.14; found 547.

EXAMPLE 68: (2S,4S)-2-[(4-Aminobutyl)amino]methyl]-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid



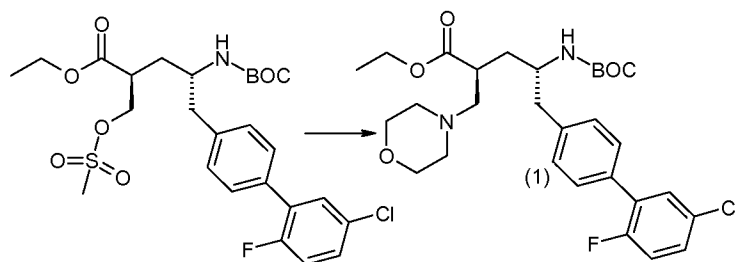
15 4-*t*-Butoxycarbonylaminobutyric acid (2.3 mg, 11 μ mol) and HATU (4.3 mg, 11 μ mol) were dissolved in DMF (0.5 mL) and stirred at room temperature for 10 minutes. DIPEA (1 eq.) was added and stirred for 1 minute. (2S,4S)-2-aminomethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid (5 mg, 11 μ mol) was dissolved in DMF (1 mL) and DIPEA (5.9 μ L, 34 μ mol) was added, followed

20 by addition of the activated acid solution. The resulting mixture was stirred for 30 minutes, followed by the addition of EtOAc (1 mL) and saturated aqueous $NaHCO_3$ (1 mL). The organic layer was separated and the solution was concentrated *in vacuo* to yield Compound 1.

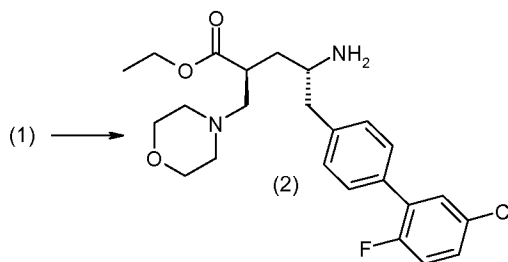


Compound 1 (7 mg, 11 μ mol) was dissolved in MeCN (0.4 mL) and 4N HCl in dioxane (0.1 mL). The mixture was stirred for 30 minutes and the solvent was evaporated. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield the title compound as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{28}ClFN_6O_4$, 531.18; found 531.

EXAMPLE 69a: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-morpholin-4-ylmethyl-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

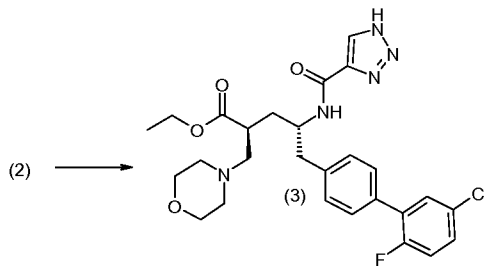


(2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic acid ethyl ester (28 mg, 50 μ mol) was combined with EtOH (2 mL), followed by Na_2CO_3 (16.0 mg, 151 μ mol) and morpholine (13.1 mg, 151 μ mol) and stirred at room temperature overnight. EtOAc (1 mL) and water (1 mL) were added, the organic layer was separated and concentrated under reduced pressure to yield Compound 1.

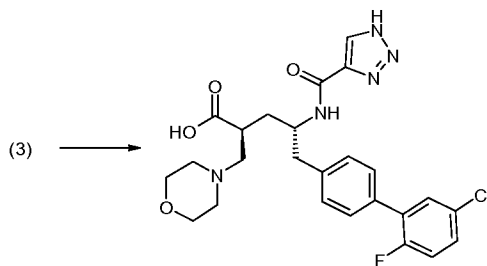


Compound 1 (27 mg, 49 μ mol) was dissolved in MeCN (0.5 mL) and dry 4N HCl in dioxane (0.1 mL). The mixture was stirred for 10 minutes and was then concentrated under reduced pressure. The residue was dissolved in AcOH (1 mL) and purified by

reverse phase chromatography to yield Compound 2 (5 mg).

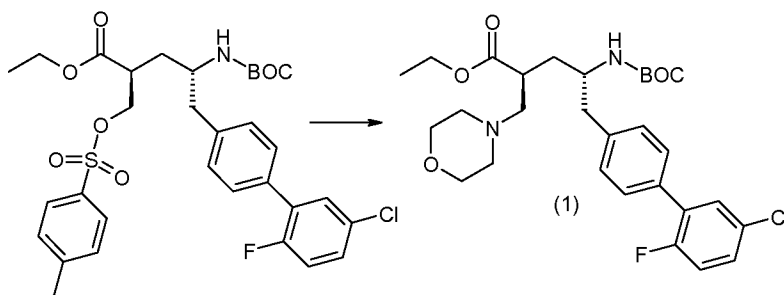


1H-1,2,3-triazole-5-carboxylic acid (1.1 mg, 10.0 μmol) was combined with HATU (3.0 mg, 7.8 μmol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (5.0 mg, 11 μmol) was dissolved in DMF (1 mL) and DIPEA (5.8 μL , 33 μmol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes to yield Compound 3.



Compound 3 (6 mg, 11 μmol) was dissolved in 1N LiOH (55.1 μL , 55 μmol) in THF (0.5 mL). The mixture was stirred for 40 minutes and AcOH was added. The solution was purified by reverse phase chromatography to yield the title compound. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{25}\text{H}_{27}\text{ClFN}_5\text{O}_4$, 516.17; found 516.

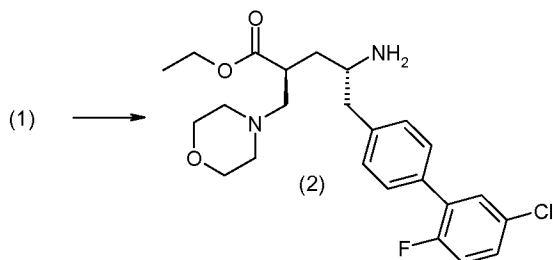
EXAMPLE 69b: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-morpholin-4-ylmethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester



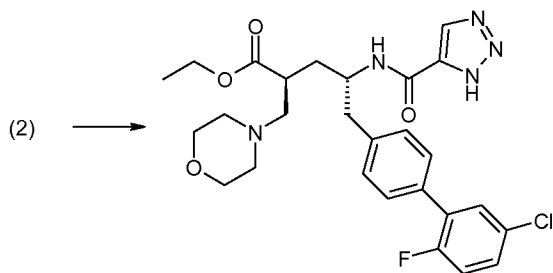
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(2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μmol) was dissolved in EtOH (2 mL), followed by addition of Na_2CO_3 (10 eq.) and morpholine (24 mg, 276 μmol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the

desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (12 mg).

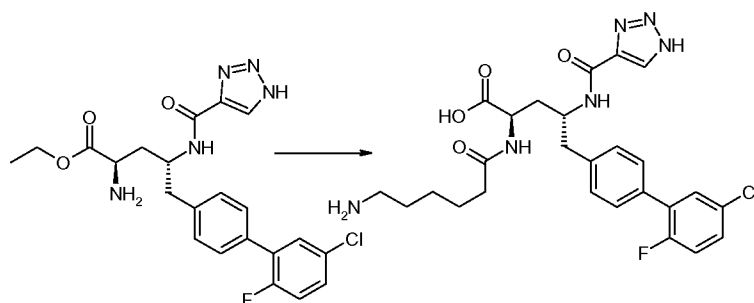


Compound 1 (12 mg, 50 μmol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.



3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μmol) was combined with HATU (8.4 mg, 22 μmol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μmol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μL , 22 μmol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes, concentrated, and purified by preparative HPLC to yield the title compound. MS m/z $[\text{M}+\text{H}]^+$ calc'd for C₂₇H₃₁ClFN₅O₄, 544.21; found 544.2.

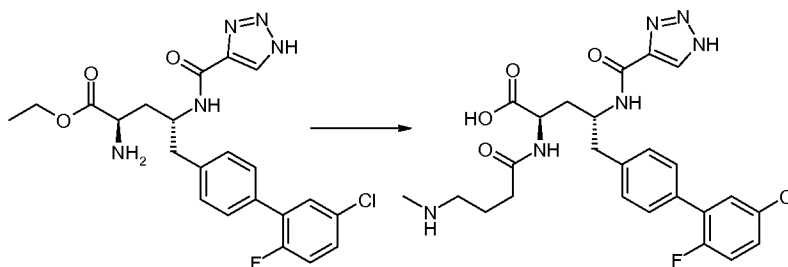
EXAMPLE 70: (2R,4R)-2-(6-Aminohexanoylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



6-*t*-Butoxycarbonylamino-hexanoic acid (8.3 mg, 36 μmol) and HATU (13.6 mg, 36

μmol) were dissolved in DMF (2 mL) and stirred at room temperature for 15 minutes.
 (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-
 carbonyl)amino]pentanoic acid ethyl ester (15 mg, 33 μmol) and DIPEA (17 μL, 98 μmol)
 were then added, and the mixture was stirred at room temperature for 15 minutes (LC/MS
 5 showed reaction completion) then concentrated *in vacuo*. The residue was dissolved in
 MeCN (2 mL) and a solution of 4*N* HCl in dioxane (122 μL, 489 μmol) was added. The
 mixture was stirred at room temperature for 20 minutes (LC/MS showed the mass of the
 desired product) then concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL).
 A solution of 1*N* LiOH in water (261 μL, 261 μmol) was added and the mixture was stirred
 10 at room temperature for 30 minutes (LC/MS showed reaction completion) then
 concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title
 compound (21.3 mg; purity 100%) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for
 C₂₆H₃₀ClFN₆O₄, 545.20; found 545.2.

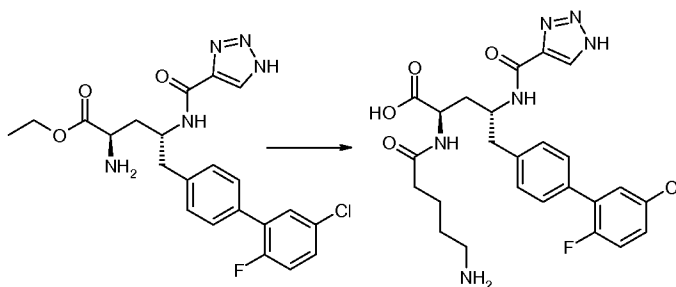
15 EXAMPLE 71: (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(4-methylamino-
 butyrylamino)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



4-(*t*-Butoxycarbonylmethylamino)butyric acid (7.8 mg, 36 μmol) and HATU (13.6
 mg, 36 μmol) were dissolved in DMF (2 mL) and stirred at room temperature for 15
 minutes. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-
 20 carbonyl)amino]pentanoic acid ethyl ester (15 mg, 33 μmol) and DIPEA (17 μL, 98 μmol)
 were then added, and the mixture was stirred at room temperature for 15 minutes (LC/MS
 showed reaction completion) then concentrated *in vacuo*. The residue was dissolved in
 MeCN (2 mL) and a solution of 4*N* HCl in dioxane (122 μL, 489 μmol) was added. The
 mixture was stirred at room temperature for 20 minutes (LC/MS showed the mass of the
 25 desired product) then concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL).
 A solution of 1*N* LiOH in water (261 μL, 261 μmol) was added and the mixture was
 stirred at room temperature for 30 minutes (LC/MS showed reaction completion) then
 concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title

compound (20.5 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{28}ClFN_6O_4$, 531.18; found 531.2.

EXAMPLE 72: (2R,4R)-2-(5-Amino-pentanoylamino)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

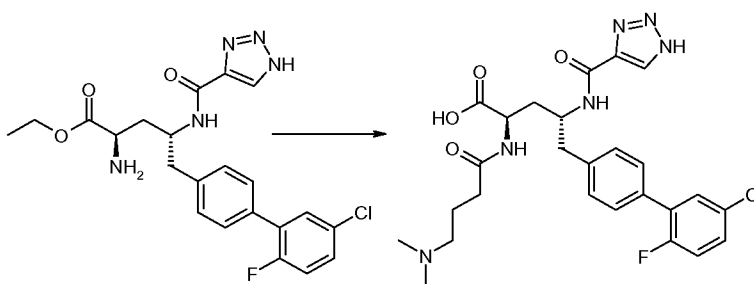


5

5-*t*-Butoxycarbonylamino-pentanoic acid (7.8 mg, 36 μ mol) and HATU (13.6 mg, 36 μ mol) were dissolved in DMF (2 mL) and stirred at room temperature for 15 minutes. (2R,4R)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester (15 mg, 33 μ mol) and DIPEA (17 μ L, 98 μ mol) were then added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed reaction completion) then concentrated *in vacuo*. The residue was dissolved in MeCN (2 mL) and a solution of 4N HCl in dioxane (122 μ L, 489 μ mol) was added. The mixture was stirred at room temperature for 20 minutes (LC/MS showed the mass of the desired product) then concentrated *in vacuo* and the residue was dissolved in EtOH (2 mL). A solution of 1N LiOH in water (261 μ L, 261 μ mol) was added and the mixture was stirred at room temperature for 30 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (20.7 mg; purity 100%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{28}ClFN_6O_4$, 531.18; found 531.2.

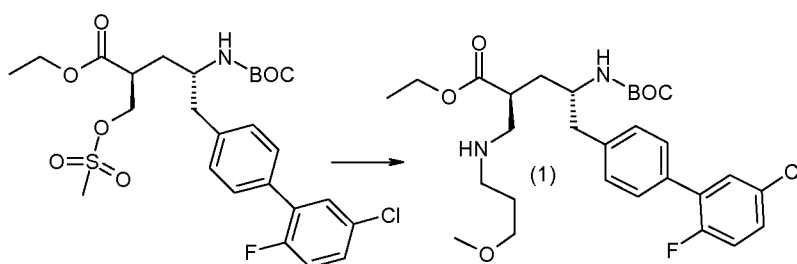
20

EXAMPLE 73: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(4-dimethylaminobutyrylamino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



4-Dimethylaminobutyric acid hydrochloride (6.0 mg, 36 μmol) and HATU (13.6 mg, 36 μmol) were dissolved in DMF (2 mL) and stirred at room temperature for 15 minutes. (2*R*,4*R*)-2-Amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester (15 mg, 33 μmol) and DIPEA (17 μL , 98 μmol) were then added, and the mixture was stirred at room temperature for 15 minutes (LC/MS showed reaction completion) then concentrated *in vacuo*. The residue was dissolved in EtOH (2 mL). A solution of 1*N* LiOH in water (261 μL , 261 μmol) was added and the mixture was stirred at room temperature for 30 minutes (LC/MS showed reaction completion) then concentrated *in vacuo* and the residue was purified by preparative HPLC to yield the title compound (24.3 mg; purity 100%) as a TFA salt. MS *m/z* [*M*+*H*]⁺ calc'd for C₂₆H₃₀ClFN₆O₄, 545.20; found 545.2.

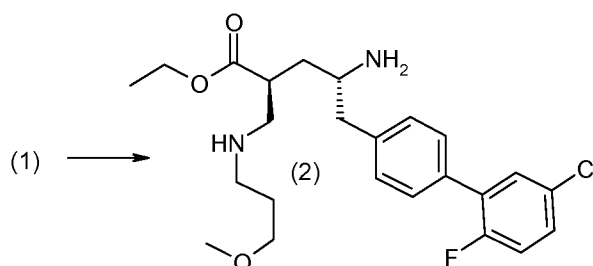
EXAMPLE 74: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(3-methoxypropylamino)-methyl]-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



15

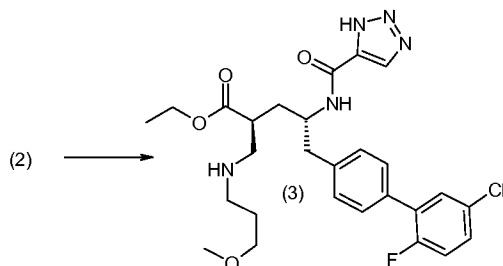
To a stirred solution of (2*S*,4*S*)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic acid ethyl ester (60 mg, 108 μmol) in EtOH (2 mL), was added 2-methoxypropylamine (19.2 mg, 215 μmol). The resulting mixture was stirred at 50°C overnight. EtOAc (2 mL) and water (1 mL) were added, the organic layer was separated and washed with water (3x), dried over Na₂SO₄, then concentrated under reduced pressure and purified by normal phase chromatography (0-60% EtOAc:hexanes) to yield Compound 1 (15 mg).

20

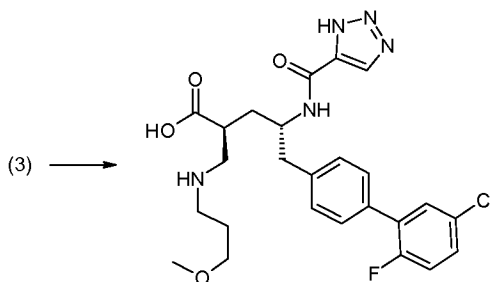


Compound 1 (10.0 mg, 18 μmol) was dissolved in MeCN (0.5 mL) and dry 4*N* HCl

in dioxane (0.3 mL). The mixture was stirred for 10 minutes and was then concentrated under reduced pressure to yield Compound 2 as an HCl salt.



1H-1,2,3-triazole-5-carboxylic acid (2.3 mg, 20 μ mol) was combined with HATU (5.9 mg, 15 μ mol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10.0 mg, 22 μ mol) was dissolved in DMF (1 mL) and DIPEA (11.6 μ L, 66 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and then concentrated *in vacuo* to yield Compound 3.

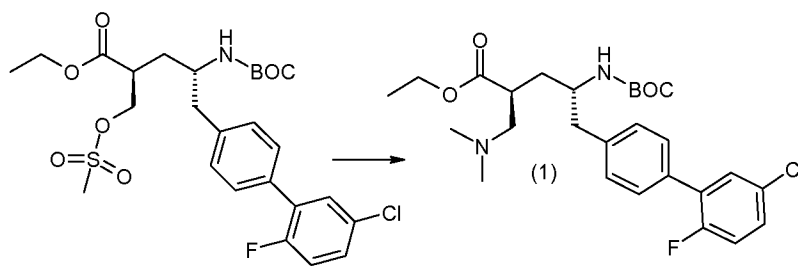


10

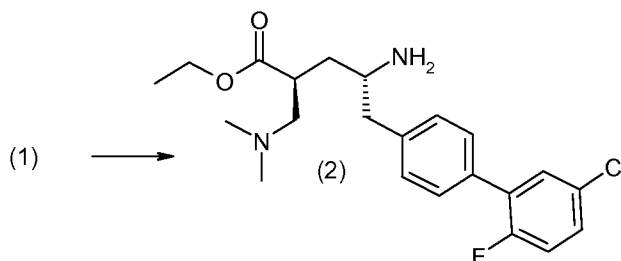
To the crude solution of Compound 3 (10.0 mg, 18 μ mol) was added 1N LiOH (92 μ L, 92 μ mol) and THF (0.5 mL), followed by MeOH (0.1 mL). The mixture was stirred for 1 hour and AcOH (1 mL) was added. The solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₅H₂₉ClFN₅O₄, 518.19; found 518.

15

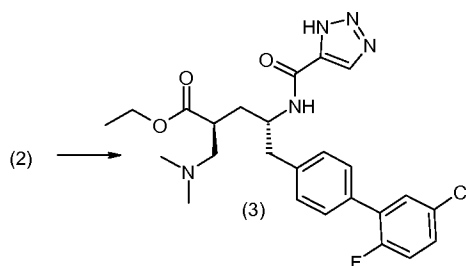
EXAMPLE 75: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-dimethylaminomethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



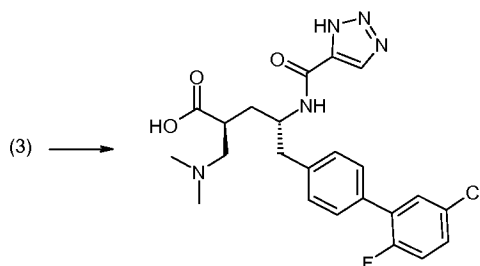
To a stirred solution of (2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-methanesulfonyloxymethylpentanoic acid ethyl ester (60 mg, 108 μ mol) in EtOH (2 mL), was added dimethylamine in THF (108 μ L, 215 μ mol). The resulting mixture was stirred at 50°C overnight. EtOAc (2 mL) and water (2 mL) were added. The organic layer was separated and washed with water (3x), then concentrated under reduced pressure and purified by normal phase chromatography (0-60% EtOAc:hexanes) to yield Compound 1 (10 mg).



