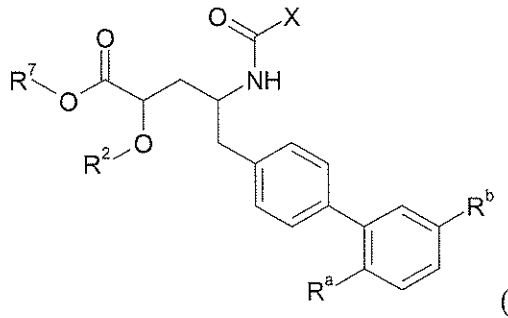
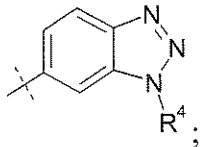
SUMMARY OF THE INVENTION

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

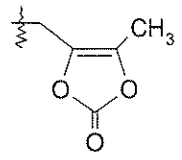


(XII)

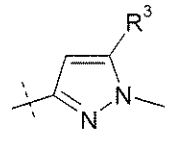
where:

(i) R^a is H; R^b is Cl; X is  ; and

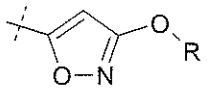
R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2\text{-}3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)\text{-}C_{1\text{-}4}alkyl$, $-CHR^cOC(O)O\text{-}C_{2\text{-}4}alkyl$, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2\text{-}4}alkylene\text{-}N(CH_3)_2$, $-CH_2OC(O)CHR^d\text{-}NH_2$, $-CH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}alkyl$, benzyl, and

 ;

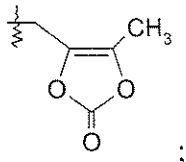
or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)\text{-}C_{1\text{-}4}alkyl$, $-OCH_2OC(O)CHR^d\text{-}NH_2$, and $-OCH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}alkyl$, and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is selected from $-C(O)\text{-}C_{1\text{-}6}alkyl$, $-C(O)CHR^d\text{-}NH_2$, $-C(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}alkyl$, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ii) R^a is H; R^b is Cl; X is  ; and

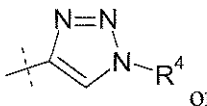
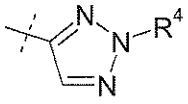
R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2\text{-}3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)\text{-}C_{1\text{-}4}alkyl$, $-CHR^cOC(O)O\text{-}C_{2\text{-}4}alkyl$, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2\text{-}4}alkylene\text{-}N(CH_3)_2$, $-CH_2OC(O)CHR^d\text{-}NH_2$, $-CH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}alkyl$, benzyl, and

(vii) R^a is H; R^b is Cl; X is  ; R is H or $-CH_3$; and

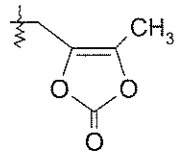
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

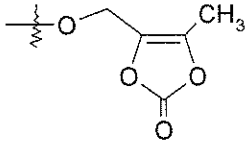
or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(viii) R^a is F; R^b is Cl; X is  or  ; and

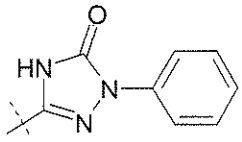
R^2 is H, R^4 is -OH, and R^7 is selected from ~~$-CH_2CH_3$,~~ $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

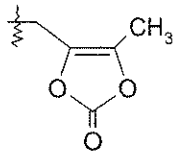
or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$ and

 ,

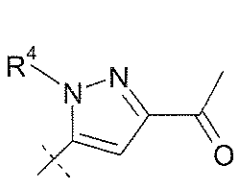
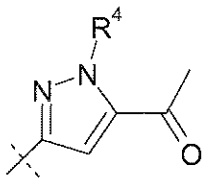
and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ix) R^a is H; R^b is Cl; X is  ; and

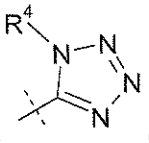
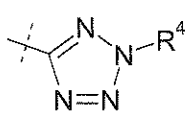
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(x) R^a is H; R^b is H; X is  or  ; and

R^2 and R^4 are H, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, ~~$-(CH_2)_2OCH_3$~~, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$; or

(xi) R^a is H; R^b is Cl; X is  or  ; and

R^2 and R^4 are H, and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$,

-$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -$CHR^cOC(O)$-C_{1-4}alkyl, -$CHR^cOC(O)O$-C_{2-4}alkyl, -$CHR^cOC(O)O$-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -$CH_2OC(O)CHR^d$-NH_2, -$CH_2OC(O)CHR^d$-$NHC(O)O$-C_{1-6}alkyl, and benzyl; or R^2 is H, R^4 is selected from -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$ and -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from -$C(O)$-C_{1-6}alkyl, -$C(O)CHR^d$-NH_2, -$C(O)CHR^d$-$NHC(O)O$-C_{1-6}alkyl, and -$P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is -$CH_2OP(O)(OR^e)_2$ or -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is -CH_2CH_3; or R^2 is -$C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is -CH_2CH_3;

where each R^c is independently H or -C_{1-3}alkyl; each R^d is independently H, -CH_3, -$CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, -C_{1-6}alkyl, or phenyl;

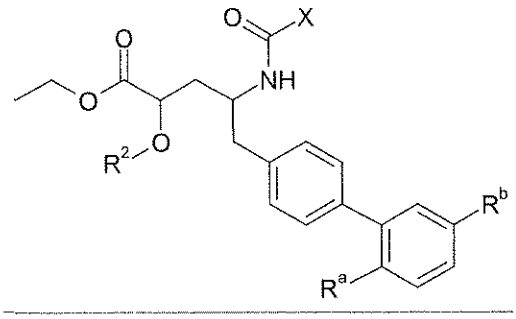
or a pharmaceutically acceptable salt thereof.

The present ~~invention~~ disclosure provides compounds which are metabolized *in vivo* to 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 patients suffering from a disease or disorder that is treated by inhibiting the NEP enzyme or by increasing the levels of its peptide substrates. Thus, one ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to a method of treating hypertension, heart failure, or renal disease, comprising administering to a patient a therapeutically effective amount of a compound of the invention.

Another aspect of the ~~invention~~ disclosure relates to pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a compound of the invention, optionally together with an additional therapeutic agent.

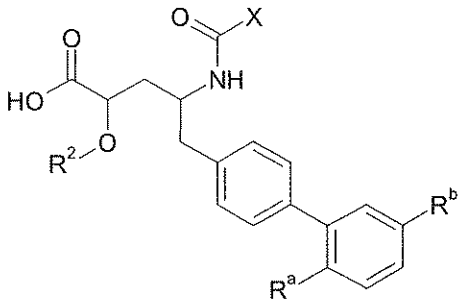
Yet another ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to processes and intermediates useful for preparing compounds of the invention. Another ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to a process of preparing a pharmaceutically acceptable salt of a compound of formula I, comprising contacting a compound of formula I in free acid or base form with a pharmaceutically acceptable base or acid. In an aspect, there is provided a process for preparing a compound of the invention, comprising the step of:

(a) reacting a compound of formula



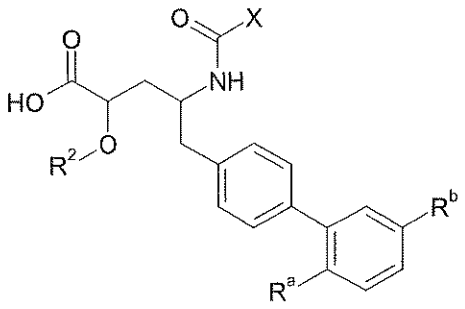
with a compound of formula HO-R^7 in a transesterification reaction; or

(b) reacting a compound of formula



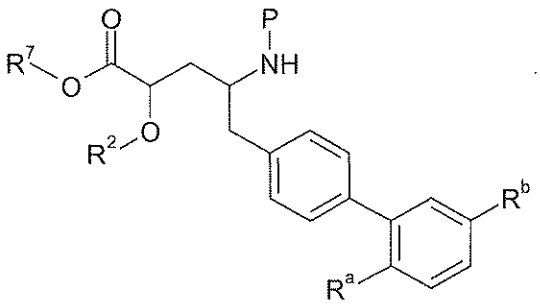
with a compound of formula L-R^7 in a nucleophilic substitution reaction, where L is a leaving group; or

(c) reacting a compound of formula



with a compound of formula L-R^2 in a nucleophilic substitution reaction, where L is a leaving group; or

(d) reacting a compound of formula



with a compound of formula HOOC-X in a coupling reaction, where P is H or an amino-

protecting group;

to produce a compound of formula XII.