Compound 1 (9.2 mg, 18 μ mol) was dissolved in MeCN (0.5 mL) and dry 4N HCl in dioxane (0.3 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt.



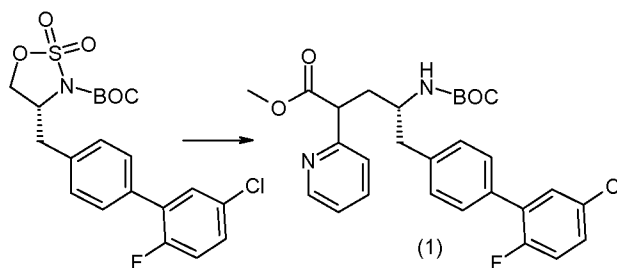
1H-1,2,3-triazole-5-carboxylic acid (2.3 mg, 20 μ mol) was combined with HATU (5.9 mg, 15 μ mol) in DMF (0.5 mL) and stirred for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (9.0 mg, 22 μ mol) was dissolved in DMF (1 mL) and DIPEA (11.6 μ L, 66 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and the solution was concentrated *in vacuo* to yield Compound 3.



To a solution of crude Compound 3 (9.0 mg, 18 μ mol) was added 1N LiOH (92 μ L, 92 μ mol) and THF (0.5 mL), followed by MeOH (0.1 mL). The mixture was stirred for 1 hour and AcOH was added. The solution was purified by reverse phase chromatography to yield the title compound (2 mg; purity 95%) as a TFA salt. MS m/z $[M+H]^+$ calc'd for

5 $C_{23}H_{25}ClFN_5O_3$, 474.16; found 474.

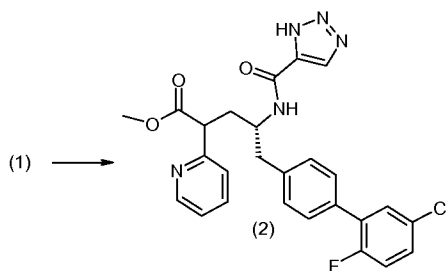
EXAMPLE 76: (S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-pyridin-2-yl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



10 A 1M solution of lithium bis(trimethylsilyl)amide in hexanes (88 μ L, 88 μ mol) in THF (110 μ L) was cooled to 0°C and methyl 2-(pyridin-2-yl)acetate (12 μ L, 88 μ mol) was added. After stirring at this temperature for 30 minutes, a solution of (*R*)-*t*-butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (46 mg, 105 μ mol) in THF (0.5 mL) was added. The resulting mixture was stirred

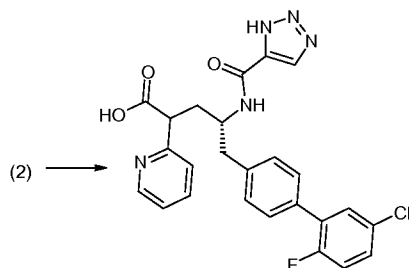
15 at this temperature for 1 hour and then slowly warmed up to room temperature overnight. 1N HCl (0.5 mL) was added and the solution was stirred at room temperature for 10 minutes. DCM (1.5 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (2x1.5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (0-

20 30% EtOAc in hexanes over 20 minutes) to yield Compound 1 (21.8 mg) as a clear oil.



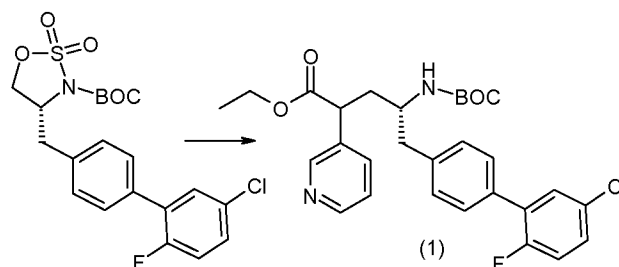
A solution of Compound 1 (8.9 mg, 18 μ mol) in HCl (88 μ L, 351 μ mol) was stirred at room temperature for 20 minutes. After this time, LCMS indicated that the BOC group had been cleaved so the solution was concentrated *in vacuo*. In a separate flask, a solution

of 3H-[1,2,3]triazole-4-carboxylic acid (2.4 mg, 21 μ mol) and HATU (8.0 mg, 21 μ mol) in DMF (180 μ L) was stirred at room temperature for 30 minutes. After this time, a solution of the crude amine in DMF (180 μ L) was added, followed by DIPEA (9.2 μ L, 53 μ mol). The resulting solution was stirred overnight at room temperature. LCMS indicated that the reaction was complete and the solution was concentrated *in vacuo* to yield Compound 2 (8.9 mg), which was used without further purification.



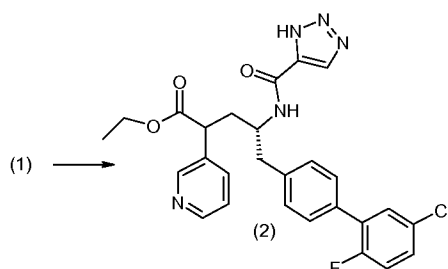
To a solution of Compound 2 (9.1 mg, 18 μ mol) in MeOH (180 μ L) was added 10N NaOH (144 μ L, 144 μ mol). The resulting solution was stirred at room temperature overnight. LCMS indicated that a large amount of starting material was present so additional 10N NaOH (144 μ L, 144 μ mol) was added. After stirring at room temperature for 2 hours, the reaction was complete and the solution was concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title compound (3.8 mg; purity 97%) as a mixture of diastereomers at the pyridine center. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{21}ClFN_5O_3$, 494.13; found 494.0.

EXAMPLE 77: (S)-5-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-2-pyridin-3-yl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (diastereomers a and b)

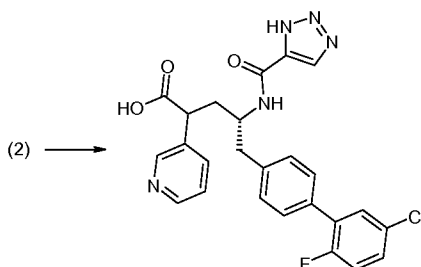


A 1M solution of lithium bis(trimethylsilyl)amide in hexanes (87 μ L, 87 μ mol) in THF (110 μ L) was cooled to 0°C and ethyl 2-(pyridin-3-yl)acetate (13 μ L, 87 μ mol) was added. After stirring at this temperature for 30 minutes, a solution of (*R*)-*t*-butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (46 mg, 104 μ mol) in THF (0.5 mL) was added. The resulting mixture was stirred at this temperature for 1 hour and then slowly warmed up to room temperature overnight.

1N HCl (0.5 mL) was added and the solution was stirred at room temperature for 10 minutes. DCM (1.5 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (2x1.5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (0-
 5 30% EtOAc in hexanes over 20 minutes) to yield Compound 1 (9.7 mg) as a clear oil.

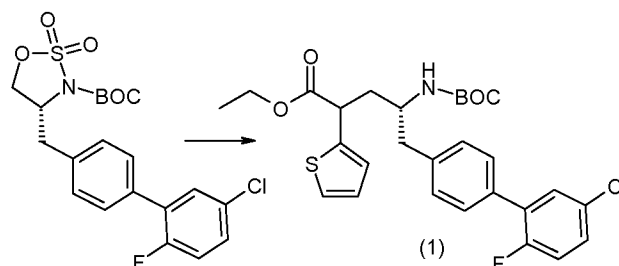


To a solution of Compound 1 (9.7 mg, 18 μmol) in dioxane (180 μL) was added HCl (92 μL, 368 μmol). The resulting solution was stirred at room temperature for 2 hours, and then concentrated *in vacuo*. In a separate flask, a solution of 3H-[1,2,3]triazole-
 10 4-carboxylic acid (2.5 mg, 22 μmol) and HATU (8.4 mg, 22 μmol) in DMF (180 μL) was stirred at room temperature for 30 minutes. After this time, a solution of the crude amine in DMF (180 μL) was added, followed by DIPEA (9.6 μL, 55 μmol). The resulting solution was stirred for 1 hour at room temperature then concentrated *in vacuo* when the reaction was deemed complete by LCMS to yield Compound 2 (9.6 mg), which was used
 15 without further purification.



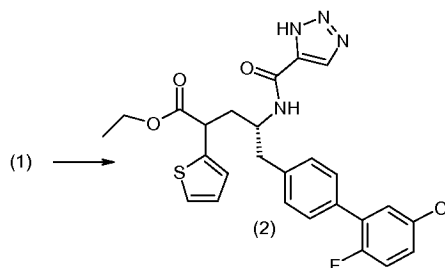
To a solution of Compound 2 (9.4 mg, 18 μmol) in EtOH (180 μL) was added 10N NaOH (288 μL, 288 μmol). The resulting solution was stirred at room temperature for 1 hour and then concentrated *in vacuo*. The residue was purified by preparative HPLC to
 20 yield the title compound (diastereomer a; 3.1 mg; purity 96% and diastereomer b; 1.3 mg; purity 100%). MS *m/z* [M+H]⁺ calc'd for C₂₅H₂₁ClFN₅O₃, 494.13; found 494.2.

EXAMPLE 78: (S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-thiophen-2-yl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

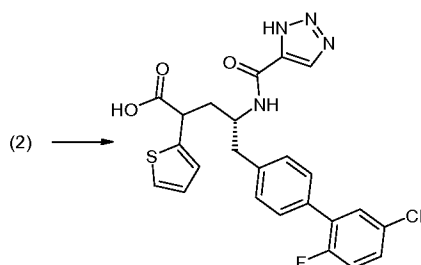


A 1M solution of lithium bis(trimethylsilyl)amide in hexanes (87 μ L, 87 μ mol) in THF (110 μ L) was cooled to 0°C and ethyl 2-(thiophen-2-yl)acetate (13 μ L, 87 μ mol) was added. After stirring at this temperature for 30 minutes, a solution of (R)-*t*-butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (46 mg, 104 μ mol) in THF (0.5 mL) was added. The resulting mixture was stirred at this temperature for 1 hour and then slowly warmed up to room temperature overnight.

1N HCl (0.5 mL) was added and the solution was stirred at room temperature for 10 minutes. DCM (1.5 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (2x1.5 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography (0-30% EtOAc in hexanes over 20 minutes) to yield Compound 1 (15.9 mg) as a clear oil.

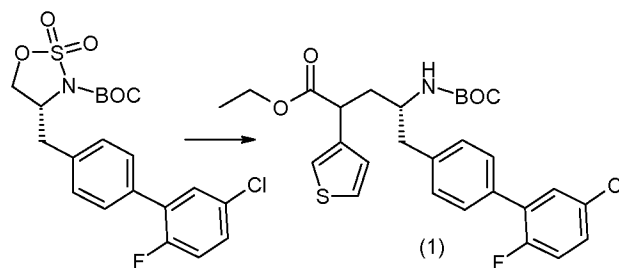


To a solution of Compound 1 (15.9 mg, 30 μ mol) in dioxane (0.3 mL) was added HCl (149 μ L, 598 μ mol). The resulting solution was stirred at room temperature for 2 hours, and then concentrated *in vacuo*. In a separate flask, a solution of 3H-[1,2,3]triazole-4-carboxylic acid (4.1 mg, 36 μ mol) and HATU (14 mg, 36 μ mol) in DMF (0.3 mL) was stirred at room temperature for 30 minutes. After this time, a solution of the crude amine in DMF (0.3 mL) was added, followed by DIPEA (16 μ L, 90 μ mol). The resulting solution was stirred for 1 hour at room temperature then concentrated *in vacuo* when the reaction was deemed complete by LCMS to yield Compound 2 (16 mg), which was used without further purification.



To a solution of Compound 2 (15.8 mg, 30 μ mol) in EtOH (0.3 mL) was added 10N NaOH (240 μ L, 240 μ mol). The resulting solution was stirred at room temperature for 1 hour and then concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title compound (2.6 mg; purity 99.5%) as a mixture of diastereomers at the point of attachment of the thiophene ring. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{20}ClFN_4O_3S$, 499.09; found 499.0.

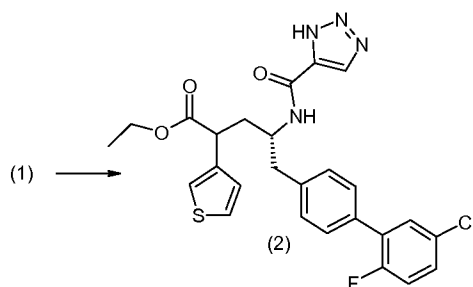
EXAMPLE 79: (S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-thiophen-3-yl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



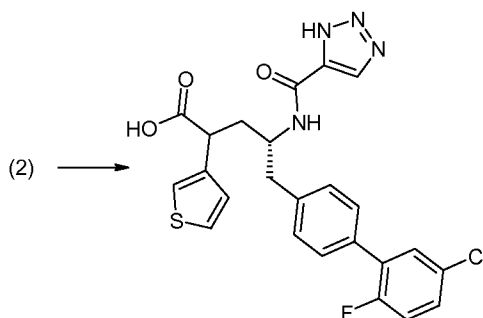
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A 1M solution of lithium bis(trimethylsilyl)amide in hexanes (87 μ L, 87 μ mol) in THF (110 μ L) was cooled to 0°C and ethyl 2-(thiophen-3-yl)acetate (13 μ L, 87 μ mol) was added. After stirring at this temperature for 30 minutes, a solution of (*R*)-*t*-butyl 4-((5'-chloro-2'-fluoro-[1,1'-biphenyl]-4-yl)methyl)-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (46 mg, 104 μ mol) in THF (0.5 mL) was added. The resulting mixture was stirred at this temperature for 1 hour and then slowly warmed up to room temperature overnight. 1N HCl (0.5 mL) was added and the solution was stirred at room temperature for 10 minutes. DCM (1.5 mL) was added, the layers were separated and the aqueous layer was extracted with DCM (2x1.5 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by column chromatography (0-30% EtOAc in hexanes over 20 minutes) to yield Compound 1 (51.3 mg) as a clear oil.

20



A solution of Compound 1 (51.3 mg, 96 μ mol) in HCl (482 μ L, 1.9 mmol) was stirred at room temperature for 2 hours, and then concentrated *in vacuo*. In a separate flask, a solution of 3H-[1,2,3]triazole-4-carboxylic acid (13 mg, 116 μ mol) and HATU (44 mg, 116 μ mol) in DMF was stirred at room temperature for 30 minutes. After this time, a solution of the crude amine in DMF was added, followed by DIPEA (51 μ L, 289 μ mol). The resulting solution was stirred for 1 hour at room temperature then concentrated *in vacuo* when the reaction was deemed complete by LCMS to yield Compound 2 (96 mg), which was used without further purification.

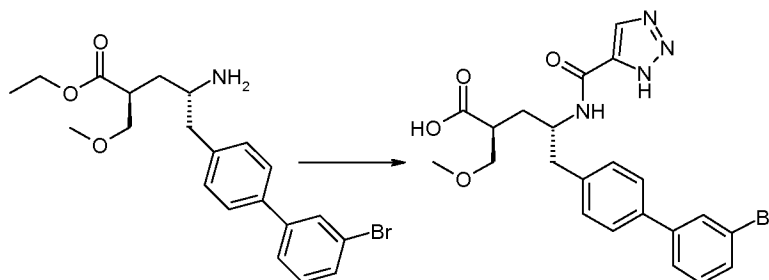


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To a solution of Compound 2 (50.6 mg, 96 μ mol) in EtOH (1.0 mL) was added 10N NaOH (768 μ L, 768 μ mol). The resulting solution was stirred at room temperature for 2 hours and then concentrated *in vacuo*. The residue was purified by preparative HPLC to yield the title compound (3.3 mg; purity 100%) as a mixture of diastereomers at the point of attachment of the thiophene ring. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{20}ClFN_4O_3S$, 499.09; found 499.2.

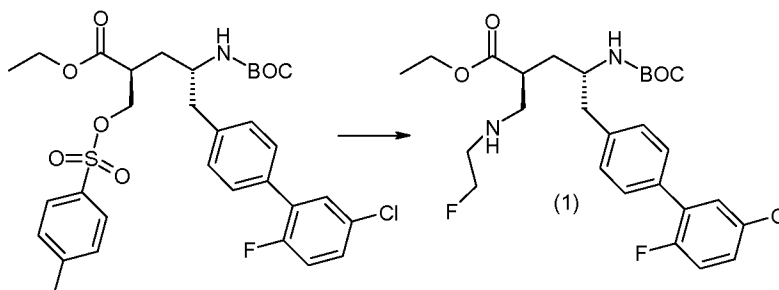
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EXAMPLE 80: (2*S*,4*S*)-5-(3'-Bromobiphenyl-4-yl)-2-methoxymethyl-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



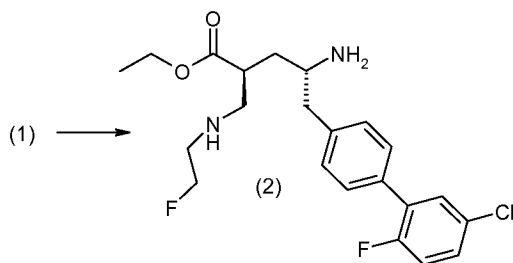
DIPEA (42 μ L, 243 μ mol) was added to a solution of (2*S*,4*S*)-4-amino-5-(3'-
 5 bromobiphenyl-4-yl)-2-methoxymethylpentanoic acid ethyl ester (34 mg, 81 μ mol), 3H-
 [1,2,3]triazole-4-carboxylic acid (11.0 mg, 97 μ mol) and HATU (46.2 mg, 122 μ mol) in
 DMF (0.3 mL), and the resulting mixture was stirred at room temperature for 15 minutes.
 5.0 M aqueous LiOH (130 μ L, 649 μ mol) was added dropwise and the mixture was stirred
 at room temperature for 15 hours then purified by preparative HPLC to yield the title
 10 compound (23.5 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{22}H_{23}BrN_4O_4$, 487.09;
 found 487.2.

EXAMPLE 81: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2-fluoroethylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid

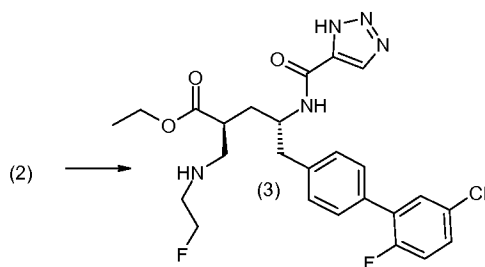


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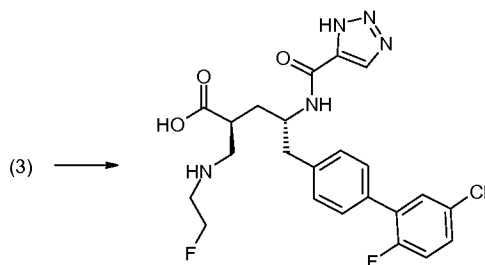
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-
 4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH
 (2 mL), followed by addition of Na_2CO_3 (10 eq.) and 2-fluoroethylamine (17 mg, 276
 μ mol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the
 20 mass of the desired compound. The mixture was concentrated under reduced pressure and
 the crude residue was purified by reverse phase chromatography to yield Compound 1 (4
 mg).



Compound 1 (4 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.

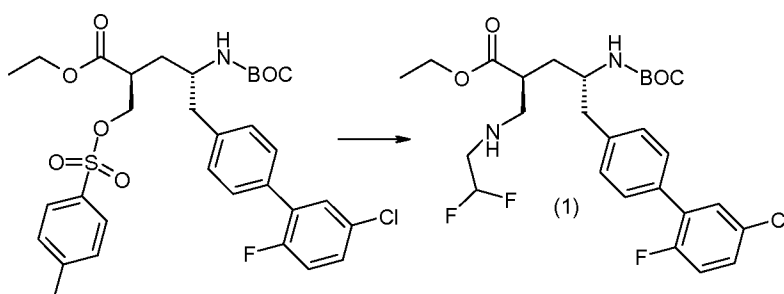


3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μ mol) was combined with HATU (8.4 mg, 22 μ mol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μ L, 22 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and concentrated to yield Compound 3, which was carried to the next step without purification.

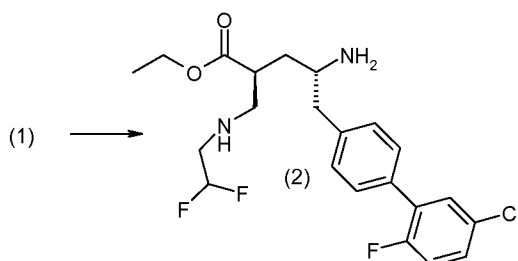


To crude Compound 3 (22 μ mol) was added 1N LiOH (88 μ L, 88 μ mol), THF (0.3 mL), and 2 drops of MeOH. The mixture was stirred overnight and AcOH was added. The solution was purified by reverse phase chromatography to yield the title compound (0.6 mg) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₃H₂₄ClF₂N₅O₃, 492.15; found 492.2.

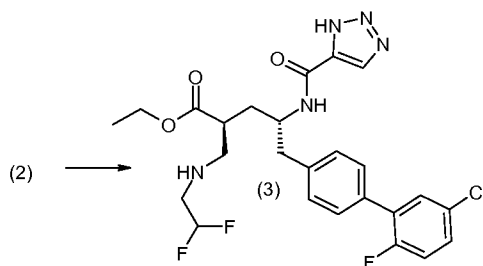
EXAMPLE 82: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2,2-difluoroethylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(2,2-difluoroethylamino)methyl]-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound b)



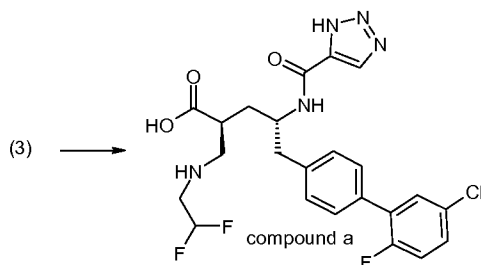
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH (2 mL), followed by addition of Na₂CO₃ (10 eq.) and 2,2-difluoroethylamine (22 mg, 276 μ mol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (6 mg).



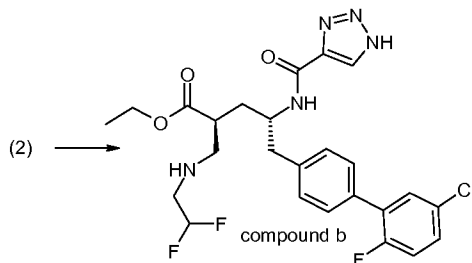
Compound 1 (6 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.



3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μ mol) was combined with HATU (8.4 mg, 22 μ mol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μ L, 22 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and concentrated to yield Compound 3, which was carried to the next step without purification.



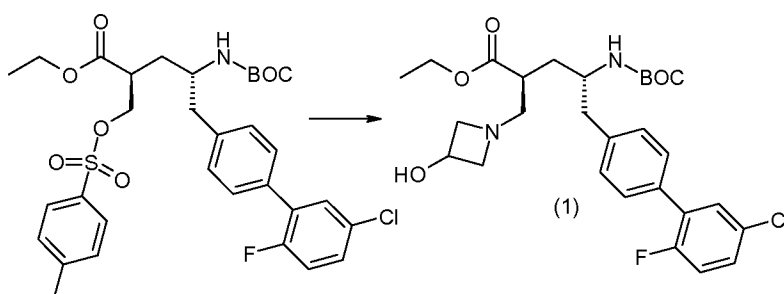
To the crude Compound 3 (22 μ mol) was added 1N LiOH (88 μ L, 88 μ mol), THF (0.3 mL), and 2 drops of MeOH. The mixture was stirred overnight and AcOH was added. The solution was purified by reverse phase chromatography to yield Compound a (1.1 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for C₂₃H₂₃ClF₃N₅O₃, 510.14; found 510.2.



1H-1,2,3-triazole-4-carboxylic acid (2.6 mg, 23 μ mol) was combined with HATU (9.6 mg, 25 μ mol) in DMF (3.0 mL) and stirred at room temperature for 15 minutes. Compound 2 (13 mg, 29 μ mol) was dissolved in DIPEA (12 μ L, 69 μ mol) and combined with the activated acid solution. The mixture was stirred at room temperature for 15 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound b (0.8 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for C₂₅H₂₇ClF₃N₅O₃, 538.18; found 538.

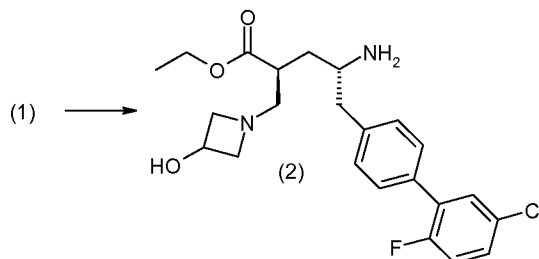
EXAMPLE 83: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxyazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxyazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

5

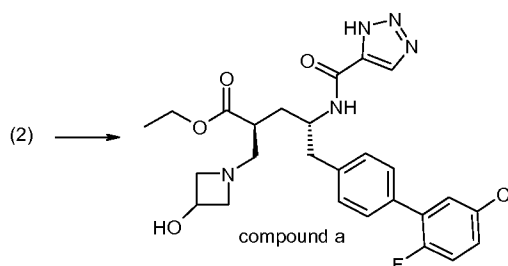


(2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH (2 mL), followed by addition of Na₂CO₃ (10 eq.) and azetidin-3-ol (20 mg, 276 μ mol).

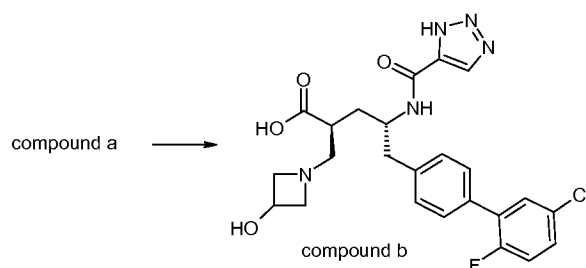
- 10 The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (13 mg).



- Compound 1 (13 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.

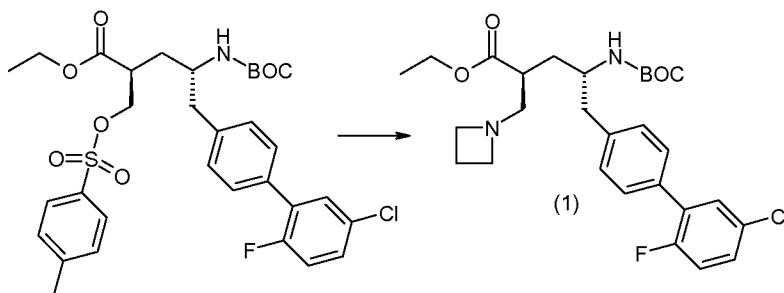


3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μ mol) was combined with HATU (8.4 mg, 22 μ mol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μ L, 22 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes, concentrated, and purified by preparative HPLC to yield Compound a (7 mg) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₆H₂₉ClFN₅O₄, 530.19; found 530.2.



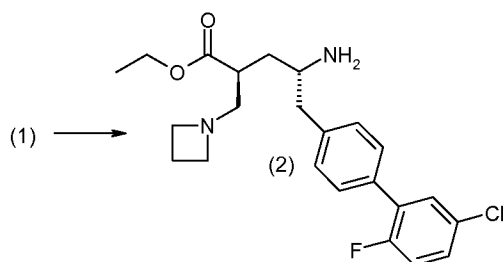
Compound a (22 μ mol) was combined with 1N LiOH (88 μ L, 88 μ mol), THF (0.3 mL), and 2 drops of MeOH. The mixture was stirred overnight and AcOH was added. The solution was purified by reverse phase chromatography to yield Compound b (3 mg) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₄H₂₅ClFN₅O₄, 502.16; found 502.

EXAMPLE 84: (2S,4S)-2-Azetidin-1-ylmethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2S,4S)-2-Azetidin-1-ylmethyl-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

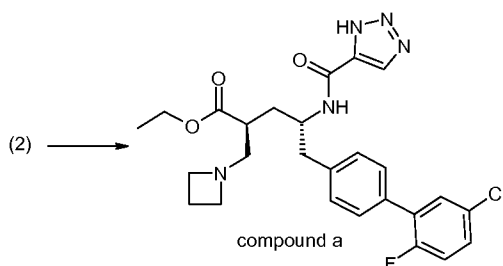


(2S,4S)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH (2 mL), followed by addition of Na₂CO₃ (10 eq.) and azetidine (15 mg, 276 μ mol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the

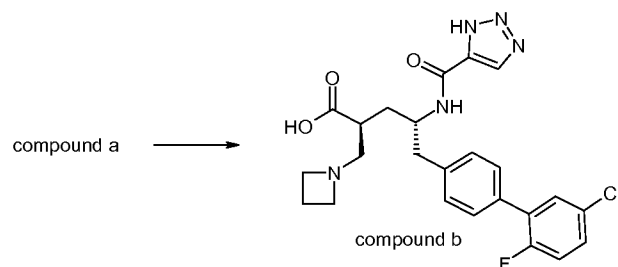
desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (15 mg).



Compound 1 (15 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.



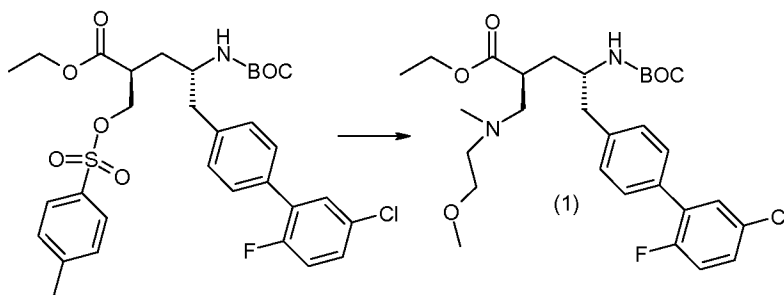
3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μ mol) was combined with HATU (8.4 mg, 22 μ mol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μ L, 22 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes, concentrated, and purified by preparative HPLC to yield Compound a (8 mg) as a TFA salt. MS m/z [M+H]⁺ calc'd for C₂₆H₂₉ClFN₅O₃, 514.19; found 514.2.



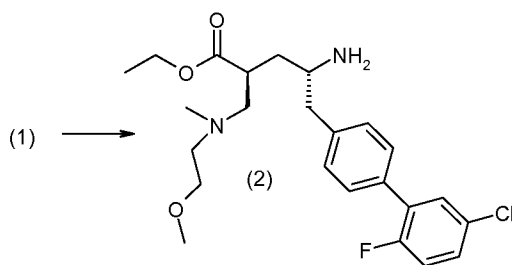
Compound a (22 μ mol) was combined with 1N LiOH (88 μ L, 88 μ mol), THF (0.3 mL), and 2 drops of MeOH. The mixture was stirred overnight and AcOH was added. The solution was purified by reverse phase chromatography to yield Compound b (3

mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{25}ClFN_5O_3$, 486.16; found 486.

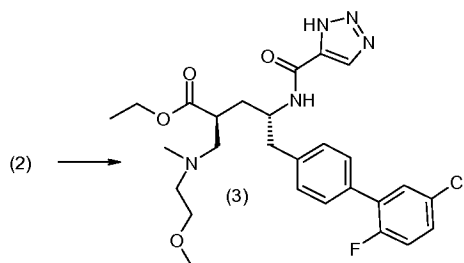
EXAMPLE 85: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-{[(2-methoxyethyl)methylamino]methyl}-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-{[(2-methoxyethyl)methylamino]methyl}-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound b)



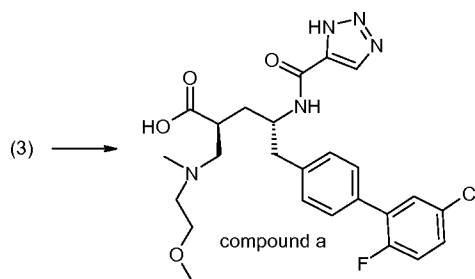
(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH (2 mL), followed by addition of Na_2CO_3 (10 eq.) and (2-methoxyethyl)methylamine (24 mg, 276 μ mol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (10 mg).



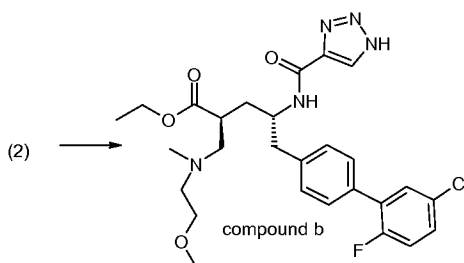
Compound 1 (10 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2, which was carried to the next step without purification.



3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μmol) was combined with HATU (8.4 mg, 22 μmol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μmol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μL , 22 μmol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes and concentrated to yield Compound 3, which was carried to the next step without purification.



To the crude Compound 3 (22 μmol) was added 1N LiOH (88 μL , 88 μmol), THF (0.3 mL), and 2 drops of MeOH. The mixture was stirred overnight and AcOH was added. The solution was purified by reverse phase chromatography to yield Compound a (3 mg). MS m/z $[\text{M}+\text{H}]^+$ calc'd for C₂₅H₂₉ClFN₅O₄, 518.19; found 518.

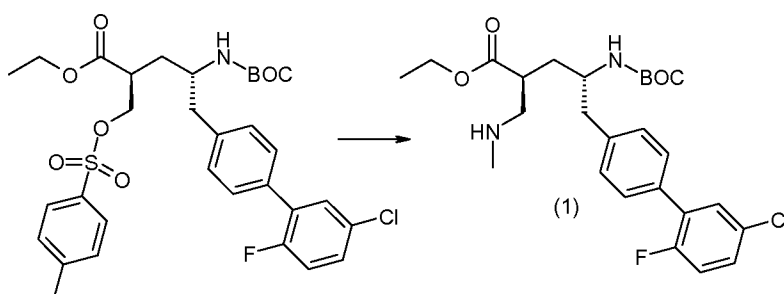


3H-1,2,3-triazole-5-carboxylic acid (3.0 mg, 27 μmol) was combined with HATU (10.1 mg, 27 μmol) in DMF (0.5 mL); DIPEA (4.7 μL , 27 μmol) was added and the mixture was stirred for 5 minutes. Compound 2 (12 mg, 27 μmol) was dissolved in DMF (0.5 mL) and DIPEA (13.9 μL , 80 μmol) and combined with the activated acid solution. The mixture was stirred for 10 minutes, at which time LCMS indicated the mass of the desired compound. The solvent was removed under reduced pressure and the residue was

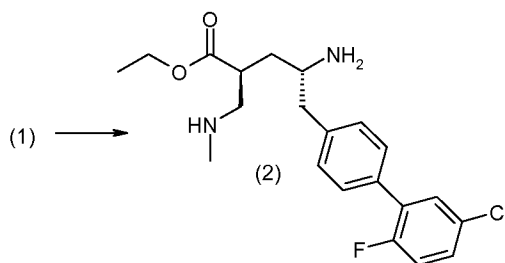
purified by reverse phase chromatography to yield Compound b (8 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{33}ClFN_5O_4$, 546.22; found 546.

EXAMPLE 86: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-methylaminomethyl-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester

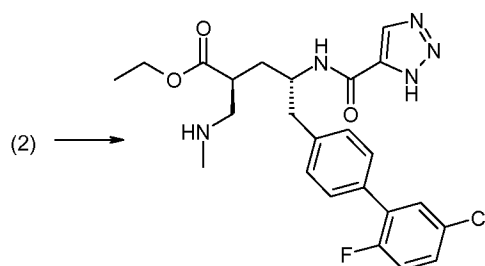
5



(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(toluene-4-sulfonyloxymethyl)pentanoic acid ethyl ester (35 mg, 55 μ mol) was dissolved in EtOH (2 mL), followed by addition of Na₂CO₃ (10 eq.) and methylamine (8 mg, 276 μ mol). The mixture was stirred at 70°C for 2 days, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was purified by reverse phase chromatography to yield Compound 1 (6 mg).

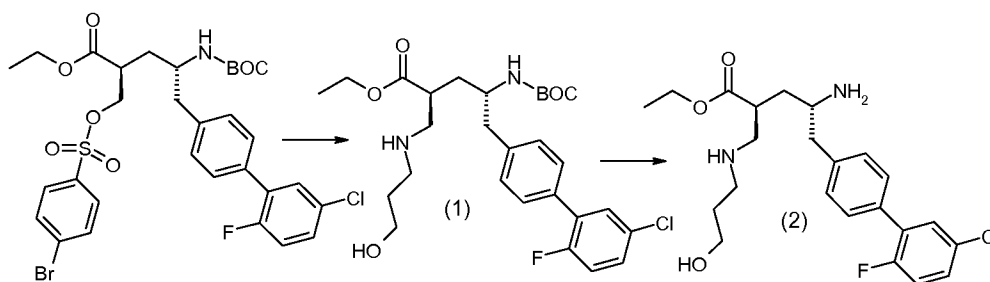


Compound 1 (6 mg, 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in
15 dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under
reduced pressure to yield Compound 2, which was carried to the next step without
purification.



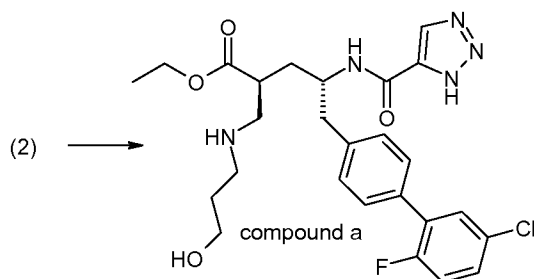
3H-1,2,3-triazole-5-carboxylic acid (2.5 mg, 22 μ mol) was combined with HATU (8.4 mg, 22 μ mol) in DMF (0.3 mL) and stirred for 10 minutes; Et₃N (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (22 μ mol) was dissolved in DMF (0.5 mL) and Et₃N (3.1 μ L, 22 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred for 30 minutes, concentrated, and purified by preparative HPLC to yield the title compound. MS m/z [M+H]⁺ calc'd for C₂₄H₂₇ClFN₅O₃, 488.18; found 488.2.

EXAMPLE 87: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(3-hydroxypropylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a)
and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[(3-hydroxypropylamino)methyl]-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

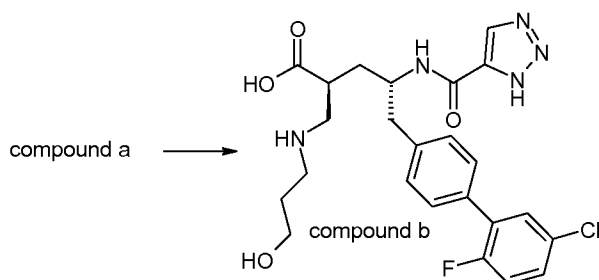


(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na₂CO₃ (152 mg, 1.4 mmol) and 3-aminopropan-1-ol (54 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H₂O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/H₂O gradient) to yield Compound 1 (25 mg).

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred at room temperature for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in without purification.



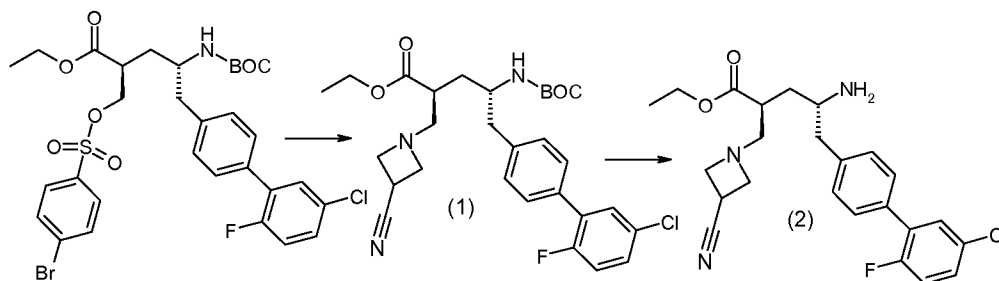
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a as a TFA salt (1 mg). MS m/z $[M+H]^+$ calc'd for $C_{26}H_{31}ClFN_5O_4$, 532.21; found 532. Half of the crude product was carried to the next step without further purification.



Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (2 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (4 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{27}ClFN_5O_4$, 504.17; found 504.

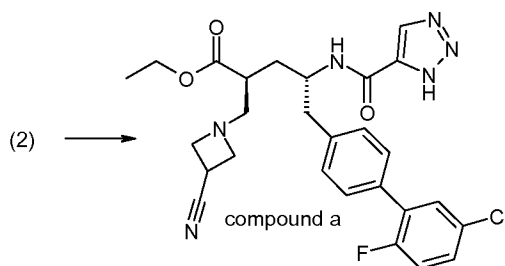
EXAMPLE 88: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-
(3-cyanoazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a)
and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-
(3-cyanoazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid (Compound b)

5



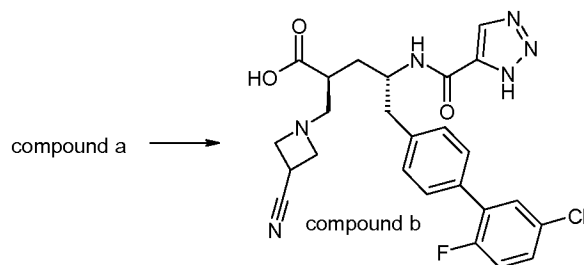
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and azetidine-3-carbonitrile (59 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H_2O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/ H_2O gradient) to yield Compound 1 (30 mg).