In other ~~aspects~~embodiments, the ~~invention~~ disclosure relates to products prepared by any of the processes described herein, as well as novel intermediates used in such process.

Yet another ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to the use of a compound of formula XII 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. Yet another aspect of the disclosure relates to a compound of the invention for use in therapy. Another ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to use of a compound of the invention for inhibiting a NEP enzyme in a mammal. Still another ~~aspect~~ embodiment of the ~~invention~~ disclosure relates to the use of a compound of the invention as a research tool. Other ~~aspects and~~ embodiments of

the ~~invention~~ disclosure are disclosed herein.

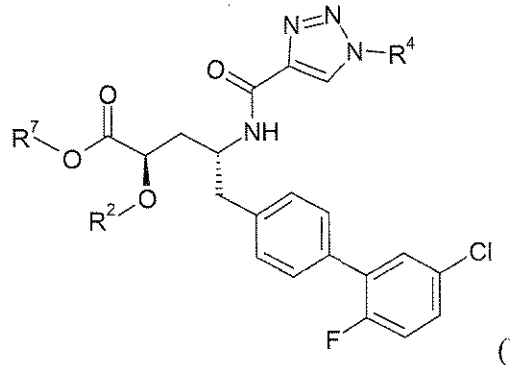
DETAILED DESCRIPTION OF THE INVENTION

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

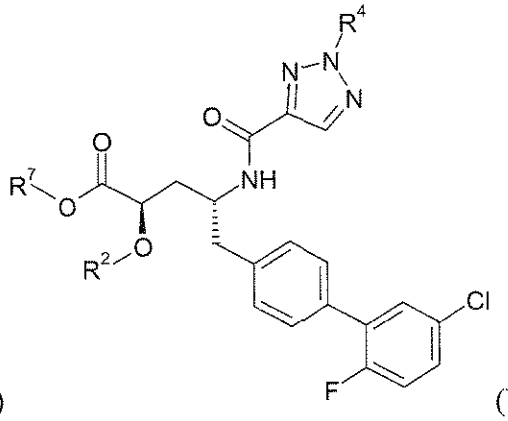
The term "alkyl" means a monovalent saturated hydrocarbon group which may be linear or branched. Unless otherwise defined, such alkyl groups typically contain from 1 to 10 carbon atoms and include, for example, -$C_{1\text{-}6}$alkyl, meaning an alkyl group having from 1 to 6 carbon atoms where the carbon atoms are in any acceptable configuration. Representative alkyl groups include, by way of example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, *s*-butyl, isobutyl, *t*-butyl, *n*-pentyl, *n*-hexyl, and the like.

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

The term "pharmaceutically acceptable" refers to a material that is not biologically or otherwise unacceptable when used in the invention. For example, the term "pharmaceutically acceptable carrier" refers to a material that can be incorporated into a composition and administered to a patient without causing unacceptable biological effects or interacting in an unacceptable manner with other components of the composition. Such pharmaceutically acceptable materials typically have met the required standards of toxicological and manufacturing testing, and include those materials identified as suitable inactive ingredients by the U.S. Food and Drug administration.

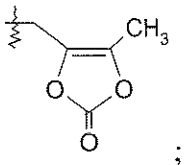


(VIIIa)



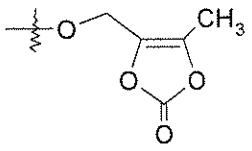
(VIIIb)

where R^2 is H, R^4 is -OH, and R^7 is selected from ~~$-CH_2CH_3$~~, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2\text{-}3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)\text{-}C_{1\text{-}4}$alkyl, $-CHR^cOC(O)O\text{-}C_{2\text{-}4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2\text{-}4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d\text{-}NH_2$, $-CH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}$alkyl, benzyl, and



;

or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)\text{-}C_{1\text{-}4}$alkyl, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]\text{-}NHC(O)OCH_3$ and



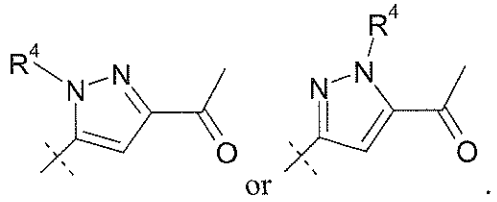
,

and R^7 is H; or R^2 is selected from $-C(O)\text{-}C_{1\text{-}6}$alkyl, $-C(O)CHR^d\text{-}NH_2$, $-C(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; where each R^c is independently H or $-C_{1\text{-}3}$alkyl; each R^d is independently H, $-CH_3$, $-CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, $-C_{1\text{-}6}$alkyl, or phenyl; or a pharmaceutically acceptable salt thereof.

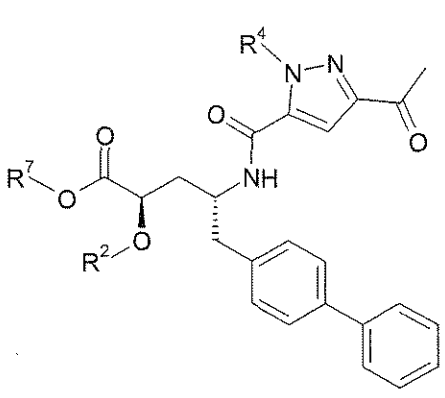
In one particular embodiment of the compounds of Formula VIIIa and VIIIb, R^2 is H, R^4 is -OH and R^7 is selected from $-CH_2CF_2CF_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)OCH_2CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, $-CH(CH_3)OC(O)O$-cyclohexyl, $-CH_2OC(O)CH[CH(CH_3)_2]\text{-}NHC(O)OCH_3$,and

In one embodiment, this compound is referred to as the active form and is administered as a prodrug, which is metabolized *in vivo* to form the compound of formula X'. U.S. Patent Publication No. 2012/0157383 also disclosed the ethyl ester, butyl ester, methoxyethyl ester, medoxomil ester, mofetil ester, and methanesulfonylethyl ester prodrugs of the compound of formula X'.

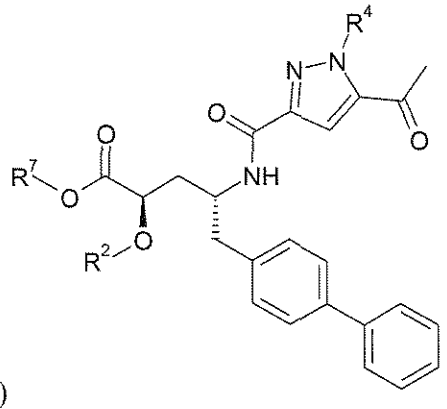
Another aspect of the invention relates to other prodrugs of the compound of formula X'. These prodrugs are represented by formula XII, where R^a is H, R^b is H, and X is:



In one embodiment, these compounds are represented by formula Xa or Xb:



(Xa)



(Xb)

where R^2 and R^4 are H, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, ~~$-(CH_2)_2OCH_3$~~, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$; and where each R^c is independently H or $-C_{1-3}$alkyl; each R^d is independently H, $-CH_3$, $-CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, $-C_{1-6}$alkyl, or phenyl; or a pharmaceutically acceptable salt thereof.

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,

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 AT_1 receptor antagonist, also known as angiotensin II type 1 receptor blockers (ARBs). Representative ARBs include, but are not limited to, abitesartan, azilsartan (e.g., azilsartan medoxomil), benzyllosartan, candesartan, candesartan cilexetil, elisartan, embusartan, enoltasosartan, eprosartan, EXP3174, fonsartan, forasartan, glycyllosartan, irbesartan, isoteoline, losartan, medoxomil, milfasartan, olmesartan (e.g., olmesartan medoxomil), opomisartan, pratosartan, ripisartan, saprisartan, saralasin, sarmesin, TAK-591, tasosartan, telmisartan, valsartan, zolasartan, and combinations thereof. In a particular embodiment, the ARB is selected from azilsartan medoxomil, candesartan cilexetil, eprosartan, irbesartan, losartan, olmesartan medoxomil, 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 AT_1 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

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

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

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

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

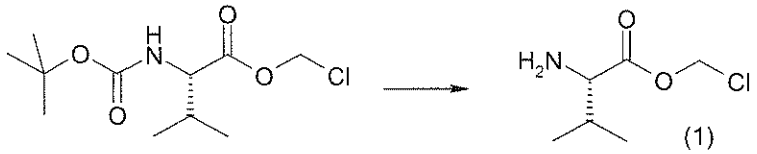
In one embodiment, compounds of the invention are administered in combination with a tricyclic antidepressant (TCA), examples of which include, by way of illustration and not limitation, amitriptyline, amitriptylinoxide, butriptyline, clomipramine, demexiptiline, desipramine, dibenzepin, dimetacrine,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

In one embodiment, compounds of the invention are administered in combination with a vasopressin receptor antagonist, examples of which include, by way of illustration and not limitation, conivaptan and tolvaptan.

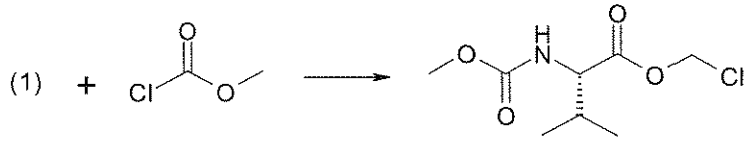
Combined secondary therapeutic agents may also be helpful in further combination therapy with compounds of the invention. For example, compounds of the invention can be combined with a diuretic and an ARB, or a calcium channel blocker and an ARB, or a diuretic and an ACE inhibitor, or a calcium channel blocker and a statin. Specific examples include, a combination of the ACE inhibitor enalapril (in the maleate salt form)

compound as a yellow solid (35 g). LC-MS: 266 $[M+H]^+$.

Preparation 19: *(S)*-2-Methoxycarbonylamino-3-methylbutyric Acid Chloromethyl Ester

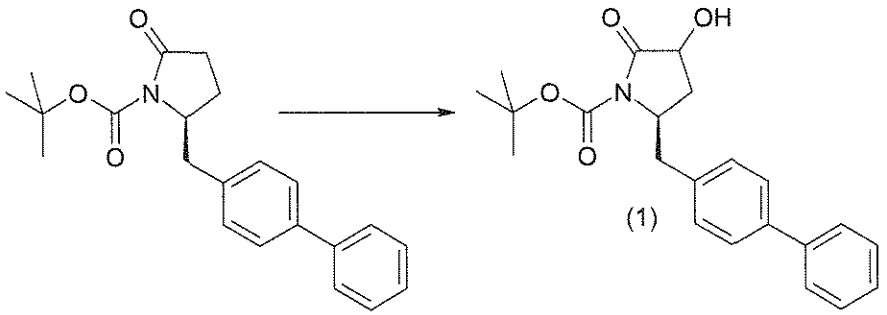


A solution of *(S)*-2-*t*-butoxycarbonylamino-3-methylbutyric acid chloromethyl ester (35 g, 132 mmol) in DCM (200 mL) was added dropwise a solution of TFA (50 mL) in DCM (100 mL) at 0°C. The resulting mixture was stirred at room temperature overnight and then concentrated *in vacuo* to yield crude Compound 1 as a yellow oil (21.8 g). LC-MS: 166 $[M+H]^+$.



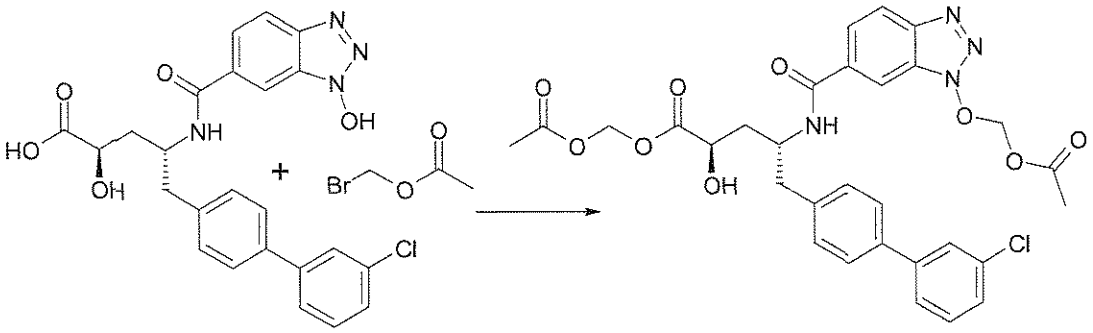
To a mixture of Compound 1 (21.8 g, 139 mmol) and methyl chloroformate (12 mL, 157 mmol) in THF (1 L) was added TEA (38 mL, 278 mmol) at 0°C. The resulting mixture was stirred at room temperature for 12 hours, then concentrated *in vacuo*. The residue was purified by flash column (petroleum ether:EtOAc=6:1) to yield the title compound as a yellow solid (20.3 g). LC-MS: 224 $[M+H]^+$. ^1H NMR (400MHz, DMSO-d_6): δ 0.97-1.02 (m, 6H), 2.16-2.21 (m, 1H), 3.68 (s, 1H), 4.14 (d, *J*=4Hz, 1H), 5.76-5.91(m, 2H).

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



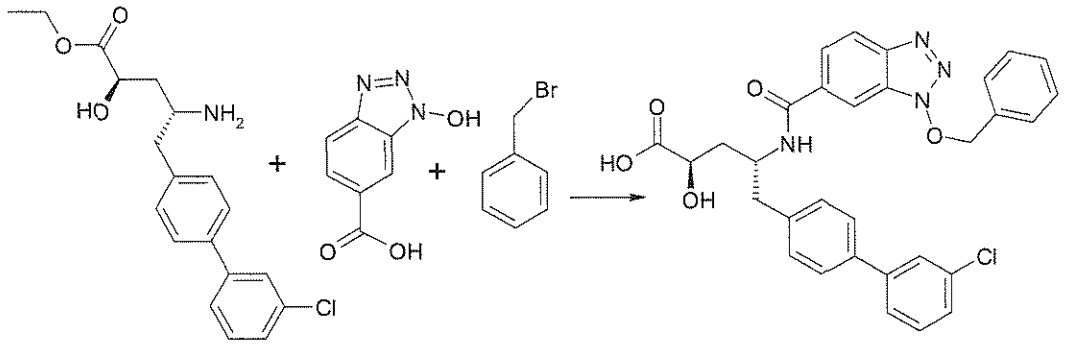
To a stirred solution of *(S)*-2-biphenyl-4-ylmethyl-5-oxopyrrolidine-1-carboxylic acid *t*-butyl ester (4.4 g, 12.4 mmol) in anhydrous THF (70 mL) was added a solution of 1 M LiHMDS in THF (28 mL) over 15 minutes at -65°C under nitrogen. After stirring for 3 hours at -65°C, oxodiperoxymolybdenum(pyridine) (hexamethylphosphorictriamide) (9 g, 18.6 mmol) was added. The mixture was stirred for another 2 hours at -35°C, then saturated aqueous $Na_2S_2O_3$ (60 mL) was added. The organic layer was collected and

EXAMPLE 1H: *(2R,4R)*-4-[(3-Acetoxymethoxy-3H-benzotriazole-5-carbonyl)amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic Acid Acetoxymethyl Ester



Et_3N (7.0 µL, 50 µmol) was added to a solution of *[(2R,4R)*-5-(3'-chlorobiphenyl-4-yl)-2-hydroxy-4-[(3-hydroxy-3H-benzotriazole-5-carbonyl)amino]pentanoic acid (20.0 mg, 42 µmol) and bromomethyl acetate (6.52 µL, 67 µmol) in acetone (1.3 mL, 17.2 mmol), and the resulting mixture was stirred in a sealed vial at 65°C for 5 hours. 1:1 TFA/DCM (0.50 mL, 3.1 mmol) was added, and the mixture was stirred at room temperature for 30 minutes and concentrated to yield a clear yellow liquid. The crude liquid was purified by preparative HPLC (C18 column chromatography, small column, using 30-90% MeCN in water with 0.05% TFA) to yield the title compound (5.2 mg, purity 100%). MS *m/z* $[M+H]^+$ calc'd for $C_{30}H_{29}ClN_4O_9$, 625.16; found 625.1.