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used without purification.



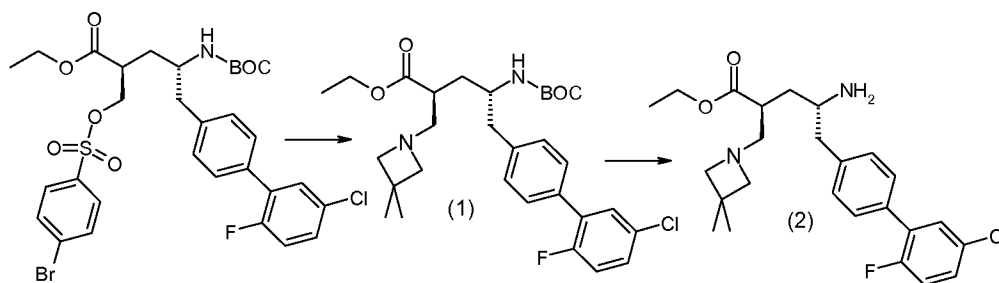
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added,

followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (7.7 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{28}ClFN_6O_3$, 539.19; found 539. Half of the crude product was carried to the next step without further purification.



Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (3 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (3 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{24}ClFN_6O_3$, 511.16; found 511.

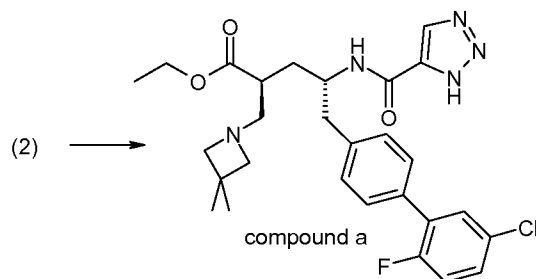
EXAMPLE 89: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3,3-dimethylazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3,3-dimethylazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)



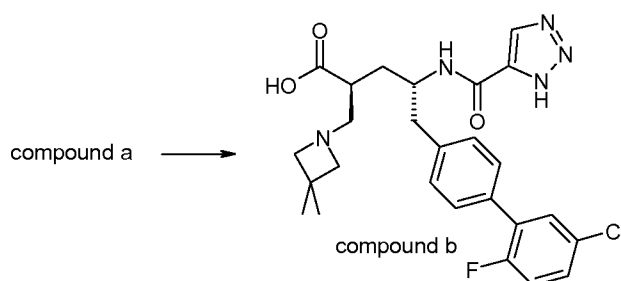
(2S,4S)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and 3,3-dimethylazetidine (61 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL)

and H₂O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/H₂O gradient) to yield Compound 1 (40 mg).

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was carried to the next step without purification.



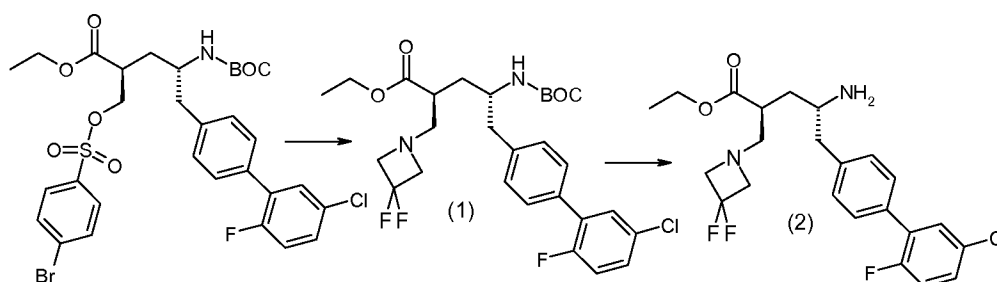
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (12.1 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for C₂₈H₃₃ClFN₅O₃, 542.23; found 542. Half of the crude product was used in the next step without purification.



Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (2 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (7 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for C₂₆H₂₉ClFN₅O₃, 514.19; found 514.

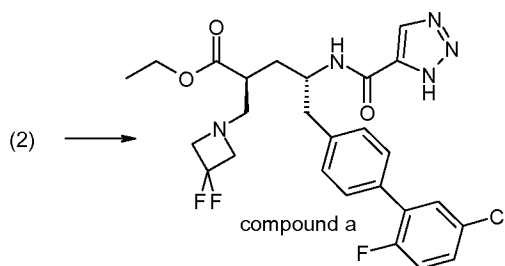
EXAMPLE 90: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3,3-
difluoroazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic
Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-
4-yl)-2-(3,3-difluoroazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid (Compound b)

5



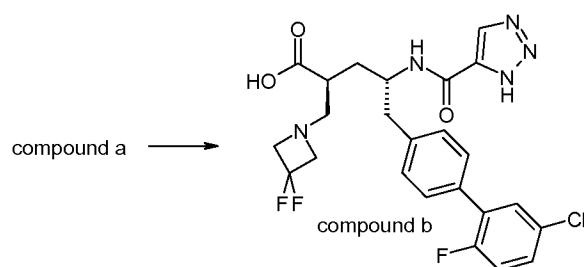
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and 3,3-difluoroazetidine (67 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H_2O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/ H_2O gradient) to yield Compound 1 (8 mg).

Compound 1 (28 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without further purification.



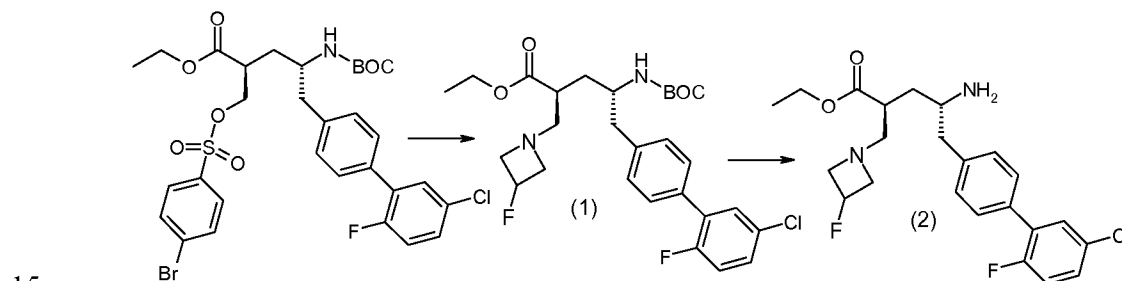
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added,

followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (1.4 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{27}ClF_3N_5O_3$, 550.18; found 550. Half of the crude product was used in the next step without further purification.



Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (0.8 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{23}ClF_3N_5O_3$, 522.14; found 522.

EXAMPLE 91: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-fluoroazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-fluoroazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

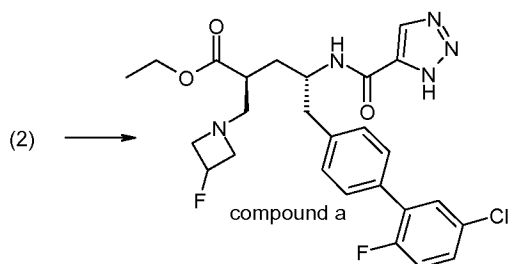


15

(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and 3-fluoroazetidine (54 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H_2O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/ H_2O gradient) to yield Compound 1 (25 mg).

20

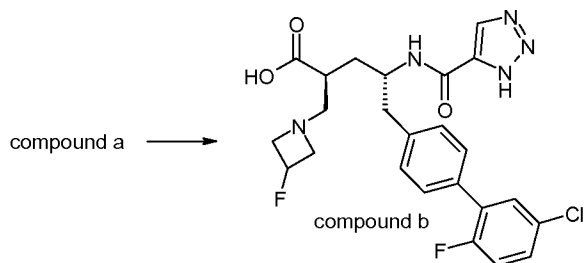
Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without further purification.



5

1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (3.5mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{28}ClF_2N_5O_3$, 532.19; found 532. Half of the crude product was carried to the next step without purification.

10

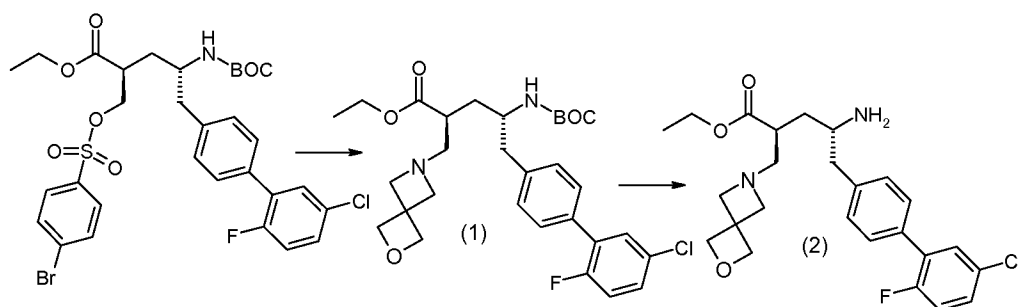


15

Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (1.2 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{24}ClF_2N_5O_3$, 504.15; found 504.

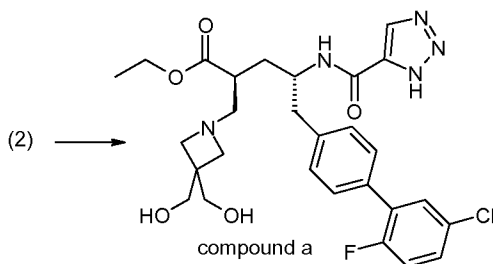
EXAMPLE 92: (2*S*,4*S*)-2-(3,3-Bis-hydroxymethylazetidin-1-ylmethyl)-
5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-2-
(3,3-Bis-hydroxymethylazetidin-1-ylmethyl)-5-(5'-chloro-2'-fluorobiphenyl-
4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

5



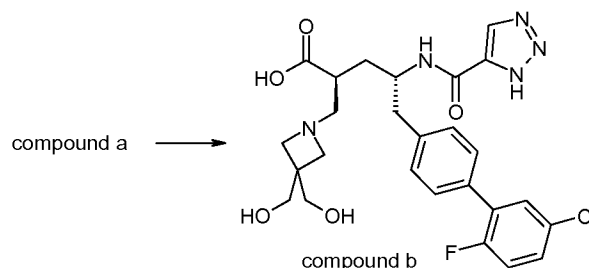
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (100 mg, 143 μ mol) was dissolved in EtOH (3 mL), followed by addition of Na_2CO_3 (152 mg, 1.4 mmol) and 2-oxa-6-aza-
 10 spiro[3.3]heptane (71 mg, 715 μ mol). The resulting mixture was stirred for 2 days at 70°C, at which time LCMS indicated the mass of the desired compound. The mixture was concentrated under reduced pressure and the crude residue was dissolved in AcOH (4 mL) and H_2O (1 mL) and purified by reverse phase chromatography (10-80% MeCN/ H_2O gradient) to yield Compound 1 (20 mg).

15 Compound 1 (28 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without purification.



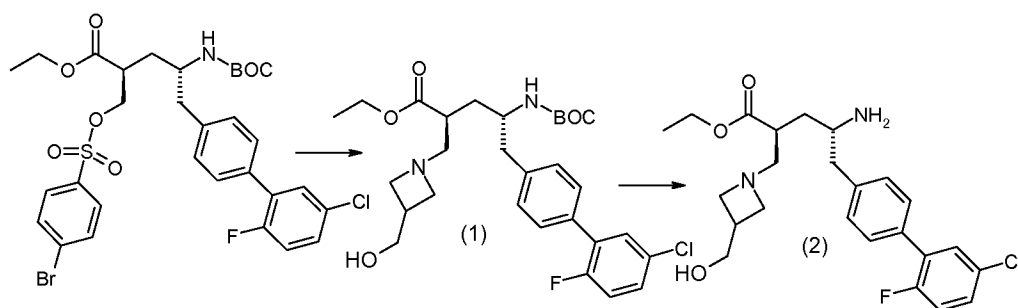
20 1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by

addition of the activated acid solution. The mixture was stirred at room temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (2.9 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{28}H_{33}ClFN_5O_5$, 574.22; found 574. Half of the crude product was used in the next step without purification.



Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (1 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{29}ClFN_5O_5$, 546.18; found 546.

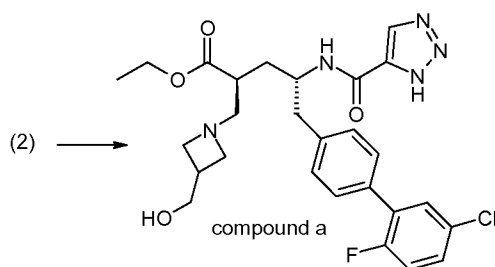
EXAMPLE 93: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxymethyl-azetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxymethyl-azetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)



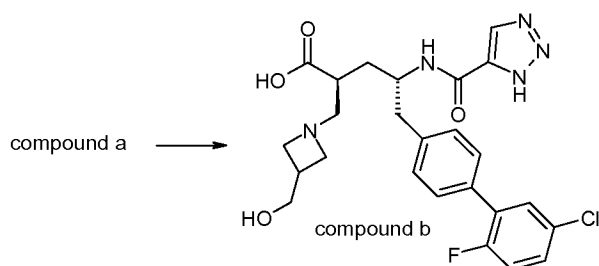
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (75 mg, 107 μ mol) was dissolved in EtOH (2 mL), followed by the addition of azetidin-3-yl-methanol (9.4 mg, 107 μ mol). The resulting mixture was stirred at 70°C overnight, at which time LCMS indicated the mass of the desired compound. The organic layer was evaporated and the residue was purified by reverse phase chromatography to yield Compound 1 (30 mg).

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in

dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without purification.



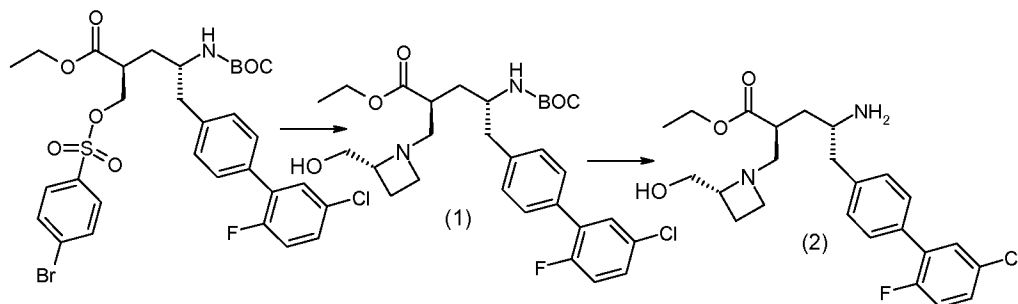
- 5 1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room
- 10 temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (20 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}ClFN_5O_4$, 544.21; found 544. Half of the crude product was used in the next step without purification.



- 15 Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (10 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

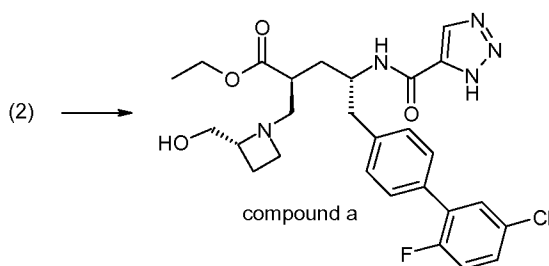
EXAMPLE 94: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((*R*)-2-hydroxymethylazetidin-1-ylmethyl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and
(2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((*R*)-2-hydroxymethylazetidin-1-ylmethyl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

5



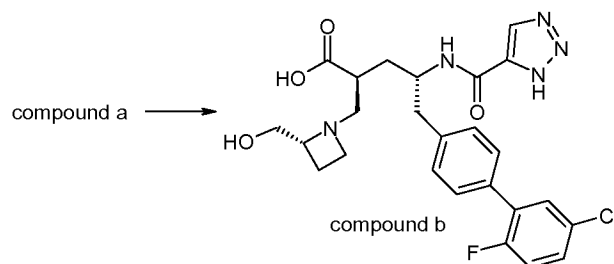
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (75 mg, 107 μ mol) was dissolved
 10 in EtOH (2 mL), followed by the addition of (2*R*)-2-azetidinylmethanol (18.7 mg, 215 μ mol). The resulting mixture was stirred at 70°C overnight, at which time LCMS indicated the mass of the desired compound. The organic layer was evaporated and the residue was purified by reverse phase chromatography to yield Compound 1 (28 mg).

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4*N* HCl in
 15 dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without purification.



1*H*-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU
 20 (11 mg, 30 μ mol) in DMF (0.3 mL) stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room temperature for 30

minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (5.2 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}ClFN_5O_4$, 544.21; found 544. Half of the crude product was used in the next step without purification.



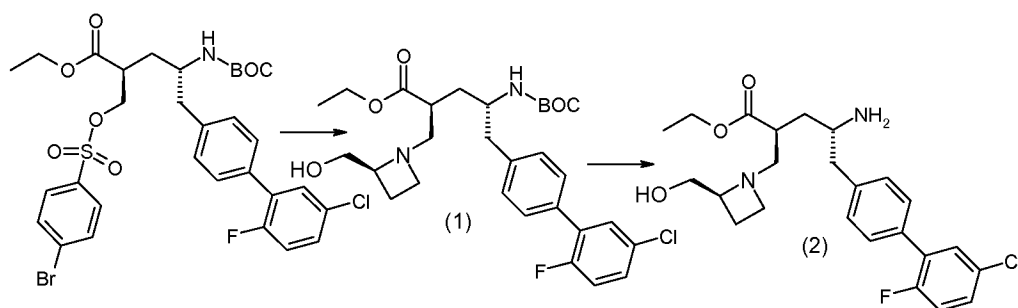
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Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (10 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

10

EXAMPLE 95: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((*S*)-2-hydroxymethylazetidin-1-ylmethyl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((*S*)-2-hydroxymethylazetidin-1-ylmethyl)-4-[(3*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

15

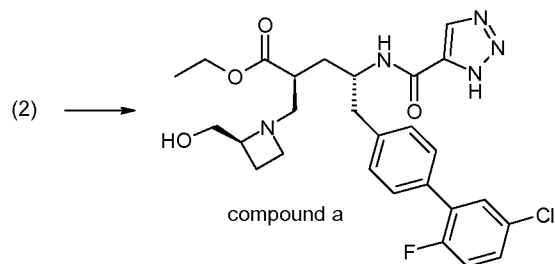


(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (75 mg, 107 μ mol) was dissolved in EtOH (2 mL), followed by the addition of (2*S*)-2-azetidinylmethanol (9.4 mg, 107 μ mol). The resulting mixture was stirred at 70°C overnight, at which time LCMS indicated the mass of the desired compound. The organic layer was evaporated and the residue was purified by reverse phase chromatography to yield Compound 1 (10 mg).

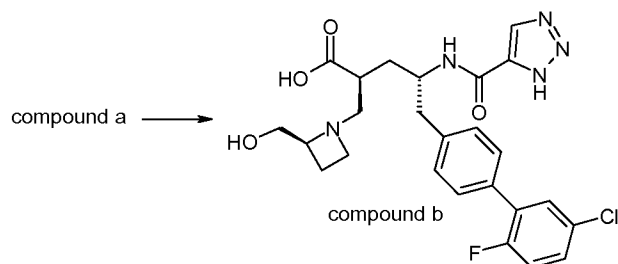
20

Compound 1 (27 mg; 50 μ mol) was dissolved in MeCN (1 mL) and dry 4N HCl in

dioxane (0.5 mL). The mixture was stirred for 10 minutes and then concentrated under reduced pressure to yield Compound 2 as an HCl salt, which was used in the next step without purification.