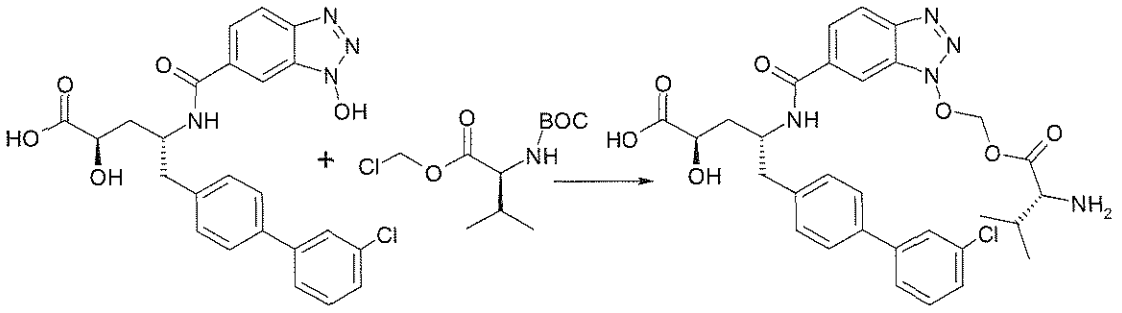
EXAMPLE 1I: *(2R,4R)*-4-[(3-Benzyloxy-3H-benzotriazole-5-carbonyl)amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic Acid



HATU (246 mg, 647 µmol) was added to a solution of 1-hydroxy-1H-1,2,3-benzotriazole-6-carboxylic acid (116 mg, 647 µmol) in DMF (2.0 mL, 25.8 mmol) and the resulting mixture was stirred at room temperature for 10 minutes. DIPEA (225 µL, 1.3 mmol) was added to the mixture, followed by *(2R,4R)*-4-amino-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic acid ethyl ester (150 mg, 431 µmol) and the mixture was stirred at room temperature for 1 hour. 3.0 M LiOH in water (1.7 mL, 5.2 mmol) was added to the mixture and stirred at room temperature for 30 minutes. The mixture was then purified

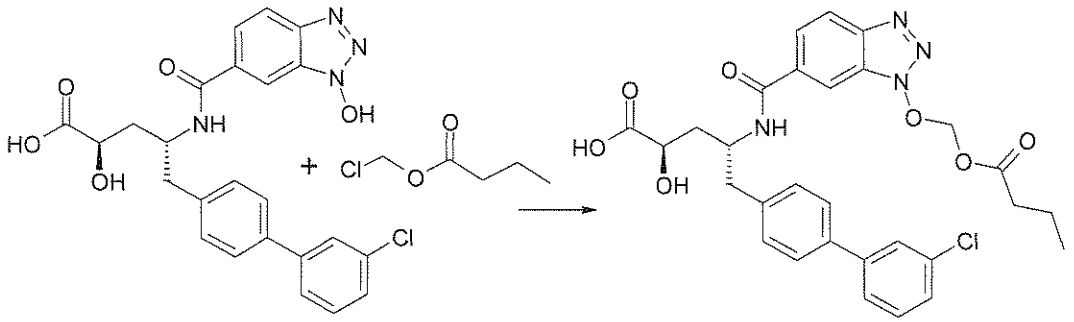
to a solution of *(2R,4R)*-4-[(3-benzyloxy-3H-benzotriazole-5-carbonyl)amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic acid (30.0 mg, 52.5 μmol) in acetone (1.0 mL, 13.6 mmol) and the resulting mixture was stirred at 45°C for 1 hour. A drop of AcOH was added to neutralize the reaction and the mixture was concentrated to yield a clear yellow liquid. The crude liquid was purified (C18 column chromatography, 55g column, using 40-90% MeCN in water with 0.05% TFA) to yield a white solid. The solid was dissolved in THF (1.0 mL, 12.3 mmol) and 10% Pd/C, 50% wet (0.45 mmol/g loading; 5.8 mg, 2.6 μmol) was added to the solution, which was stirred under hydrogen for 1 hour. The mixture was filtered and the filtrate was concentrated to yield a clear colorless liquid. The crude liquid was purified (preparative scale C18 column chromatography, small column, using 30-90% MeCN in water with 0.05% TFA) to yield the title compound as a white solid (10.0 mg, purity 99%). MS *m/z* $[M+H]^+$ calc'd for $C_{27}H_{25}ClN_4O_7$, 553.14; found 553.1.

EXAMPLE 1L: *(2R,4R)*-4-{[3-*((R)*-2-Amino-3-methylbutyryloxymethoxy)-3H-benzotriazole-5-carbonyl]amino}-5-(3'-chlorobiphenyl-4-yl)-2-hydroxy-pentanoic Acid



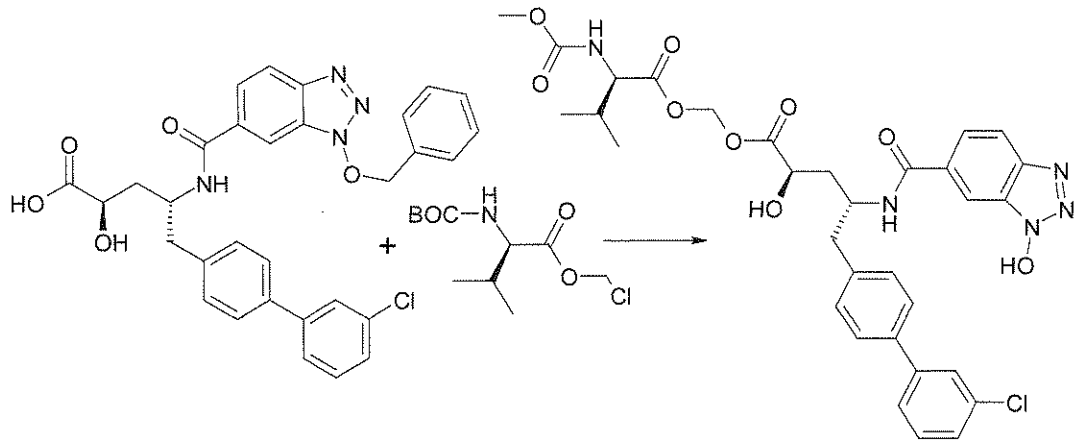
Et_3N (7.0 μL, 50 μmol) was added to a solution of [*(2R,4R)*-5-(3'-chlorobiphenyl-4-yl)-2-hydroxy-4-[(3-hydroxy-3H-benzotriazole-5-carbonyl)amino]pentanoic acid (20.0 mg, 42 μmol) and *(S)*-2-*t*-butoxycarbonylamino-3-methylbutyric acid chloromethyl ester (17.7 mg, 67 μmol) in acetone (1.3 mL, 17.2 mmol), and the resulting mixture was stirred in a sealed vial at 65°C for 5 hours. 1:1 TFA/DCM (0.50 mL, 3.1 mmol) was added, and the mixture was stirred at room temperature for 30 minutes and concentrated to yield a clear yellow liquid. The crude liquid was purified by preparative HPLC (C18 column chromatography, small column, using 30-90% MeCN in water with 0.05% TFA) to yield ~~to yield~~ the title compound as a white solid HCl salt (6.2 mg, purity 96%). MS *m/z* $[M+H]^+$ calc'd for $C_{30}H_{32}ClN_5O_7$, 610.20; found 610.1.