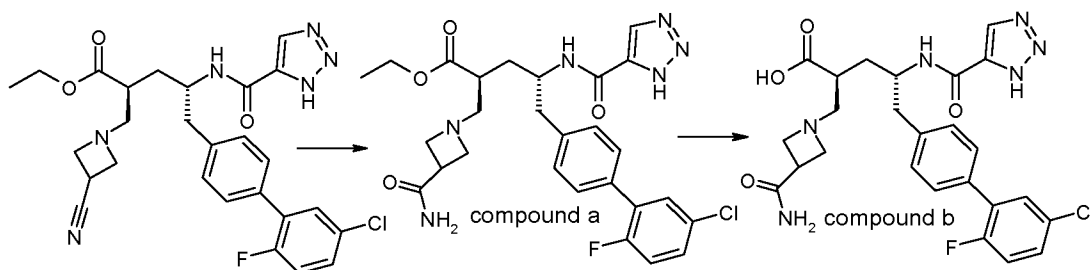
- 5 1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) was dissolved in DMF (0.5 mL) and DIPEA (5.2 μ L, 30 μ mol) was added, followed by addition of the activated acid solution. The mixture was stirred at room
- 10 temperature for 30 minutes, after which time LCMS indicated desired product formation. Half of the crude product was purified using reverse phase chromatography to yield Compound a (4.3 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}ClFN_5O_4$, 544.21; found 544. Half of the crude product was used in the next step without purification.



- 15 Crude Compound a (12 mg, 22 μ mol) was dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred for 2 hours at 50°C. AcOH (1 mL) was added and the solution was purified by reverse phase chromatography to yield Compound b (10 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

EXAMPLE 96: (2*S*,4*S*)-2-(3-Carbamoylazetid-1-ylmethyl)-5-
(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a) and (2*S*,4*S*)-2-(3-
Carbamoylazetid-1-ylmethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-
[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b)

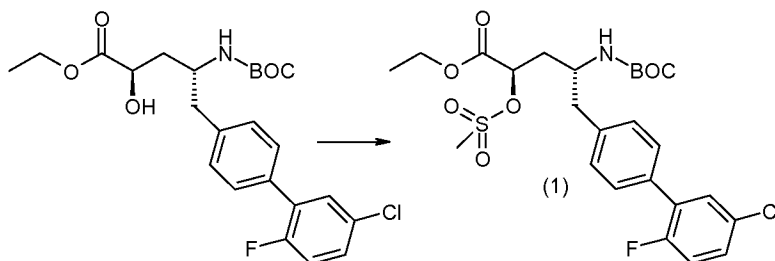
5



(2*S*,4*S*)-5-(5'-Chloro-2'-fluoro-biphenyl-4-yl)-2-(3-cyanoazetidin-1-ylmethyl)-4-
 [(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic acid ethyl ester (12 mg, 22 μ mol) was
 dissolved in THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and MeOH (2 drops), and stirred
 10 for 2 hours at 50°C to yield a mixture of the title compounds. AcOH (1 mL) was added
 and the solution was purified by reverse phase chromatography to yield Compound a (4.3
 mg) as a TFA salt (MS m/z $[M+H]^+$ calc'd for $C_{27}H_{30}ClFN_6O_4$, 557.20; found 557) and
 Compound b (2 mg) as a TFA salt (MS m/z $[M+H]^+$ calc'd for $C_{25}H_{26}ClFN_6O_4$, 529.17;
 found 529).

15

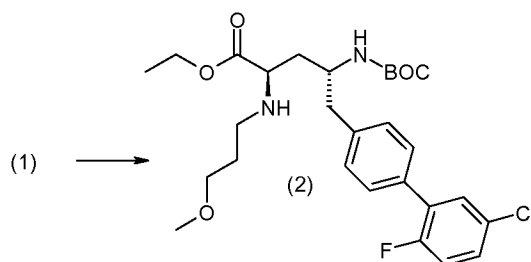
EXAMPLE 97: (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-
(3-methoxypropylamino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic
Acid (Compound a) and (2*R*,4*R*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-
2-(3-methoxypropylamino)-4-[(1H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid Ethyl Ester (Compound b)



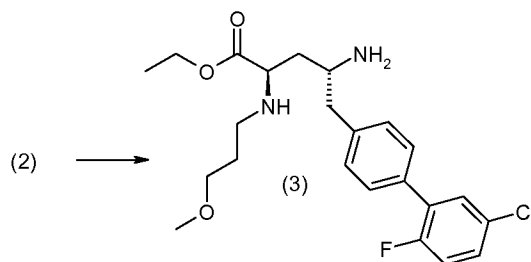
20

(2*R*,4*R*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-
 pentanoic acid ethyl ester (137 mg, 294 μ mol) was dissolved in DCM (5 mL).
 Methanesulfonyl chloride (23 μ L, 294 μ mol) was added, followed by Et₃N (82 μ L, 0.6
 mmol). The mixture was stirred at room temperature for 10 minutes, at which time LCMS

indicated the mass of the desired compound. The solvent was removed *in vacuo* to yield crude Compound 1, which was used directly in the next step.



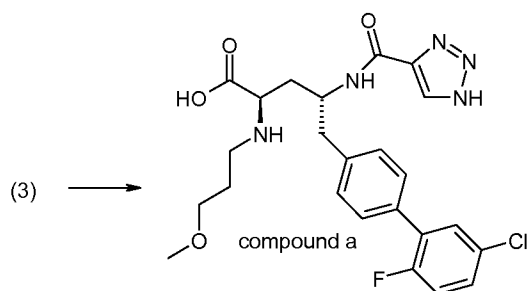
Compound 1 (53 mg, 97 μ mol) was dissolved in DMF (4 mL). 3-methoxypropylamine (10.9 μ L, 107 μ mol) and Na_2CO_3 (31.0 mg, 292 μ mol) were then added, and the resulting mixture was stirred overnight at 70°C, at which time LCMS indicated the mass of the desired compound. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound 2 (10 mg).



10

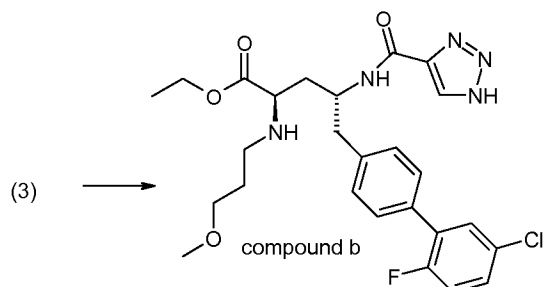
Compound 2 (10 mg, 19 μ mol) was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (70 μ L, 279 μ mol) was added, and the mixture was stirred at room temperature for 10 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* to yield the Compound 3 as an HCl salt, which was used without further purification.

15



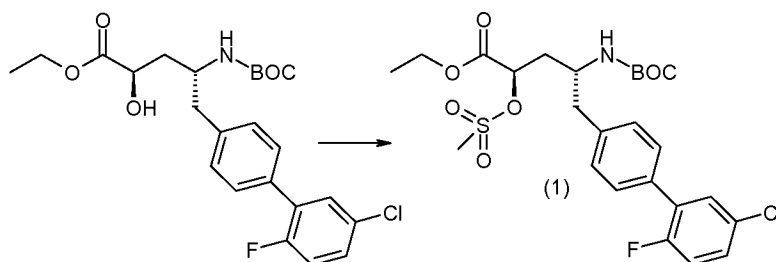
1H-1,2,3-triazole-4-carboxylic acid (2.3 mg, 20 μ mol) was combined with HATU (7.7 mg, 20 μ mol) in DMF (2 mL) and stirred at room temperature for 15 minutes. Compound 3 (8 mg, 18 μ mol) and DIPEA (9.6 μ L, 55 μ mol) were then added. The

solution was stirred at room temperature for 15 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was dissolved in EtOH (2 mL). A solution of 1N LiOH (183 μ L, 183 μ mol) in water was added, and the resulting solution was stirred at room temperature for 30 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound a (3 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{24}H_{27}ClFN_5O_4$, 504.17; found 504.



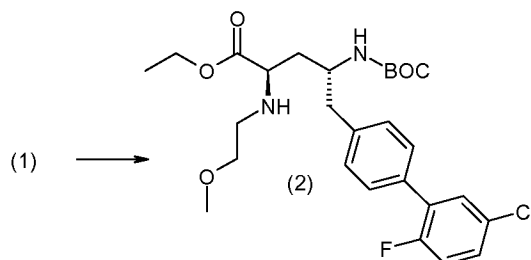
1H-1,2,3-triazole-4-carboxylic acid (3.8 mg, 34 μ mol) was combined with HATU (12.9 mg, 34 μ mol) in DMF (2 mL) and stirred at room temperature for 15 minutes. Compound 3 (60 mg, 137 μ mol) and DIPEA (16 μ L, 92 μ mol) were then added. The solution was stirred at room temperature for 15 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound b (18.5 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{31}ClFN_5O_4$, 532.21; found 532.

EXAMPLE 98: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-methoxyethylamino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound a) and (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-methoxyethylamino)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound b)



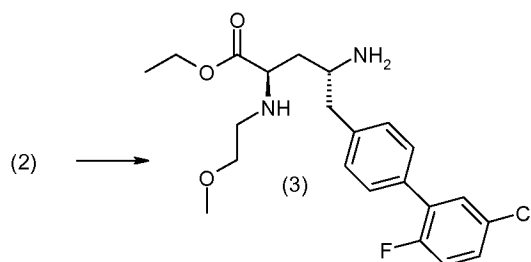
(2R,4R)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxy-pentanoic acid ethyl ester (137 mg, 294 μ mol) was dissolved in DCM (5 mL).

Methanesulfonyl chloride (23 μ L, 294 μ mol) was added, followed by Et₃N (82 μ L, 0.6 mmol). The mixture was stirred at room temperature for 10 minutes, at which time LCMS indicated the mass of the desired compound. The solvent was removed *in vacuo* to yield crude Compound 1, which was used directly in the next step.

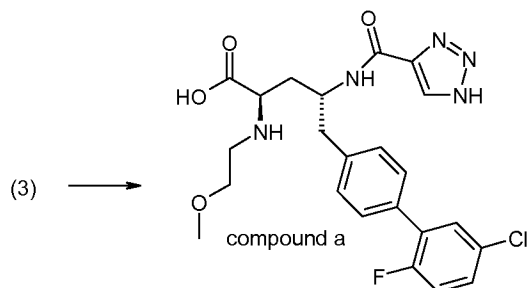


5

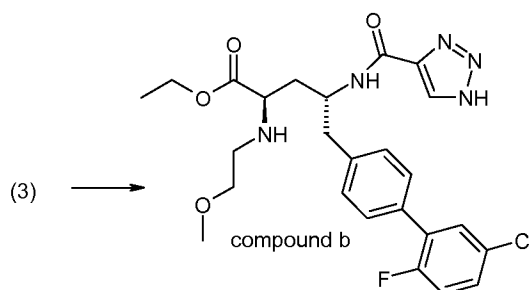
Compound 1 (53 mg, 97 μ mol) was dissolved in DMF (4 mL). 2-methoxyethylamine (9.3 μ L, 107 μ mol) and Na₂CO₃ (31.0 mg, 292 μ mol) were then added, and the resulting mixture was stirred overnight at 70°C, at which time LCMS indicated the mass of the desired compound. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound 2 (10 mg).



Compound 2 (10 mg, 19 μ mol) was dissolved in MeCN (2 mL). A solution of 4N HCl in dioxane (70 μ L, 279 μ mol) was added, and the mixture was stirred at room temperature for 10 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* to yield Compound 3 as an HCl salt, which was used without further purification.

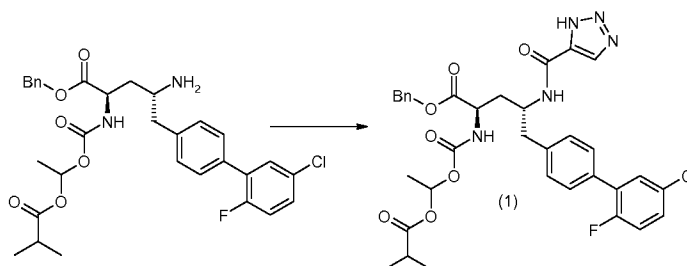


1H-1,2,3-triazole-4-carboxylic acid (2.3 mg, 20 μ mol) was combined with HATU (7.7 mg, 20 μ mol) in DMF (2 mL) and stirred at room temperature for 15 minutes. Compound 3 (7.7 mg, 18 μ mol) and DIPEA (9.6 μ L, 55 μ mol) were then added. The solution was stirred at room temperature for 15 minutes, at which time LCMS showed
 5 reaction completion. The solvent was removed *in vacuo* and the crude residue was dissolved in EtOH (2 mL). A solution of 1N LiOH (183 μ L, 183 μ mol) in water was added, and the resulting solution was stirred at room temperature for 30 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound a (3 mg) as a
 10 TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{23}H_{25}ClFN_5O_4$, 490.16; found 488.



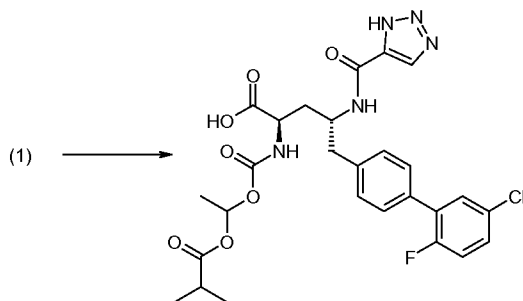
1H-1,2,3-triazole-4-carboxylic acid (3.8 mg, 34 μ mol) was combined with HATU (12.9 mg, 34 μ mol) in DMF (2 mL) and stirred at room temperature for 15 minutes. Compound 3 (13 mg, 31 μ mol) and DIPEA (16 μ L, 92 μ mol) were then added. The
 15 solution was stirred at room temperature for 15 minutes, at which time LCMS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound b (15 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{29}ClFN_5O_4$, 518.19; found 518.

20 EXAMPLE 99: (2R,4R)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(1-isobutyryloxyethoxycarbonylamino)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



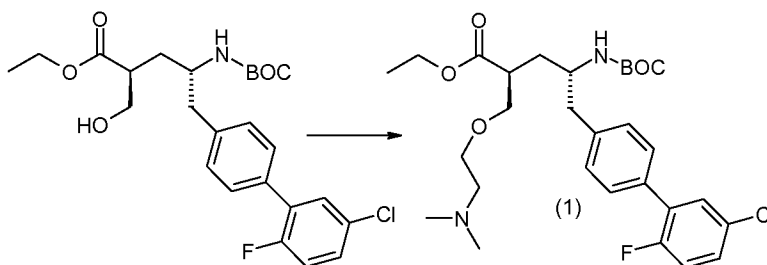
1H-1,2,3-triazole-5-carboxylic acid (3.4 mg, 30 μ mol) and HATU (11.4 mg, 30 μ mol) were dissolved in DMF (0.5 mL) and stirred at room temperature. A solution of

(2*R*,4*R*)-4-amino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-(1-isobutyryloxy-ethoxycarbonylamino)pentanoic acid benzyl ester (19 mg, 27 μ mol) in DMF (0.5 mL) was added to this solution, followed by DIPEA (14 μ L, 82 μ mol). The resulting solution was stirred at room temperature for 90 minutes and then concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (0-100% EtOAc:hexanes) to yield Compound 1 (13 mg) as a clear oil.



Compound 1 (13 mg, 19 μ mol) and palladium (10wt% on carbon, 20.3 mg, 19 μ mol) were mixed in EtOAc (956 μ L) and AcOH (956 μ L). Hydrogen was bubbled through the resulting solution at room temperature for 50 minutes. The mixture was filtered through Celite[®] and the solution was concentrated *in vacuo*. The residue was diluted in a 1:1 mixture of AcOH:H₂O (1.5 mL) and purified by preparative HPLC to yield the title compound (6.2 mg). MS *m/z* [M+H]⁺ calc'd for C₂₇H₂₉ClFN₅O₇, 590.17; found 612.2; two peaks were observed in the MS trace due to the presence of diastereomers; note that the mass of the title compound plus the mass of sodium (+23) was observed in the MS rather than the expected +1.

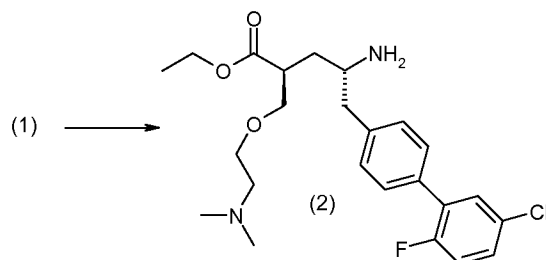
EXAMPLE 100: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(2-(dimethylamino)ethoxymethyl)-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



20

(2*S*,4*S*)-4-*t*-Butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-2-hydroxymethylpentanoic acid ethyl ester (66 mg, 138 μ mol) was dissolved in dry toluene (4 mL). 2-Bromo-*N,N*-dimethylethanamine (418 mg, 2.8 mmol), silver oxide (382 mg, 1.7

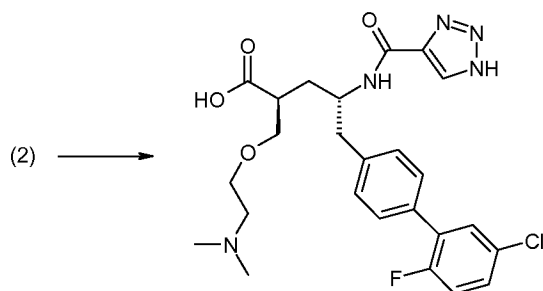
mmol) and tetrabutylammonium iodide (25.4 mg, 69 μ mol) were then added. The mixture was stirred overnight at 50°C. LC/MS showed the mass of the desired product. The solids were filtered and the solvent was removed *in vacuo*. The crude residue was purified by normal phase chromatography (20-95% EtOAc/hexanes) to yield Compound 1 (109 mg).



5

Compound 1 (109 mg, 198 μ mol) was dissolved in MeCN (4.0 mL). A solution of 4N HCl in dioxane (742 μ L, 3.0 mmol) was added. The solution was stirred at room temperature for 15 minutes; LC/MS showed reaction completion. The solvent was removed *in vacuo*, to yield Compound 2 as an HCl salt, was used in the next step without purification.

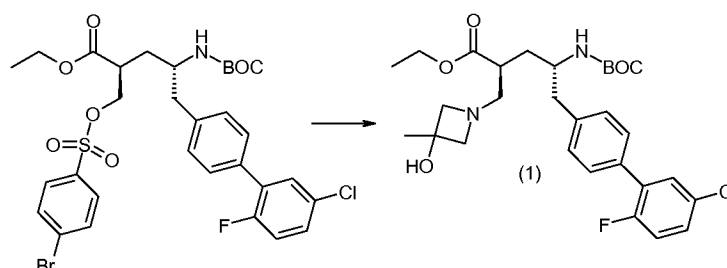
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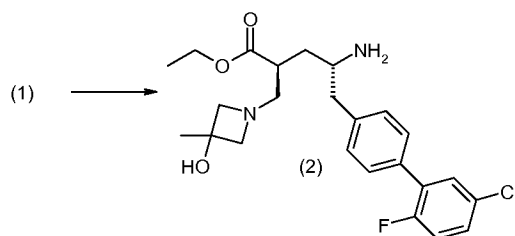
1H-1,2,3-triazole-4-carboxylic acid (24.6 mg, 217 μ mol) was combined with HATU (83 mg, 217 μ mol) in DMF (0.3 mL) and stirred at room temperature for 15 minutes. Compound 2 (89 mg, 197 μ mol) and DIPEA (103 μ L, 592 μ mol) were then added. The resulting solution was stirred at room temperature for 15 minutes; LC/MS showed the mass of the desired product. The solvent was removed *in vacuo* and the crude residue was dissolved in EtOH (3.0 mL). A solution of 1N LiOH in water (1.6 mL, 1.6 mmol) was added, and the mixture was stirred overnight at 40°C. LC/MS showed the mass of the desired product. The solvent was removed *in vacuo* and the crude residue was purified by preparative HPLC to yield the title compound (5 mg) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for C₂₅H₂₉ClFN₅O₄, 518.19; found 518.2.

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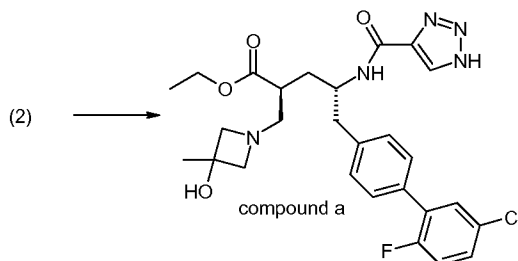
EXAMPLE 101: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxy-3-methylazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a), (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxy-3-methylazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b), and (2*R*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-hydroxy-3-methylazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound c)



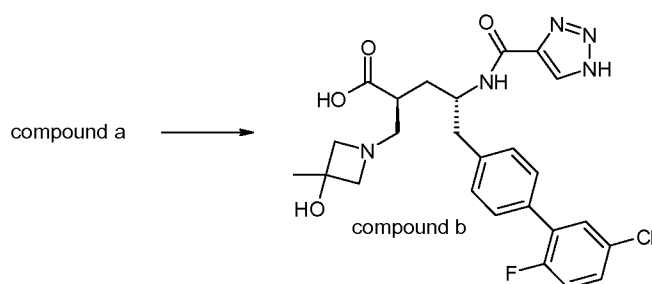
(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (50 mg, 72 μ mol) was dissolved in EtOH (3.0 mL). 3-Methyl-azetidin-3-ol (62 mg, 358 μ mol) and Na₂CO₃ (76 mg, 715 μ mol) were added, and the resulting mixture was stirred at 70°C for 2 days, after which time LCMS indicated desired product formation. The solvent was removed under reduced pressure and the crude residue was purified by reverse phase chromatography (10-80% MeCN/H₂O) to yield Compound 1 (40 mg).



Compound 1 (16 mg) was combined with MeCN (1 mL) and 4 N HCl in dioxane (0.5 mL) and stirred for 10 minutes. The solvent was removed under reduced pressure to yield Compound 2 as an HCl salt, which was used directly in the next step.



3H-1,2,3-triazole-4-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) in DMF (0.5 mL) was combined with DIPEA (5.2 μ L, 30 μ mol), then added to
5 the activated acid solution. The resulting solution was stirred at room temperature for 30 minutes; LC/MS showed the mass of the desired product. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound a (6.1 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}ClFN_5O_4$, 544.21; found 545.2.

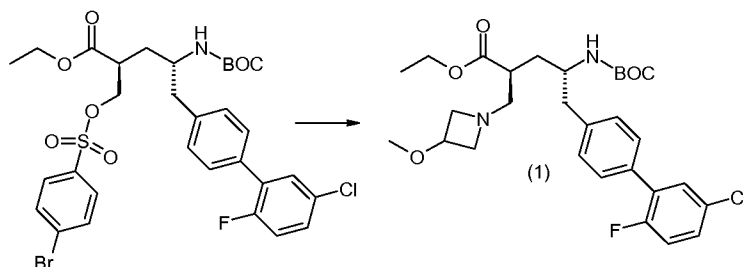


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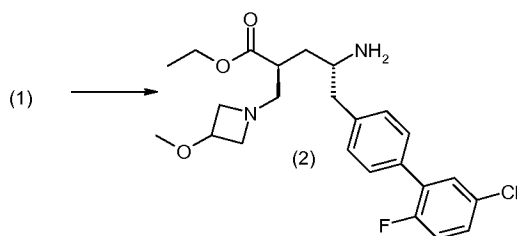
Compound a (12 mg, 22 μ mol) was combined with THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and 2 drops of MeOH. The resulting mixture was stirred for 2 hours at 50°C; LC/MS showed the mass of the desired product. The solution was then purified by reverse phase chromatography to yield Compound b as a TFA salt. MS m/z $[M+H]^+$ calc'd for
15 $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

Compound c was prepared in a similar manner using the appropriate starting materials. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

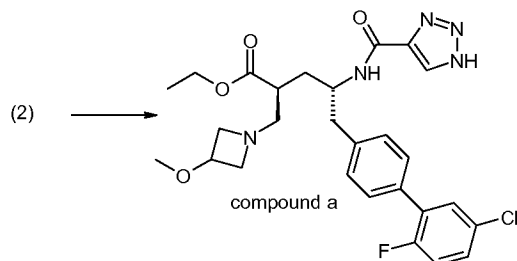
EXAMPLE 102: (2S,4S)-5-(5'-(5-Chloro-2'-fluorobiphenyl-4-yl)-2-(3-methoxy-
azetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic
Acid Ethyl Ester (Compound a), (2S,4S)-5-(5'-(5-Chloro-2'-fluorobiphenyl-
4-yl)-2-(3-methoxyazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-4-
 5 carbonyl)amino]pentanoic Acid (Compound b), and (2R,4S)-5-(5'-(5-Chloro-
2'-fluorobiphenyl-4-yl)-2-(3-methoxyazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-
4-carbonyl)amino]pentanoic Acid (Compound c)



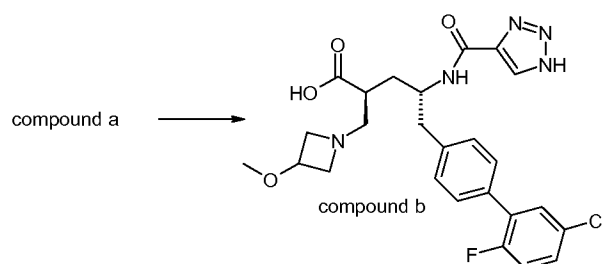
(2S,4S)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-
 10 chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (50 mg, 72 μ mol) was dissolved in
 EtOH (3.0 mL). 3-Methoxy-azetidine (62 mg, 358 μ mol) and Na_2CO_3 (76 mg, 715 μ mol)
 were added, and the resulting mixture was stirred at 70°C for 2 days, after which time
 LCMS indicated desired product formation. The solvent was removed under reduced
 pressure and the crude residue was purified by reverse phase chromatography (10-80%
 15 MeCN/ H_2O) to yield Compound 1 (8 mg).



Compound 1 (16 mg) was combined with MeCN (1 mL) and 4 N HCl in dioxane
 (0.5 mL) and stirred for 10 minutes. The solvent was removed under reduced pressure to
 yield Compound 2 as an HCl salt, which was used directly in the next step.



3H-1,2,3-triazole-4-carboxylic acid (3.4 mg, 30 μ mol) was combined with HATU (11 mg, 30 μ mol) in DMF (0.3 mL) and stirred at room temperature for 10 minutes; DIPEA (1 eq.) was added and the mixture was stirred for 1 minute. Compound 2 (10 mg, 30 μ mol) in DMF (0.5 mL) was combined with DIPEA (5.2 μ L, 30 μ mol), then added to
5 the activated acid solution. The resulting solution was stirred at room temperature for 30 minutes; LC/MS showed the mass of the desired product. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound a (8.5 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{27}H_{31}ClFN_5O_4$, 544.21; found 545.2.

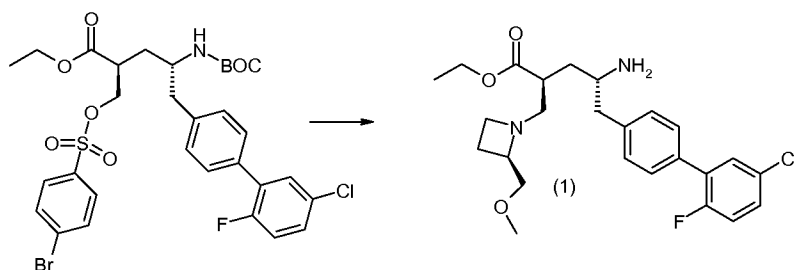


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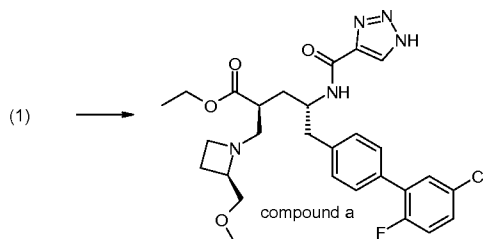
Compound a (12 mg, 22 μ mol) was combined with THF (0.3 mL), 1N LiOH (88 μ L, 88 μ mol) and 2 drops of MeOH. The resulting mixture was stirred for 2 hours at 50°C; LC/MS showed the mass of the desired product. The solution was then purified by reverse phase chromatography to yield Compound b as a TFA salt. MS m/z $[M+H]^+$ calc'd for
15 $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

Compound c was prepared in a similar manner using the appropriate starting materials. MS m/z $[M+H]^+$ calc'd for $C_{25}H_{27}ClFN_5O_4$, 516.17; found 516.

EXAMPLE 103: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((R)-2-methoxymethylazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl Ester (Compound a), (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((R)-2-methoxymethylazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid (Compound b),
(2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((S)-2-methoxymethylazetidin-1-ylmethyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid Ethyl
Ester (Compound c), and (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-((S)-2-methoxymethylazetidin-1-ylmethyl)-4-[(3H-[1,2,3]triazole-4-
carbonyl)amino]pentanoic Acid (Compound d)



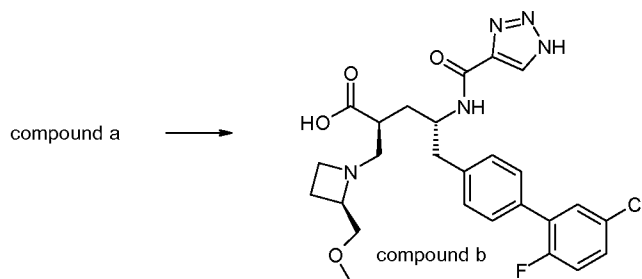
(2S,4S)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (80 mg, 114 μ mol) was dissolved in EtOH (3.0 mL). (*R*)-2-(methoxymethyl)azetidine (34.7 mg, 343 μ mol) and Na₂CO₃ (121 mg, 1.1 mmol) were added, and the resulting mixture was stirred at 70°C overnight, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography (26.4 mg). The residue was dissolved in MeCN (3.0 mL). A solution of 4N HCl in dioxane (653 μ L, 2.6 mmol) was added, and the resulting solution was stirred at room temperature for 20 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* to yield Compound 1 as an HCl salt.



1H-1,2,3-triazole-4-carboxylic acid (9.8 mg, 87 μ mol) and HATU (36.4 mg, 96 μ mol) were combined in DMF (3.0 mL) and stirred at room temperature for 15 minutes.

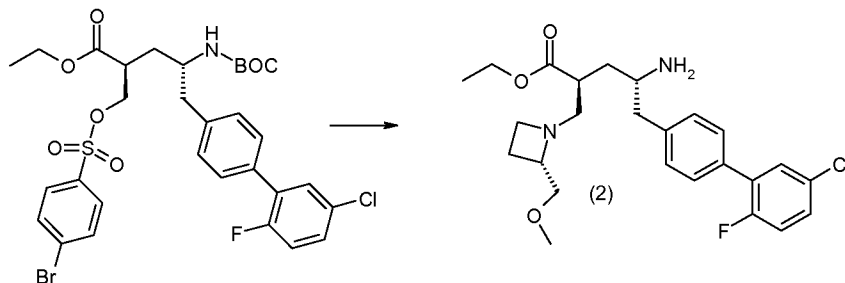
Compound 1 (40.3 mg, 87 μmol) and DIPEA (46 μL , 261 μmol) were added and the resulting solution was stirred at room temperature for 15 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound a (5.2 mg) as a

5 TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{28}\text{H}_{33}\text{ClFN}_5\text{O}_4$, 558.22; found 558.



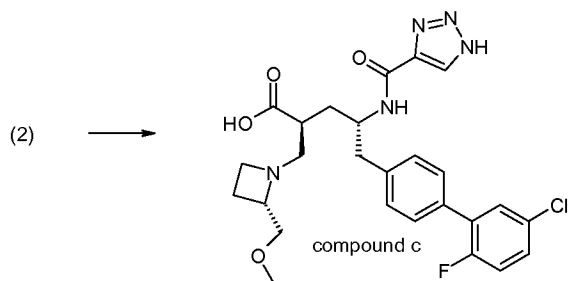
Compound a (5.2 mg, 9.3 μmol) was dissolved in EtOH (3.0 mL). A solution of 1N LiOH (75 μL , 75 μmol) in water was added, and the resulting solution was stirred at room temperature overnight, after which time LCMS indicated desired product formation.

10 The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound b (4.0 mg) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{26}\text{H}_{29}\text{ClFN}_5\text{O}_4$, 530.19; found 530.

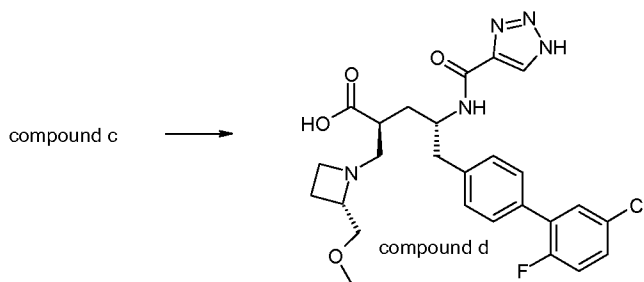


(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (80 mg, 114 μmol) was dissolved in EtOH (3.0 mL). (*S*)-2-(methoxymethyl)azetidine (34.7 mg, 343 μmol) and Na_2CO_3 (121 mg, 1.1 mmol) were added, and the resulting mixture was stirred at 70°C overnight, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography (49 mg). The residue

20 was dissolved in MeCN (3.0 mL). A solution of 4N HCl in dioxane (653 μL , 2.6 mmol) was added, and the resulting solution was stirred at room temperature for 20 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* to yield Compound 2 as an HCl salt.

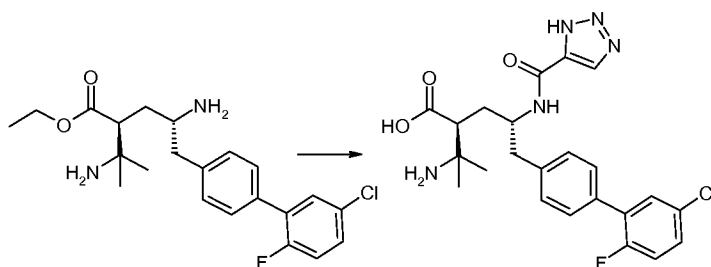


1H-1,2,3-triazole-4-carboxylic acid (9.8 mg, 87 μ mol) and HATU (36.4 mg, 96 μ mol) were combined in DMF (3.0 mL) and stirred at room temperature for 15 minutes. Compound 2 (40.3 mg, 87 μ mol) and DIPEA (46 μ L, 261 μ mol) were added and the resulting solution was stirred at room temperature for 15 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound c (34.5 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{28}H_{33}ClFN_5O_4$, 558.22; found 558.



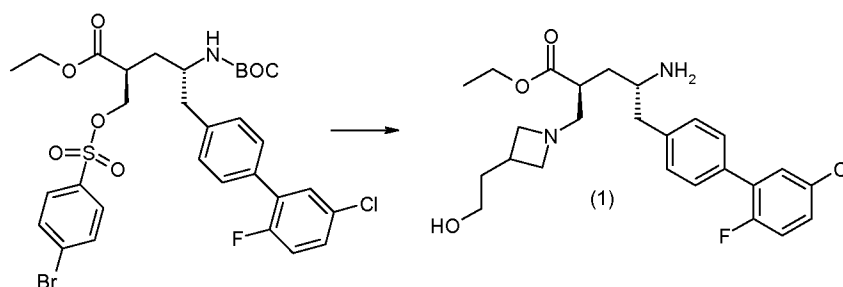
Compound c (26 mg, 47 μ mol) was dissolved in EtOH (3.0 mL). A solution of 1N LiOH (75 μ L, 75 μ mol) in water was added, and the resulting solution was stirred at room temperature overnight, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield Compound d (15 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{29}ClFN_5O_4$, 530.19; found 530.

EXAMPLE 104: (2S,4S)-2-(1-Amino-1-methylethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)-4-[(3H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



1H-1,2,3-triazole-5-carboxylic acid (15.3 mg, 135 μ mol) and HATU (51.4 mg, 135 μ mol) were mixed in DMF (4 mL) and stirred at room temperature for 15 minutes. (2*S*,4*S*)-4-Amino-2-(1-amino-1-methylethyl)-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (50 mg, 123 μ mol) and DIPEA (64 μ L, 369 μ mol) were added. The resulting solution was stirred at room temperature for 15 minutes, at which point LC/MS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was diluted in EtOH (4 mL). A solution of 1N LiOH (983 μ L, 983 μ mol) in water was then added. The resulting solution was stirred at 60°C for 2 days, at which point LC/MS showed reaction completion. The solvent was removed *in vacuo* and the crude residue was purified by preparative HPLC to yield the title compound (4.2 mg) as a TFA salt. MS *m/z* [M+H]⁺ calc'd for C₂₃H₂₅ClFN₅O₃, 474.16; found 474.2.

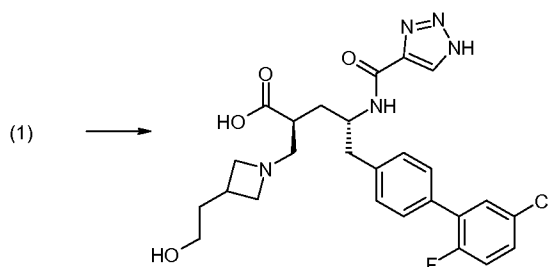
EXAMPLE 105: (2*S*,4*S*)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-[3-(2-hydroxyethyl)azetidin-1-ylmethyl]-4-[(1*H*-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



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(2*S*,4*S*)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (60 mg, 86 μ mol) was dissolved in EtOH (3.0 mL). 2-(Azetidin-3-yl)ethan-1-ol HCl (26.0 mg, 258 μ mol) and Na₂CO₃ (91 mg, 858 μ mol) were added, and the resulting mixture was stirred at 70°C overnight, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography (60 mg). The residue (60 mg, 107 μ mol) was dissolved in MeCN (3.0 mL). A solution of 4N HCl in dioxane (653 μ L, 2.6 mmol) was added, and the resulting solution was stirred at room temperature for 20 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* to yield Compound 1 as an HCl salt.

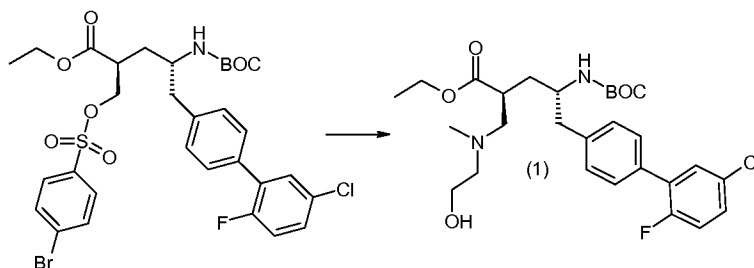
25



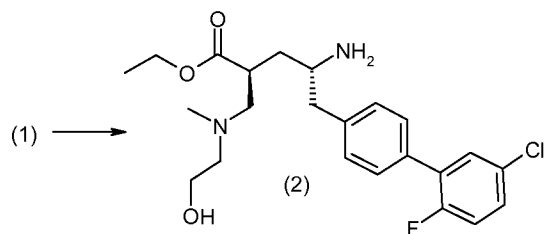
1H-1,2,3-triazole-4-carboxylic acid (9.8 mg, 87 μ mol) and HATU (36.4 mg, 96 μ mol) were combined in DMF (3.0 mL) and stirred at room temperature for 15 minutes. Compound 1 (49.3 mg, 106 μ mol) and DIPEA (46 μ L, 261 μ mol) were added and the resulting solution was stirred at room temperature for 15 minutes, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography.

The residue (56.8 mg, 87 μ mol) was dissolved in EtOH (3.0 mL). A solution of 1N LiOH (696 μ L, 696 μ mol) in water was added, and the resulting solution was stirred at room temperature overnight, after which time LCMS indicated desired product formation. The solvent was removed *in vacuo* and the crude residue was purified by reverse phase chromatography to yield the title compound (36 mg) as a TFA salt. MS m/z $[M+H]^+$ calc'd for $C_{26}H_{29}ClFN_5O_4$, 530.19; found 530.

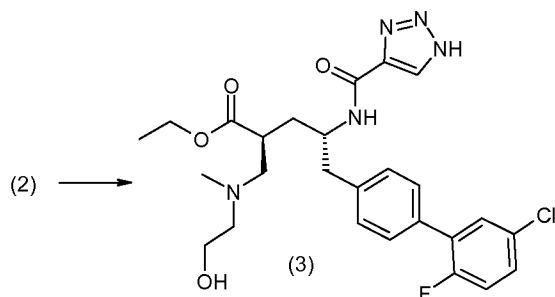
EXAMPLE 106: (2S,4S)-5-(5'-Chloro-2'-fluorobiphenyl-4-yl)-2-([(2-hydroxyethyl)-methylamino]methyl)-4-[(1H-[1,2,3]triazole-4-carbonyl)amino]pentanoic Acid



(2S,4S)-2-(4-Bromobenzenesulfonyloxymethyl)-4-*t*-butoxycarbonylamino-5-(5'-chloro-2'-fluorobiphenyl-4-yl)pentanoic acid ethyl ester (50 mg, 72 μ mol) was dissolved in EtOH (2 mL). 2-methoxy-N-methylethanamine (19.1 mg, 215 μ mol) was added and the resulting mixture was stirred at 50°C for 2 days, after which time LCMS indicated desired product formation. The organic layer was evaporated and the crude residue was purified by reverse phase chromatography to yield Compound 1 (20 mg).