EXAMPLE 1M: *(2R,4R)*-4-[(3-Butyryloxymethoxy-3H-benzotriazole-5-carbonyl)amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic Acid



Et_3N (7.0 μL, 50 μmol) was added to a solution of *[(2R,4R)*-5-(3'-chlorobiphenyl-4-yl)-2-hydroxy-4-[(3-hydroxy-3H-benzotriazole-5-carbonyl)amino]pentanoic acid (20.0 mg, 42 μmol) and chloromethyl butyrate (8.3 μL, 67 μmol) in acetone (1.3 mL, 17.2 mmol), and the resulting mixture was stirred in a sealed vial at 65°C for 5 hours. The mixture was then concentrated to yield a yellow liquid. The crude liquid was purified by preparative HPLC (C18 column chromatography, small column, using 30-90% MeCN in water with 0.05% TFA) to yield the title compound as a white solid (3.3 mg, purity 94%). MS *m/z* $[M+H]^+$ calc'd for $C_{29}H_{29}ClN_4O_7$, 581.17; found 581.1.

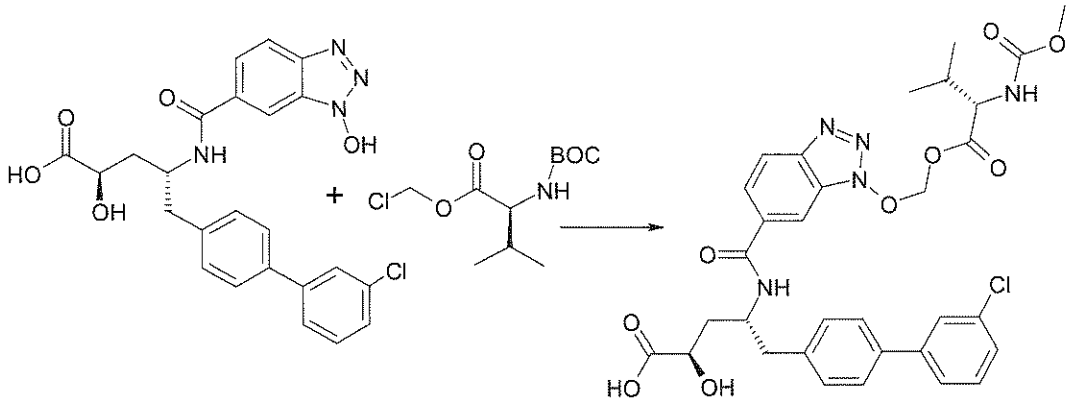
EXAMPLE 1N: *(2R,4R)*-5-(3'-Chlorobiphenyl-4-yl)-2-hydroxy-4-[(3-hydroxy-3H-benzotriazole-5-carbonyl)amino]pentanoic Acid *(R)*-2-Methoxycarbonylamino-3-methylbutyryloxymethyl Ester



(S)-2-*t*-Butoxycarbonylamino-3-methyl-butyric acid chloromethyl ester (18.1 mg, 68.3 μmol) and Et_3N (11.7 μL, 84 μmol) were added to a solution of *(2R,4R)*-4-[(3-benzyloxy-3H-benzotriazole-5-carbonyl)amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic acid (30.0 mg, 52.5 μmol) in acetone (1.00 mL, 13.6 mmol) and stirred at 60°C for 3 hours. The mixture was concentrated to yield a yellow liquid, which was

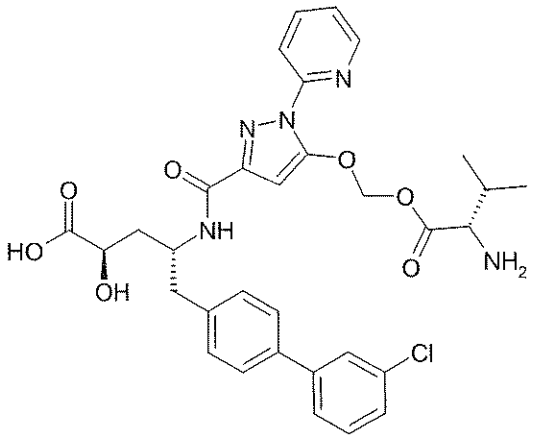
combined with 1:1 TFA/DCM (1.0 mL, 6.2 mmol) and stirred at room temperature for 1 hour. The mixture was concentrated *in vacuo* and the resulting crude liquid was purified (C18 column chromatography, 55g column, using 30-90% MeCN in water with 0.05% TFA) to yield a white solid. The solid was dissolved in DCM (0.5 mL, 7.8 mmol) at 0°C. Methyl chloroformate (6.1 μL, 78.8 μmol) was added followed by Et_3N (18.3 μL, 131 μmol) and the resulting mixture was stirred at room temperature for 30 minutes. A drop of AcOH was added to neutralize the reaction and the mixture was concentrated to yield a clear yellow liquid. The crude liquid was combined with 10% Pd/C, 50% wet (0.45 mmol/g loading; 5.8 mg, 2.6 μmol) and stirred under hydrogen for 1 hour. The mixture was filtered and the filtrate was concentrated to yield a clear yellow liquid. The crude liquid was purified (preparative scale C18 column chromatography, small column, using 30-90% MeCN in water with 0.05% TFA) to yield the title compound as a white solid TFA salt (7.5 mg, 99% purity,). MS *m/z* $[M+H]^+$ calc'd for $C_{32}H_{34}ClN_5O_9$, 668.20; found 668.1.

EXAMPLE 1O: *(2R,4R)*-5-(3'-Chlorobiphenyl-4-yl)-2-hydroxy-4-{[3-*((S)*-2-methoxycarbonylamino-3-methylbutyryloxymethoxy)-3H-benzotriazole-5-carbonyl]amino}pentanoic Acid



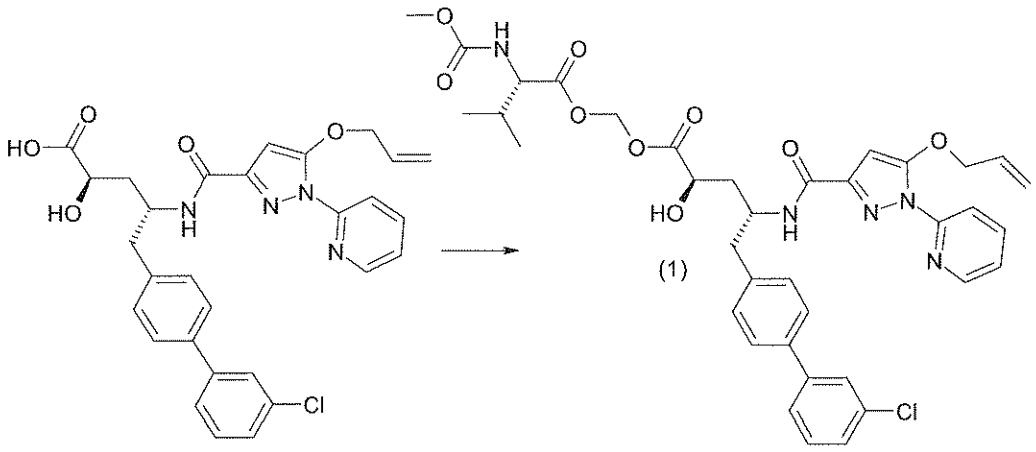
Et_3N (7.0 μL, 50 μmol) was added to a solution of [*(2R,4R)*-5-(3'-chlorobiphenyl-4-yl)-2-hydroxy-4-[(3-hydroxy-3H-benzotriazole-5-carbonyl)amino]pentanoic acid (20.0 mg, 42 μmol) and *(S)*-2-*t*-butoxycarbonylamino-3-methylbutyric acid chloromethyl ester (17.7 mg, 67 μmol) in acetone (1.3 mL, 17.2 mmol), and the resulting mixture was stirred in a sealed vial at 65°C for 5 hours. The mixture was then concentrated to yield a yellow liquid. Methyl chloroformate (4.8 ML, 62 μmol) was added to a solution of the yellow liquid and Et_3N (11.6 μL, 83 μmol) in DCM (0.5 mL, 7.8 mmol) at 0°C and the mixture was stirred at room temperature for 15 minutes. The mixture was concentrated *in vacuo* and the resulting clear colorless liquid was purified by preparative scale HPLC (C18

EXAMPLE 3G: *(2R,4R)*-4-{[5-(*(S)*-2-Amino-3-methylbutyryloxymethoxy)-1-pyridin-2-yl-1H-pyrazole-3-carbonyl]amino}-5-(3'-chloro-biphenyl-4-yl)-2-hydroxypentanoic Acid

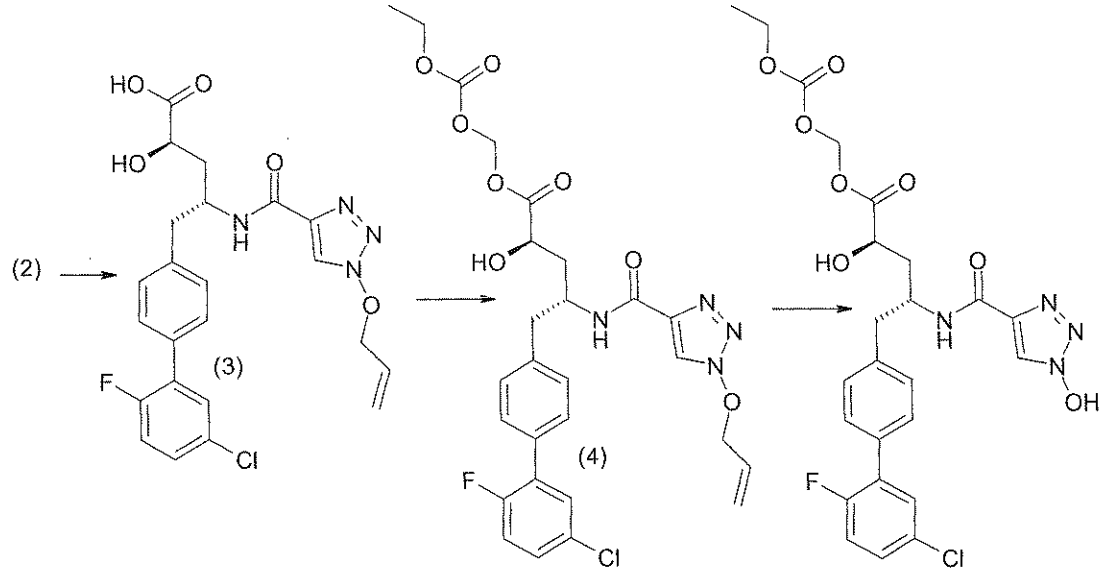


Using the procedures described herein, the title compound can also be prepared.

EXAMPLE 3H: *(2R,4R)*-5-(3'-Chlorobiphenyl-4-yl)-2-hydroxy-4-[(5-hydroxy-1-pyridin-2-yl-1H-pyrazole-3-carbonyl)amino]pentanoic Acid *(S)*-2-methoxycarbonylamino-3-methylbutyryloxymethyl Ester



To a solution of *(2R,4R)*-4-[(5-allyloxy-1-pyridin-2-yl-1H-pyrazole-3-carbonyl)-amino]-5-(3'-chlorobiphenyl-4-yl)-2-hydroxypentanoic acid (220 mg, 0.4 mmol) and *(S)*-2-methoxycarbonylamino-3-methylbutyric acid chloromethyl ester (180 mg, 0.8 mmol) in DMF (2 mL) was added 2,6-lutidine (130mg, 1.2 mmol) and NaI (60 mg, 0.4 mmol). After stirring at room temperature for 24 hours, the mixture was diluted with water (20 mL) and extracted with EtOAc (2x20 mL). The combined organic layers were washed with saturated aqueous NaCl (2x70 mL), dried over anhydrous Na_2SO_4, filtered, concentrated and purified by preparative TLC (PE:EtOAc=1:1) to yield Compound 1 as a yellow solid (160 mg). LC-MS: 734 $[M+H]^+$.



To a solution of Compound 2 (700 mg, 1.4 mmol) in MeOH (15 mL) and water (3 mL) was added LiOH (171 mg, 4.1 mmol) at room temperature. The mixture was stirred at room temperature overnight. The mixture was concentrated, water (20 mL) was added, and the mixture was extracted with EtOAc (2x10 mL). The aqueous layer was acidified by 1N HCl to pH=3, extracted with EtOAc (3x10 mL), and the combined organic layers were washed with saturated aqueous NaCl (30 mL) and dried over anhydrous Na_2SO_4. The solution was evaporated to yield Compound 3 (650 mg) as a yellow solid. LC-MS: 489 $[M+H]^+$.

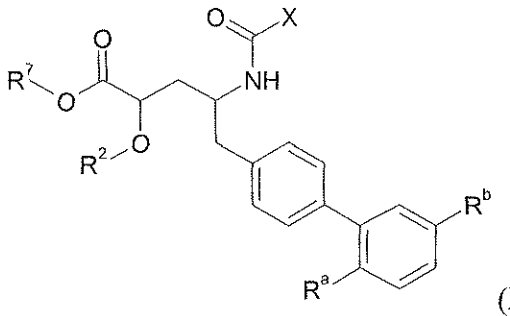
To a mixture of Compound 3 (80 mg, 160 μmol) and chloromethyl ethyl carbonate (1.0 ml) were added NaI (48 mg, 0.32 mmol) and lutidine (52 mg, 480 μmol). The mixture was stirred at 50°C for 6 hours. The mixture was then cooled to room temperature, diluted with water (15 ml), and extracted with EtOAc (2x15 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL), dried over anhydrous Na_2SO_4, concentrated, and purified by silica gel chromatography (silica gel: 200-300 mesh; elute with PE:EtOAc from 4:1 to 1:1) to yield Compound 4 (60 mg) as a light yellow solid. LC-MS: 591 $[M+H]^+$.

To a solution of Compound 4 (40 mg, 68 μmol) in MeCN (10 mL) was added NaI (10 mg, 68 μmol), and the mixture was stirred at room temperature for 5 minutes. To this stirred suspension, TMSCl (11 mg, 102 μmol) was added and stirred for another 10 minutes. The reaction was quenched by sodium thiosulphate and the mixture was extracted with EtOAc (2x10 mL). The combined organic layers were washed with saturated aqueous NaCl (20 mL) and dried over anhydrous Na_2SO_4. The residue was purified by pre-HPLC

CLAIMS

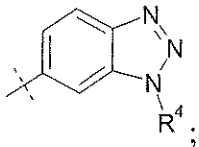
WHAT IS CLAIMED IS:

1. A compound of formula XII:

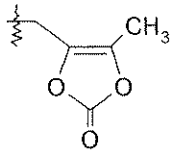


(XII)

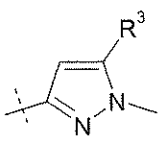
where:

(i) R^a is H; R^b is Cl; X is  ; and

R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2\text{-}3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)\text{-}C_{1\text{-}4}$alkyl, $-CHR^cOC(O)O\text{-}C_{2\text{-}4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2\text{-}4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d\text{-}NH_2$, $-CH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}$alkyl, benzyl, and

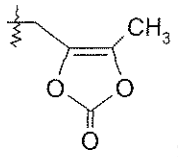
 ;

or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)\text{-}C_{1\text{-}4}$alkyl, $-OCH_2OC(O)CHR^d\text{-}NH_2$, and $-OCH_2OC(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}$alkyl, and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is selected from $-C(O)\text{-}C_{1\text{-}6}$alkyl, $-C(O)CHR^d\text{-}NH_2$, $-C(O)CHR^d\text{-}NHC(O)O\text{-}C_{1\text{-}6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ii) R^a is H; R^b is Cl; X is  ; and