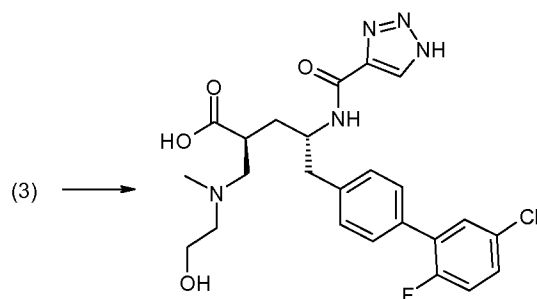


Compound 1 (15 mg, 28 μmol) was combined with MeCN (0.5 mL) and dry 4N HCl in dioxane (0.3 mL) and stirred for 10 minutes. The solvent was removed under reduced pressure to yield crude Compound 2, which was used directly in the next step.



5

1H-1,2,3-triazole-5-carboxylic acid (3.1 mg, 27 μmol) was combined with HATU (10.4 mg, 27 μmol) in DMF (0.5 mL), and stirred for 10 minutes. DIPEA (4.8 μL , 27 Mmol) was added and the resulting mixture was stirred for 1 minute. Compound 2 (12 mg, 27 μmol) dissolved in DMF (1 mL) was combined with added DIPEA (14.4 μL , 82 μmol) followed by addition of the activated acid solution. The resulting mixture was stirred for 30 minutes then purified by reverse phase chromatography (0-100% EtOAc/hexanes to yield Compound 3 (10 mg).



Compound 3 (9.0 mg, 17 μmol) was combined with 1N LiOH (84 μL , 84 μmol), THF (0.5 mL), and MeOH (0.1 mL). The mixture was stirred at room temperature for 1 hour, then purified by reverse phase chromatography to yield the title compound (1 mg) as a TFA salt. MS m/z $[\text{M}+\text{H}]^+$ calc'd for $\text{C}_{24}\text{H}_{27}\text{ClFN}_5\text{O}_4$, 504.17; found 504.

15

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

The inhibitory activities of compounds at human and rat neprilysin (EC 3.4.24.11; 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 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 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 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 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 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 ZnSO₄). The respective enzymes were used at concentrations that resulted in quantitative

proteolysis of 1 μ M of substrate after 20 minutes at 37°C.

Test compounds were assayed over the range of concentrations from 10 μ M to 20 pM. Test compounds were added to the enzymes and incubated for 30 minute at 37°C prior to initiating the reaction by the addition of substrate. Reactions were terminated after
 5 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 regression of the data using the equation (GraphPad Software, Inc., San Diego, CA):

$$10 \quad v = v_0 / [1 + (I / K')]$$

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 at human NEP as follows. In some instances, prodrug compounds did not inhibit the
 15 enzyme in this *in vitro* assay, or the prodrugs (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 necessarily possess pharmacological activity at NEP, but may be administered orally or parenterally and thereafter metabolized in the body to form
 20 compounds that are pharmacologically active at NEP) were not tested (n.d.) since activity would not be expected.

Ex.	pK_i
1	≥ 9.0
2-1	≥ 9.0
2-2	≥ 9.0
2-3	8.5-8.9
2-4	≥ 9.0
2-5	≥ 9.0
2-6	≥ 9.0
2-7	≥ 9.0
2-8	≥ 9.0
2-9	≥ 9.0
2-10	8.5-8.9
2-11	≥ 9.0
2-12	≥ 9.0
2-13	≥ 9.0
2-14	≥ 9.0
2-15	≥ 9.0

Ex.	pK_i
16-35	≥ 9.0
16-36	n.d.
17	≥ 9.0
18-1	8.0-8.5
18-2	≥ 9.0
18-3	≥ 9.0
18-4	8.0-8.5
18-5	8.5-8.9
18-6	≥ 9.0
18-7	7.5-8.0
18-8	≥ 9.0
18-9	8.0-8.5
18-10	≥ 9.0
18-11	≥ 9.0
18-12	8.0-8.5
19	n.d.

Ex.	pK_i
53	≥ 9.0
54	8.5-8.9
55	8.0-8.5
56	8.5-8.9
57	≥ 9.0
58	8.0-8.5
59	≥ 9.0
60	8.0-8.5
61a	≥ 9.0
61b	≥ 9.0
62	≥ 9.0
63	8.5-8.9
64	8.5-8.9
65	8.5-8.9
66	8.5-8.9
67	≥ 9.0

Ex.	pK _i
2-16	≥ 9.0
3	≥ 9.0
4-1	≥ 9.0
4-2	≥ 9.0
4-3	≥ 9.0
5	≥ 9.0
6	≥ 9.0
7-1	≥ 9.0
7-2	≥ 9.0
7-3	≥ 9.0
7-4	≥ 9.0
7-5	≥ 9.0
7-6	≥ 9.0
7-7	8.5-8.9
7-8	8.5-8.9
7-9	≥ 9.0
7-10	≥ 9.0
7-11	≥ 9.0
8	≥ 9.0
9-1	≥ 9.0
9-2	≥ 9.0
9-3	≥ 9.0
9-4	≥ 9.0
9-5	≥ 9.0
10	≥ 9.0
11	8.5-8.9
12	8.5-8.9
13	≥ 9.0
14a	7.5-8.0
14b	7.0-7.5
15	≥ 9.0
16-1	8.5-8.9
16-2	8.5-8.9
16-3	8.5-8.9
16-4	8.5-8.9
16-5	8.0-8.5
16-6	8.0-8.5
16-7	8.0-8.5
16-8	8.0-8.5
16-9	≥ 9.0
16-10	7.5-8.0
16-11	8.0-8.5
16-12	n.d.
16-13	n.d.
16-14	n.d.
16-15	8.0-8.5

Ex.	pK _i
20	≥ 9.0
21-1	≥ 9.0
21-2	8.5-8.9
21-3	≥ 9.0
21-4	8.5-8.9
21-5	8.5-8.9
21-6	8.5-8.9
21-7	8.5-8.9
21-8	n.d.
21-9	n.d.
21-10	n.d.
22	8.5-8.9
23	8.5-8.9
24-1	8.0-8.5
24-2	8.5-8.9
25	8.0-8.5
26	8.0-8.5
27	8.0-8.5
28	≥ 9.0
29	≥ 9.0
30-1	≥ 9.0
30-2	≥ 9.0
30-3	≥ 9.0
30-4	≥ 9.0
30-5	≥ 9.0
30-6	≥ 9.0
30-7	≥ 9.0
30-8	8.5-8.9
30-9	≥ 9.0
30-10	≥ 9.0
30-11	≥ 9.0
30-12	≥ 9.0
31	8.5-8.9
32	8.0-8.5
33	≥ 9.0
34-1	8.5-8.9
35	8.0-8.5
36-1	8.5-8.9
36-2	8.5-8.9
37-1	≥ 9.0
38-1	8.0-8.5
38-2	8.5-8.9
39-1	≥ 9.0
40	≥ 9.0
41	≥ 9.0
42-1	8.5-8.9

Ex.	pK _i
68	8.0-8.5
69a	8.5-8.9
69b	n.d.
70	≥ 9.0
71	≥ 9.0
72	≥ 9.0
73	≥ 9.0
74	8.5-8.9
75	8.5-8.9
76	7.5-7.9
77a	8.0-8.5
77b	8.0-8.5
78	8.5-8.9
79	8.5-8.9
80	≥ 9.0
81	8.0-8.5
82a	≥ 9.0
82b	n.d.
83a	n.d.
83b	≥ 9.0
84a	n.d.
84b	≥ 9.0
85a	≥ 9.0
85b	n.d.
86	n.d.
87a	n.d.
87b	≥ 9.0
88a	n.d.
88b	≥ 9.0
89a	n.d.
89b	≥ 9.0
90a	n.d.
90b	≥ 9.0
91a	n.d.
91b	≥ 9.0
92a	n.d.
92b	≥ 9.0
93a	n.d.
93b	≥ 9.0
94a	n.d.
94b	≥ 9.0
95a	n.d.
95b	≥ 9.0
96a	n.d.
96b	≥ 9.0
97a	≥ 9.0

Ex.	pK _i	Ex.	pK _i	Ex.	pK _i
16-16	≥ 9.0	42-2	8.5-8.9	97b	n.d.
16-17	n.d.	43	≥ 9.0	98a	≥ 9.0
16-18	≥ 9.0	44-1	≥ 9.0	98b	n.d.
16-19	n.d.	44-2	n.d.	99	n.d.
16-20	8.5-8.9	45	≥ 9.0	100	≥ 9.0
16-21	≥ 9.0	46	8.5-8.9	101a	n.d.
16-22	n.d.	47	8.0-8.5	101b	≥ 9.0
16-23	≥ 9.0	48a	≥ 9.0	101c	8.5-8.9
16-24	≥ 9.0	48b	8.5-8.9	102a	n.d.
16-25	≥ 9.0	48c	n.d.	102b	≥ 9.0
16-26	8.5-8.9	49a	≥ 9.0	102c	≥ 9.0
16-27	8.5-8.9	49b	≥ 9.0	103a	n.d.
16-28	≥ 9.0	49c	n.d.	103b	≥ 9.0
16-29	≥ 9.0	50	≥ 9.0	103c	n.d.
16-30	n.d.	51	8.5-8.9	103d	≥ 9.0
16-31	≥ 9.0	52-1	≥ 9.0	104	≥ 9.0
16-32	n.d.	52-2	8.0-8.5	105	≥ 9.0
16-33	≥ 9.0	52-3	8.5-8.9	106	8.5-8.9
16-34	n.d.				

ASSAY 2: 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 60 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

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 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 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 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 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.

25 ASSAY 4: *In Vivo* Evaluation of Antihypertensive Effects
 in the Conscious DOCA-Salt Rat Model of Hypertension

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 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.

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, 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.

ASSAY 6: Rat PO Cassette Assay

Oral bioavailability, or %F, is a measure of the percentage of a drug in an oral dose that actually reaches the systemic circulation. Compound losses can occur due to incomplete formulation dissolution, incomplete absorption due to compound insolubility or instability along the GI, or metabolism in the gut or across the gut wall. The fraction of the dose which reaches the hepatic portal vein must also then pass through the liver before reaching the systemic circulation. Compound metabolism, or "first-pass extraction," can occur during this initial passage through the liver, and this is an additional potential source of compound loss. Oral bioavailability is calculated as the dose-normalized ratio of drug exposure after an oral dose to that after an intravenous dose, wherein the entire dose is delivered directly to the systemic circulation.

Each cassette study begins with 10 mM DMSO stock solutions of up to 5 different compounds. Typically, compounds are selected such no two compounds dosed in the same cassette have a molecular weight within 5 Da of each other. This simplifies subsequent bioanalysis. Appropriate volumes of each DMSO stock are added into a volume of vehicle (5% sodium bicarbonate, 5% dextrose in H₂O) such that the final concentration of each compound is 0.25 mg/mL. Intravenous dosing solutions are sterile-filtered (0.2 µm) prior to dosing.

Pre-cannulated male Sprague-Dawley rats (3 per cassette per route) between 8 and 10 weeks of age were obtained from Harlan Laboratories (Indianapolis, IN). Rats received either a single oral gavage or a single intravenous (via lateral tail vein) dose (2 mL/kg) of the dosing solution. The final dose was 0.5 mg/kg. Serial blood samples were harvested
 5 via jugular vein cannula at 3 minutes, 15 minutes, 30 minutes, 1 hours, 2 hours, 4 hours, 6 hours, and 24 hours post-dose. Sampling was performed either manually or using automated blood samplers. Samples were collected into microtainer tubes containing EDTA as the anticoagulant and are processed to plasma by refrigerated centrifugation.

Plasma samples were extracted with 3 volumes of MeCN containing a suitable
 10 internal standard. Extracts were reconstituted into 3 volumes of water containing 1% formic acid, and analyzed via HPLC-coupled MS/MS. Plasma concentration-time data were analyzed using the Phoenix software (Pharsight Corp., St. Louis, MO) to calculate pharmacokinetic parameters.

Compounds of the invention of particular interest were those having a %F > 10%,
 15 when tested in this assay. These include the following compounds:

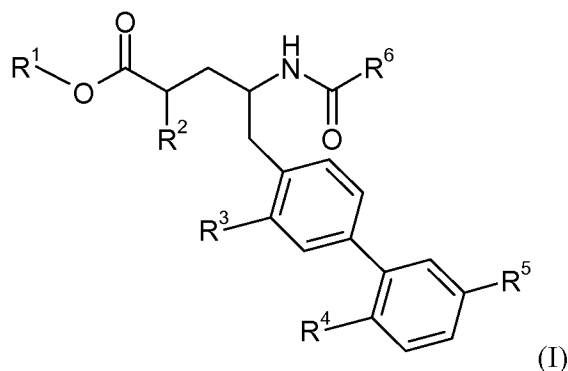
Example	Example	Example	Example
1	2-16	14b	30-4
2-1	3	16-10	30-6
2-2	5	16-23	30-12
2-6	7-1	16-24	52-1
2-8	7-2	16-32	69b
2-9	7-4	21-1	84a
2-13	14a	29	91a
2-15			

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 various changes can be made or equivalents can be substituted without departing from the
 20 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 H, -C₁₋₈alkyl, -CH(CH₃)OC(O)-O-cyclohexyl, -(CH₂)₂-morpholinyl, or -CH₂-5-methyl-[1,3]dioxol-2-one;

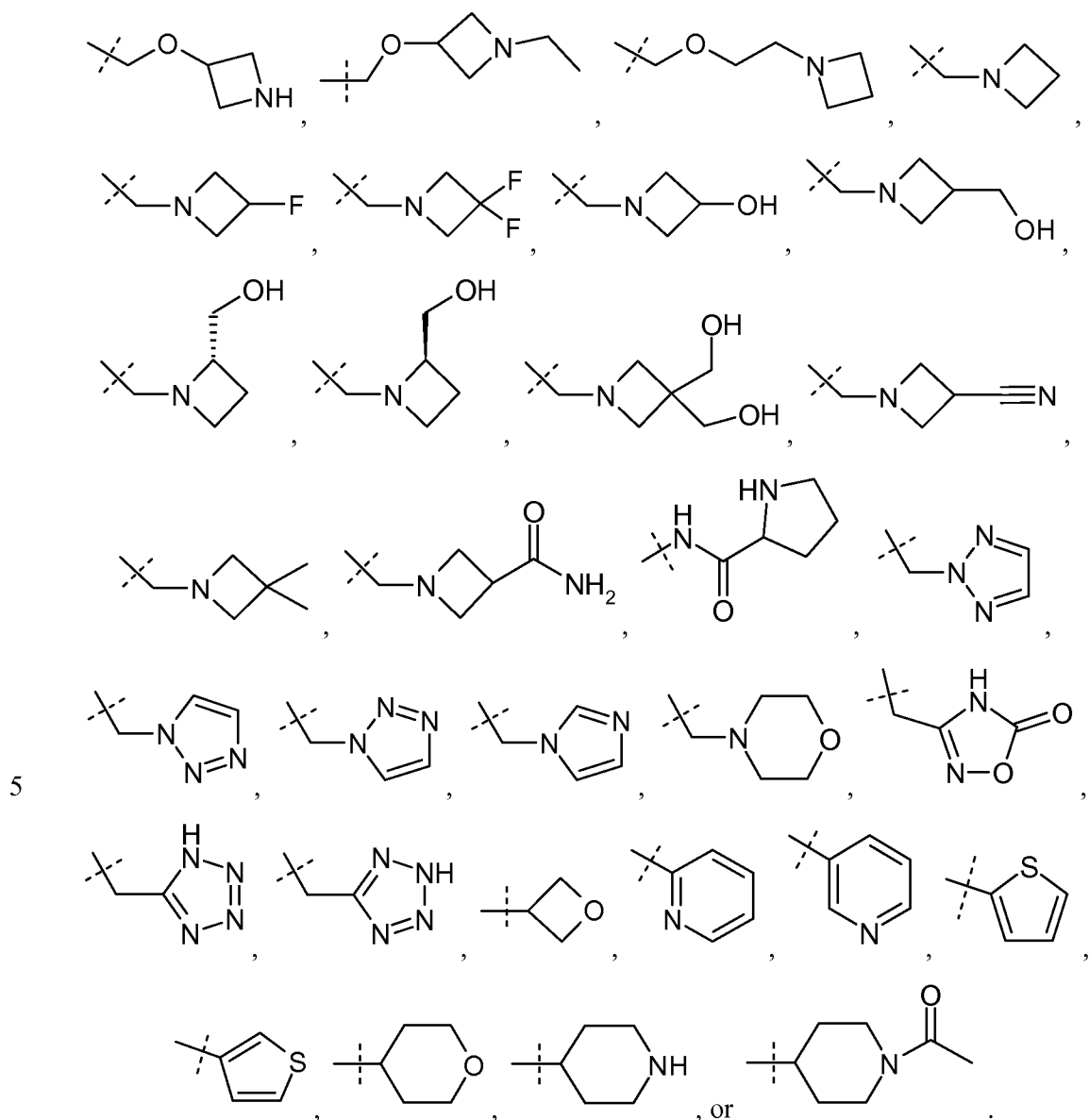
R² is -CH₂-O-R²⁰, -C₀₋₁alkylene-NHC(O)-R²¹, -C₀₋₃alkylene-NR²²R²³, -CH₂-R²⁴, oxetane, 2-pyridine, 3-pyridine, thiophene, tetrahydropyran, or piperidine and having H or
 10 -C(O)CH₃ on the nitrogen, said tetrahydropyran and piperidine being attached at the 4-position; where R²⁰ is -C₁₋₆alkyl, -CH₂NR²⁷CHR²⁸-, -C₂₋₃alkylene-OH, or -C₂₋₃alkylene-NR²⁹R³⁰; R²¹ is -C₁₋₆alkyl, -O-C₁₋₆alkyl, -C₀₋₆alkylene-NR²⁵R²⁵, -CH(NH₂)-R²⁶, -C₁₋₄alkylene-NHC(O)O-C₁₋₆alkyl, -OCH(CH₃)OC(O)CH(CH₃)₂, or pyrrolidine attached at a carbon atom; R²² is H or -C₁₋₆alkyl; R²³ is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted
 15 with 1 to 6 fluoro atoms, -SO₂-C₁₋₆alkyl, -CH₂OC(O)-C₁₋₆alkyl, -C₂₋₄alkylene-OH, -C₂₋₄alkylene-O-CH₃, or cyclopropyl optionally substituted with one or two R³¹ groups; or R²² and R²³ are taken together to form -(CH₂)₂-O-(CH₂)₂-, a 2-oxa-6-aza-spiro[3.3]heptane ring, or an azetidine ring optionally substituted with one or two R³¹ groups; R²⁴ is -CH₂OH, -CN, -C(O)NH₂, triazole or imidazole attached at a nitrogen atom, or oxadiazolone or
 20 tetrazole attached at the carbon atom; each R²⁵ is independently H or -CH₃; R²⁶ is -C₁₋₄alkylene-NH₂, -CH₂OH, or benzyl; R²⁷ is H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl; R²⁸ is H, -C₁₋₆alkyl, -C₁₋₂alkylene-OH, or -C₁₋₂alkylene-OC₁₋₆alkyl; R²⁹ and R³⁰ are independently H, -C₁₋₆alkyl, -C₁₋₆alkyl substituted with 1 to 6 fluoro atoms, -(CH₂)₂OH, or -(CH₂)₂OC₁₋₆alkyl; or R²⁹ and R³⁰ are
 25 taken together to form -CH₂-CH₂-CH₂-; and each R³¹ is independently halo, -C₁₋₆alkyl, -C₀₋₂alkylene-OH, -C₀₋₂alkylene-OC₁₋₆alkyl, -CN, or -CONH₂;

R³, R⁴ and R⁵ are independently H or halo;

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

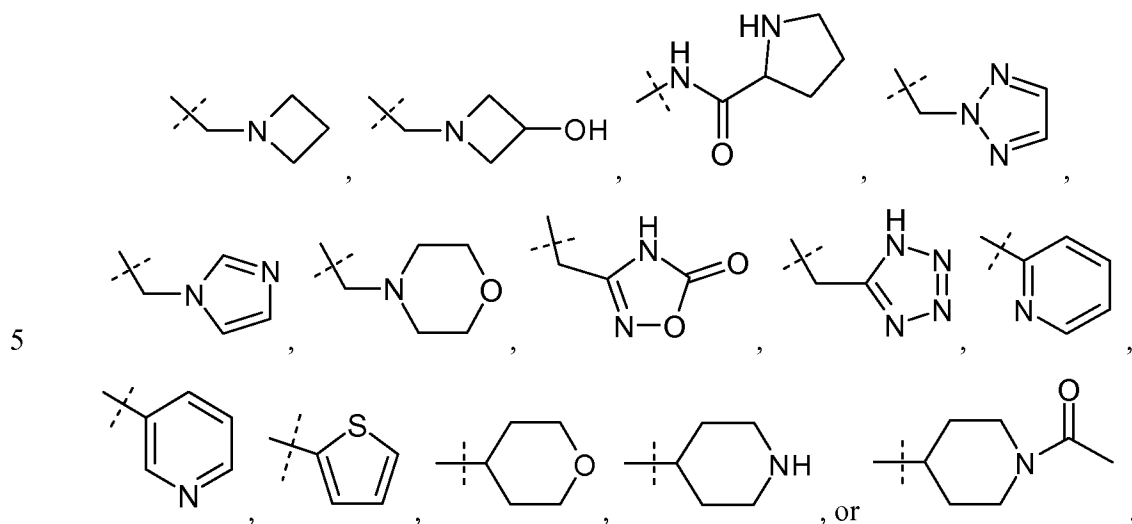
or a pharmaceutically acceptable salt thereof.

2. The compound of Claim 1, where R^1 is H, $-CH_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, or $-(CH_2)_5CH_3$.
3. The compound of Claim 1, where R^2 is $-CH_2-O-CH_3$, $-CH_2-O-CH_2CH_3$, $-CH_2-O-(CH_2)_2OH$, $-CH_2-O-(CH_2)_3OH$, $-CH_2-O-(CH_2)_2NH_2$, $-CH_2-O-(CH_2)_3NH_2$, $-CH_2-O-(CH_2)_2NHCH_3$, $-CH_2-O-(CH_2)_3NHCH_3$, $-CH_2-O-(CH_2)_2N(CH_3)_2$, $-CH_2-O-(CH_2)_2NH(CH_2CHF_2)$, $-NHC(O)CH_3$, $-NHC(O)CH_2CH_3$, $-CH_2NHC(O)CH_3$, $-NHC(O)OCH_3$, $-NHC(O)CH_2NH_2$, $-CH_2NHC(O)CH_2NH_2$, $-NHC(O)(CH_2)_2NH_2$, $-NHC(O)(CH_2)_3NH_2$, $-CH_2NHC(O)(CH_2)_3NH_2$, $-NHC(O)(CH_2)_4NH_2$, $-NHC(O)(CH_2)_5NH_2$, $-NHC(O)CH(CH_3)NH_2$, $-CH_2NHC(O)C(CH_3)_2NH_2$, $-NHC(O)CH_2NH(CH_3)$, $-NHC(O)CH_2N(CH_3)_2$, $-NHC(O)(CH_2)_3NH(CH_3)$, $-NHC(O)(CH_2)_3N(CH_3)_2$, $-NHC(O)C(CH_3)_2NH_2$, $-CH_2NHC(O)C(CH_3)_2NH_2$, $-NHC(O)CH(NH_2)-CH(CH_3)_2$, $-NHC(O)CH(NH_2)-(CH_2)_4NH_2$, $-NHC(O)CH(NH_2)-CH_2OH$, $-NHC(O)CH(NH_2)-benzyl$, $-NHC(O)OCH(CH_3)OC(O)CH(CH_3)_2$, $-CH_2NHC(O)OCH(CH_3)OC(O)CH(CH_3)_2$, $-NHC(O)-CH_2-NHC(O)O-CH_3$, $-NHC(O)-CH[CH(CH_3)_2]-NHC(O)O-CH_3$, $-NH_2$, $-CH_2NH_2$, $-CH(CH_3)NH_2$, $-C(CH_3)_2NH_2$, $-(CH_2)_2NH_2$, $-(CH_2)_3NH_2$, $-CH_2NH(CH_3)$, $-CH_2N(CH_3)_2$, $-CH_2NH-CH_2CH_2F$, $-CH_2NH-CH_2CHF_2$, $-NH-SO_2CH_3$, $-NHCH_2OC(O)CH(CH_3)_2$, $-CH_2NHCH_2OC(O)CH(CH_3)_2$, $-CH_2-NH-(CH_2)_2-OH$, $-CH_2-NH-(CH_2)_3-OH$, $-CH_2-NH-(CH_2)_2-O-CH_3$, $-CH_2-N(CH_3)-(CH_2)_2-O-CH_3$, $-CH_2-NH-(CH_2)_3-O-CH_3$, $-CH_2CN$, $-CH_2-C(O)NH_2$,

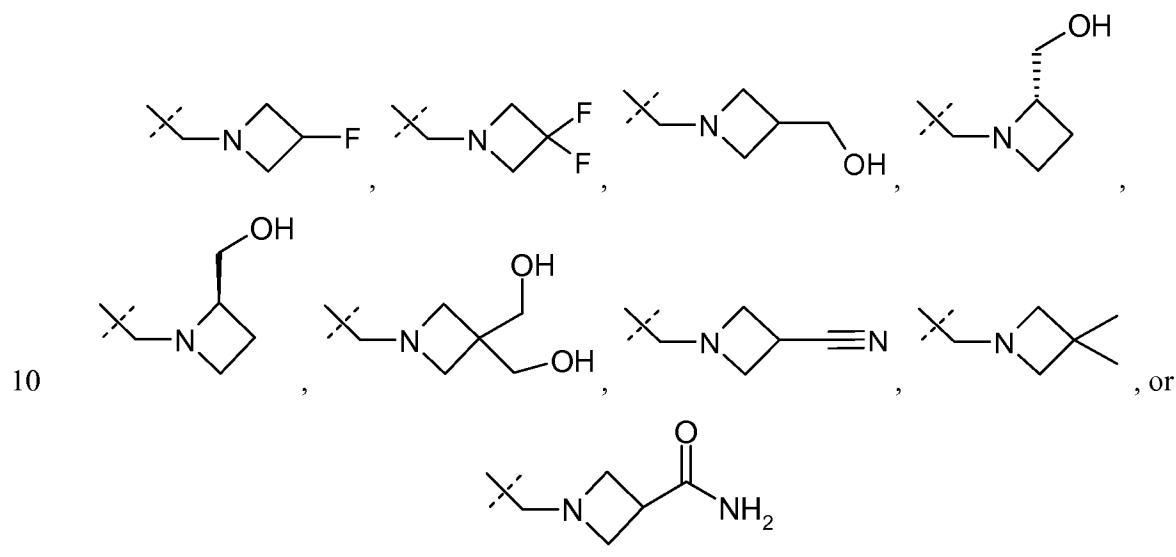


4. The compound of Claim 3, where R² is -CH₂-O-CH₃, -CH₂-O-CH₂CH₃,
-CH₂-O-(CH₂)₂OH, -CH₂-O-(CH₂)₃OH, -NHC(O)CH₃, -NHC(O)CH₂CH₃,
10 -CH₂NHC(O)CH₃, -NHC(O)OCH₃, -NHC(O)CH₂NH₂, -CH₂NHC(O)CH₂NH₂,
-NHC(O)(CH₂)₂NH₂, -NHC(O)(CH₂)₃NH₂, -CH₂NHC(O)(CH₂)₃NH₂,
-NHC(O)(CH₂)₄NH₂, -NHC(O)(CH₂)₅NH₂, -NHC(O)CH(CH₃)NH₂,
-CH₂NHC(O)C(CH₃)₂NH₂, -NHC(O)CH₂NH(CH₃), -NHC(O)CH₂N(CH₃)₂,
-NHC(O)(CH₂)₃NH(CH₃), -NHC(O)(CH₂)₃N(CH₃)₂, -NHC(O)C(CH₃)₂NH₂,
15 -NHC(O)CH(NH₂)-CH(CH₃)₂, -NHC(O)CH(NH₂)-(CH₂)₄NH₂, -NHC(O)CH(NH₂)-
CH₂OH, -NHC(O)CH(NH₂)-benzyl, -NHC(O)-CH₂-NHC(O)O-CH₃,
-NHC(O)-CH[CH(CH₃)₂]-NHC(O)O-CH₃, -NH₂, -CH₂NH₂, -(CH₂)₂NH₂, -CH₂N(CH₃)₂,

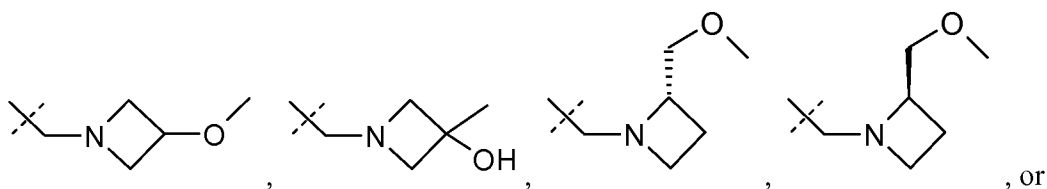
-CH₂NH-CH₂CH₂F, -CH₂NH-CH₂CHF₂, -NH-SO₂CH₃, -CH₂NH-(CH₂)₂-OH, -CH₂-NH-(CH₂)₂-O-CH₃, -CH₂-N(CH₃)-(CH₂)₂-O-CH₃, -CH₂NH-(CH₂)₃-O-CH₃, -CH₂CN, -CH₂-C(O)NH₂,

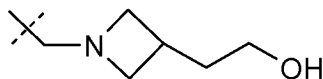


5. The compound of Claim 3, where R² is -CH₂-O-(CH₂)₂N(CH₃)₂, -NHC(O)OCH(CH₃)OC(O)CH(CH₃)₂, -C(CH₃)₂NH₂, -CH₂NH-(CH₂)₃-OH,



6. The compound of Claim 1, where R² is -CH₂-N(CH₃)-(CH₂)₂-OH, -NH-(CH₂)₂-O-CH₃, -NH-(CH₂)₃-O-CH₃,



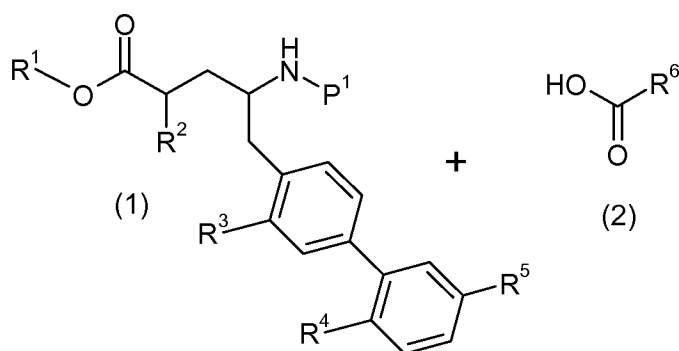


7. The compound of Claim 1, where R^3 is H or Cl.
8. The compound of Claim 1, where R^4 is H or F.
9. The compound of Claim 1, where R^5 is H or Cl.
- 5 10. The compound of Claim 1, where R^3 is H, R^4 is F, and R^5 is Cl; or R^3 and R^4 are H and R^5 is Br or Cl; or R^3 , R^4 , and R^5 are H; or R^3 is Cl, R^4 is F, and R^5 is Cl; or R^3 is H, R^4 is F, and R^5 is H.
11. The compound of Claim 10, where R^3 is H, R^4 is F, and R^5 is Cl; or R^3 and R^4 are H and R^5 is Cl; or R^3 , R^4 , and R^5 are H; or R^3 is Cl, R^4 is F, and R^5 is Cl; or R^3 is H, R^4 is F, and R^5 is H.
- 10 12. The compound of Claim 1, where R^6 is 3H-oxazol-2-one, 4H-[1,2,4]oxadiazol-5-one, [1,2,3,5]oxatriazole, [1,2,4]triazolo[1,5- α]pyridine, [1,2,3]triazole, [1,2,4]triazole, pyrazole, imidazole, oxazole, isoxazole, isothiazole, pyridine, oxadiazole, or pyrimidine.
13. The compound of Claim 12, where R^6 is 3H-oxazol-2-one, 4H-[1,2,4]oxadiazol-5-one, [1,2,4]triazolo[1,5- α]pyridine, [1,2,3]triazole, [1,2,4]triazole, pyrazole, oxazole, isoxazole, isothiazole, pyridine, or pyrimidine.
- 15 14. The compound of Claim 1, where the nitrogen atoms in the heterocycle are unsubstituted.
15. The compound of Claim 1, where R^{60} is -OH, $-(CH_2)_2OH$, $-OCH_3$, $-OCH_2CH_3$, $-CH_3$, $-CHF_2$, or $-CF_3$.
- 20 16. The compound of Claim 1, where R^{60} is phenyl.
17. The compound of Claim 1, where the carbon atoms in the heterocycle are unsubstituted.
18. The compound of Claim 1, where R^{61} is chloro, fluoro, -OH, $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-CH_2OCH_3$, $-C(O)CH_3$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, cyclopropyl, $-CF_3$, $-CH_2SO_2CH_3$, $-NH_2$, $-CH_2NH_2$, $-CH_2N(CH_3)_2$, pyrazine, or phenyl substituted with methyl or fluoro.
- 25 19. The compound of Claim 18, where R^{61} is chloro, fluoro, -OH, $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-OCH_3$, $-OCH_2CH_3$, $-C(O)CH_3$, $-C(O)NH(CH_3)$, $-C(O)N(CH_3)_2$, cyclopropyl, $-CF_3$, or phenyl substituted with methyl or fluoro.
- 30 20. The compound of Claim 1, where a first carbon atom in the heterocycle is substituted with an R^{61} group selected from the group consisting of fluoro, -OH, $-CH_3$,

-C₀₋₂alkylene-O-C₁₋₆alkyl, -C(O)CH₃, -C₃₋₆cycloalkyl, -CF₃, -CH₂SO₂CH₃, -NH₂, and -CH₂N(CH₃)₂; and a second carbon atom in the heterocycle is substituted with an R⁶¹ group selected from the group consisting of halo, -OH, -CH₃, -O-CH₂CH₃, -C(O)CH₃, cyclopropyl, -CF₃, -CH₂SO₂CH₃, -NH₂, -CH₂N(CH₃)₂, and phenyl substituted with methyl or halo.

21. The compound of Claim 20, where a first carbon atom in the heterocycle is substituted with an R⁶¹ group selected from the group consisting of fluoro and -CH₃; and a second carbon atom in the heterocycle is substituted with an R⁶¹ group selected from the group consisting of -CH₃, -O-CH₂CH₃, cyclopropyl, and phenyl substituted with methyl.

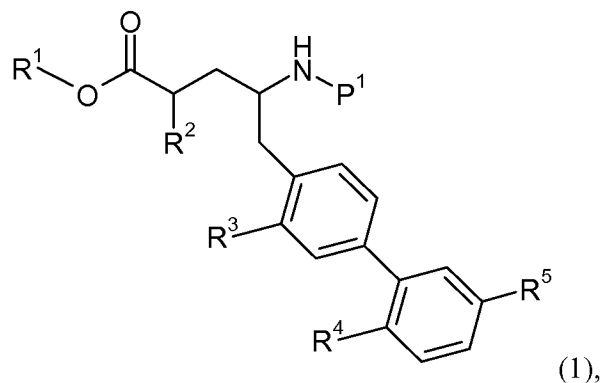
22. A process for preparing the compound of Claim 1, comprising the step of coupling a compound of formula 1 with a compound of formula 2:



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

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

23. A compound of formula 1:



where:

R^1 is H, $-C_{1-8}$ alkyl, $-\text{CH}(\text{CH}_3)\text{OC}(\text{O})-\text{O}-\text{cyclohexyl}$, $-(\text{CH}_2)_2-\text{morpholinyl}$, or $-\text{CH}_2-$ 5-methyl-[1,3]dioxol-2-one;

R^2 is $-\text{CH}_2-\text{O}-R^{20}$, $-\text{C}_{0-1}$ alkylene-NHC(O)- R^{21} , $-\text{C}_{0-3}$ alkylene-NR²²R²³, $-\text{CH}_2-R^{24}$, oxetane, 2-pyridine, 3-pyridine, thiophene, tetrahydropyran, or piperidine and having H or $-\text{C}(\text{O})\text{CH}_3$ on the nitrogen, said tetrahydropyran and piperidine being attached at the 4-position; where R^{20} is $-C_{1-6}$ alkyl, $-\text{CH}_2\text{NR}^{27}\text{CHR}^{28}-$, $-\text{C}_{2-3}$ alkylene-OH, or $-\text{C}_{2-3}$ alkylene-NR²⁹R³⁰; R^{21} is $-C_{1-6}$ alkyl, $-\text{O}-C_{1-6}$ alkyl, $-\text{C}_{0-6}$ alkylene-NR²⁵R²⁵, $-\text{CH}(\text{NH}_2)-R^{26}$, $-\text{C}_{1-4}$ alkylene-NHC(O)O- C_{1-6} alkyl, $-\text{OCH}(\text{CH}_3)\text{OC}(\text{O})\text{CH}(\text{CH}_3)_2$, or pyrrolidine attached at a carbon atom; R^{22} is H or $-C_{1-6}$ alkyl; R^{23} is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-\text{SO}_2-C_{1-6}$ alkyl, $-\text{CH}_2\text{OC}(\text{O})-C_{1-6}$ alkyl, $-\text{C}_{2-4}$ alkylene-OH, $-\text{C}_{2-4}$ alkylene-O- CH_3 , or cyclopropyl optionally substituted with one or two R^{31} groups; or R^{22} and R^{23} are taken together to form $-(\text{CH}_2)_2-\text{O}-(\text{CH}_2)_2-$, a 2-oxa-6-aza-spiro[3.3]heptane ring, or an azetidine ring optionally substituted with one or two R^{31} groups; R^{24} is $-\text{CH}_2\text{OH}$, $-\text{CN}$, $-\text{C}(\text{O})\text{NH}_2$, triazole or imidazole attached at a nitrogen atom, or oxadiazolone or tetrazole attached at the carbon atom; each R^{25} is independently H or $-\text{CH}_3$; R^{26} is $-C_{1-4}$ alkylene-NH₂, $-\text{CH}_2\text{OH}$, or benzyl; R^{27} is H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-(\text{CH}_2)_2\text{OH}$, or $-(\text{CH}_2)_2\text{OC}_{1-6}$ alkyl; R^{28} is H, $-C_{1-6}$ alkyl, $-C_{1-2}$ alkylene-OH, or $-C_{1-2}$ alkylene- OC_{1-6} alkyl; R^{29} and R^{30} are independently H, $-C_{1-6}$ alkyl, $-C_{1-6}$ alkyl substituted with 1 to 6 fluoro atoms, $-(\text{CH}_2)_2\text{OH}$, or $-(\text{CH}_2)_2\text{OC}_{1-6}$ alkyl; or R^{29} and R^{30} are taken together to form $-\text{CH}_2-\text{CH}_2-\text{CH}_2-$; and each R^{31} is independently halo, $-C_{1-6}$ alkyl, $-\text{C}_{0-2}$ alkylene-OH, $-\text{C}_{0-2}$ alkylene- OC_{1-6} alkyl, $-\text{CN}$, or $-\text{CONH}_2$;

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

P^1 is H or an amino-protecting group selected from the group consisting of *t*-butoxycarbonyl, trityl, benzyloxycarbonyl, 9-fluorenylmethoxycarbonyl, formyl, trimethylsilyl, and *t*-butyldimethylsilyl; or a salt thereof.

24. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in any one of Claims 1 to 21.

25. The pharmaceutical composition of Claim 24, further comprising a therapeutic agent selected from the group consisting of 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-glaucoma agents, anti-lipid agents, antinociceptive agents, anti-thrombotic agents, AT₁ receptor antagonists and dual-acting AT₁ receptor
- 5 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 inhibitors, estrogens, estrogen receptor agonists and/or antagonists, monoamine reuptake inhibitors, muscle relaxants, natriuretic peptides and their
- 10 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 inhibitors, selective serotonin reuptake inhibitors, sodium channel blocker, soluble guanylate cyclase stimulators and activators, tricyclic
- 15 antidepressants, vasopressin receptor antagonists, and combinations thereof.
26. The pharmaceutical composition of Claim 25, wherein the therapeutic agent is an AT₁ receptor antagonist.
27. A compound as claimed in any one of Claims 1 to 21, for use in therapy.
28. A compound as claimed in Claim 27, for use in treating hypertension, heart failure,
- 20 or renal disease.
29. The use of a compound as claimed in any one of Claims 1 to 21, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.