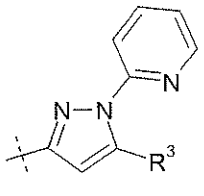
R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2\text{-}3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)\text{-}C_{1\text{-}4}$alkyl, $-CHR^cOC(O)O\text{-}C_{2\text{-}4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2\text{-}4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d\text{-}NH_2$,

-$CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

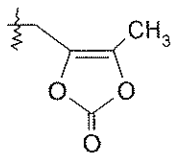


;

or R^3 is selected from -$OC(O)CH_2CH_3$, -$OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, -$OCH_2OC(O)CHR^d$-NH_2, and -$OCH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, and R^7 is H; or R^2 is selected from -C(O)-C_{1-6}alkyl, -$C(O)CHR^d$-NH_2, -$C(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, and -$P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

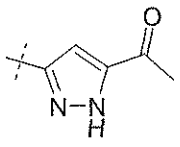
(iii) R^a is H; R^b is Cl; X is  ; and

R^2 is H, R^3 is -OH and R^7 is selected from -CH_2CH_3, -$CH_2CH(CH_3)_2$, -CH_2CF_3, -$(CH_2)_2CF_3$, -$CH_2CF_2CH_3$, -$CH_2CF_2CF_3$, -$C(CH_3)(CF_3)_2$, -$CH(CH_2CH_3)CF_3$, -$CH(CH_3)CF_2CF_3$, -$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -$CHR^cOC(O)$-C_{1-4}alkyl, -$CHR^cOC(O)O$-C_{2-4}alkyl, -$CHR^cOC(O)O$-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -$CH_2OC(O)CHR^d$-NH_2, -$CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

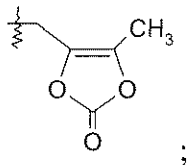


;

or R^2 is H, R^3 is selected from -$OC(O)CH_2CH_3$, -$OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, -$OCH_2OC(O)CHR^d$-NH_2, and -$OCH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, and R^7 is H; or R^2 is selected from -C(O)-C_{1-6}alkyl, -$C(O)CHR^d$-NH_2, -$C(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, and -$P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

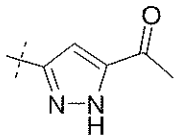
(iv) R^a is F; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, -CH_2CH_3, -CH_2CF_3, -$(CH_2)_2CF_3$, -$CH_2CF_2CH_3$, -$CH_2CF_2CF_3$, -$C(CH_3)(CF_3)_2$, -$CH(CH_2CH_3)CF_3$, -$CH(CH_3)CF_2CF_3$, -$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -$CHR^cOC(O)$-C_{1-4}alkyl, -$CHR^cOC(O)O$-C_{2-4}alkyl, -$CHR^cOC(O)O$-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -$CH_2OC(O)CHR^d$-NH_2, -$CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

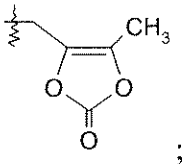


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)$(OR^e)_2$, and R^7 is H; or

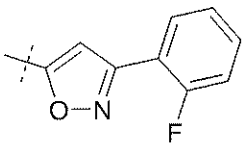
(v) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, -CHR^cOC(O)-C_{1-4}alkyl, -CHR^cOC(O)O-C_{2-4}alkyl, -CHR^cOC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d$-NH_2, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

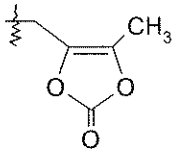


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)$(OR^e)_2$, and R^7 is H; or

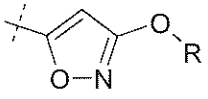
(vi) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, -CHR^cOC(O)-C_{1-4}alkyl, -CHR^cOC(O)O-C_{2-4}alkyl, -CHR^cOC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d$-NH_2, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

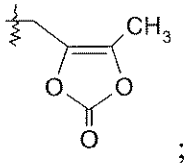


;

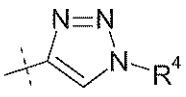
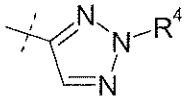
or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)$(OR^e)_2$, and R^7 is H; or

(vii) R^a is H; R^b is Cl; X is  ; R is H or $-CH_3$; and

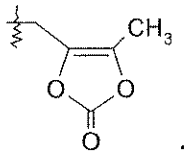
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

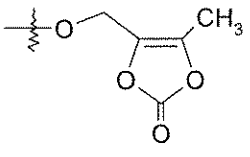
or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(viii) R^a is F; R^b is Cl; X is  or  ; and

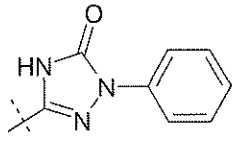
R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

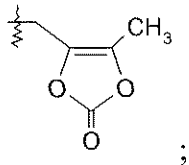
or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and

 ,

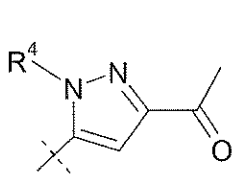
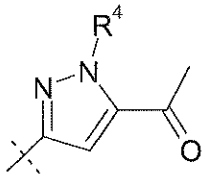
and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ix) R^a is H; R^b is Cl; X is  ; and

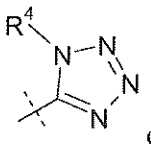
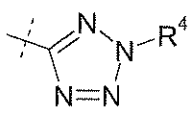
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(x) R^a is H; R^b is H; X is  or  ; and

R^2 and R^4 are H, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$; or

(xi) R^a is H; R^b is Cl; X is  or  ; and

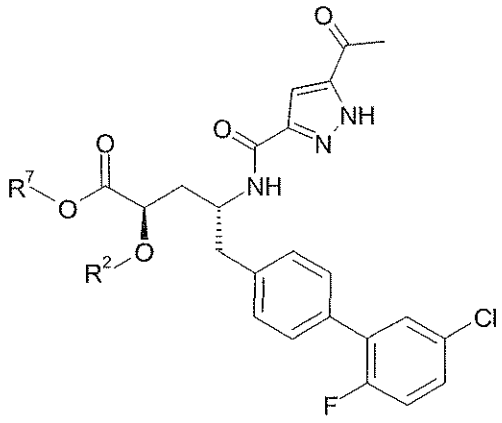
R^2 and R^4 are H, and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$,

$-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$;

where each R^c is independently H or $-C_{1-3}$alkyl; each R^d is independently H, $-CH_3$, $-CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, $-C_{1-6}$alkyl, or phenyl;

or a pharmaceutically acceptable salt thereof.

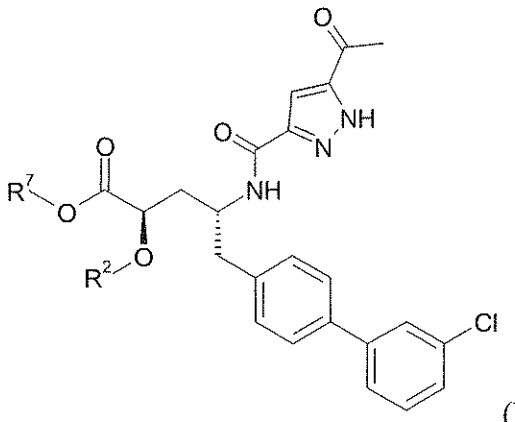
2. The compound of Claim 1, of the formula IV:



(IV)

where R^2 is H and R^7 is selected from H and $-CH_2CH_3$.

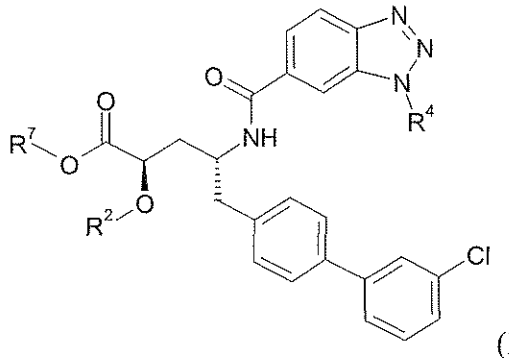
3. The compound of Claim 1, of formula V:



(V)

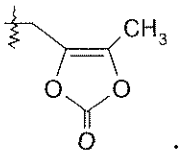
where R^2 is H and R^7 is selected from H and $-CH_2CH_3$.

4. The compound of Claim 1, of the formula I:



(I)

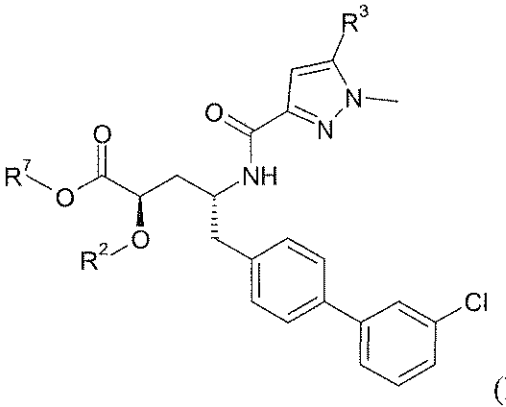
where R^2 is H, R^4 is -OH and R^7 is selected from -CH_2CF_3, -$(CH_2)_2CF_3$, -$CH_2CF_2CF_3$, -$CH_2OC(O)CH_3$, -$CH_2OC(O)(CH_2)_2CH_3$, -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, benzyl, and



;

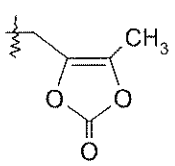
or R^2 is H, R^4 is -$OCH_2OC(O)CH_3$ and R^7 is selected from H and -$CH_2OC(O)CH_3$; or R^2 is H, R^4 is selected from -$OCH_2OC(O)(CH_2)_2CH_3$, -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and -$OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and R^7 is H; or R^2 is H, R^4 is -O-benzyl and R^7 is H.

5. The compound of Claim 1, of the formula II:



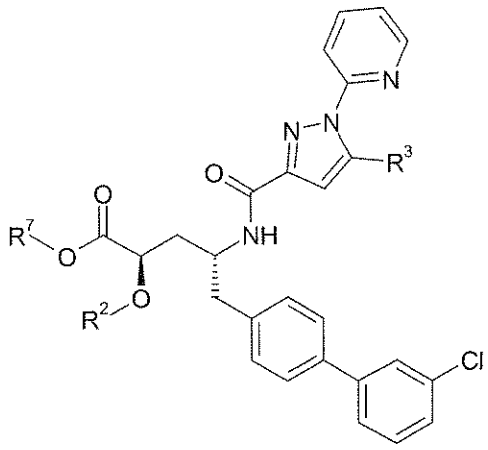
(II)

where R^2 is H, R^3 is -OH and R^7 is selected from -CH_2CH_3, -$CH_2CF_2CF_3$, -$CH(CH_2CH_3)CF_3$, -$CH(CH_3)CF_2CF_3$, -$CH_2OC(O)(CH_2)_2CH_3$, -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, benzyl, and



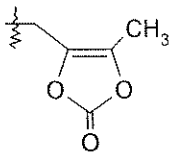
.

6. The compound of Claim 1, of the formula III:



(III)

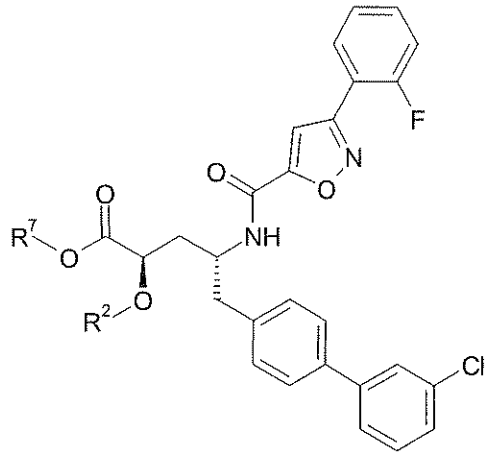
where R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and



,

where R^d is $-CH(CH_3)_2$; or R^2 is H, R^3 is $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^3 is -OH, and R^7 is H.

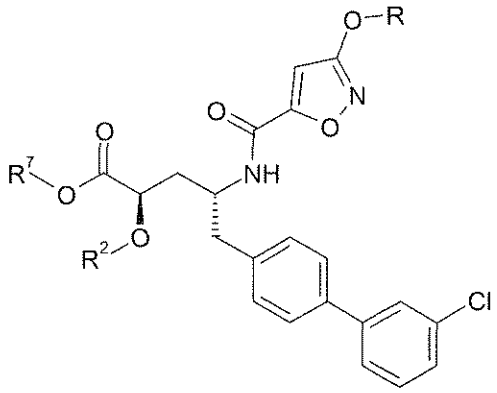
7. The compound of Claim 1, of the formula VI:



(VI)

where R^2 is H and R^7 is selected from H, $-CH_2OC(O)CH_3$, $-CH_2OC(O)OCH_2CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, and $-C(O)CH[CH(CH_3)_2]$-NHC(O)OCH_3.

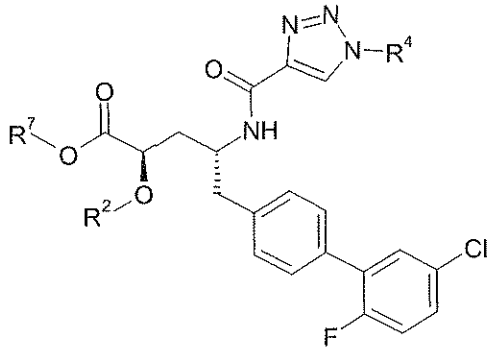
8. The compound of Claim 1, of the formula VII:



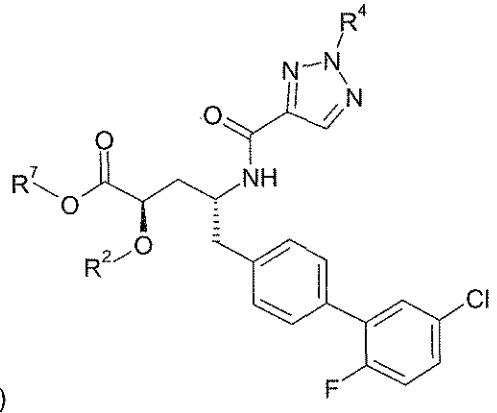
(VII)

where R is -CH_3, R^2 is H, and R^7 is selected from -$CH_2OC(O)CH_3$, -$CH_2OC(O)OCH(CH_3)_2$, -$CH_2OC(O)OCH_2CH_3$, and -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$.

9. The compound of Claim 1, of the formula VIIIa or VIIIb:

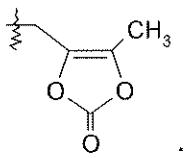


(VIIIa)



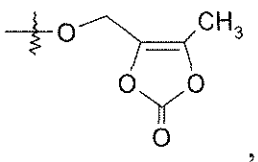
(VIIIb)

where R^2 is H, R^4 is -OH and R^7 is selected from -$CH_2CF_2CF_3$, -$CH_2OC(O)CH_3$, -$CH_2OC(O)(CH_2)_2CH_3$, -$CH_2OC(O)OCH_2CH_3$, -$CH_2OC(O)OCH(CH_3)_2$, -$CH(CH_3)OC(O)O$-cyclohexyl, -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and



;

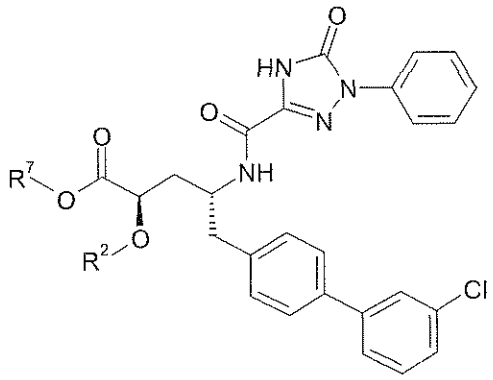
or R^2 is H, R^4 is selected from -$OCH_2OC(O)(CH_2)_2CH_3$, -$OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, -$OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and



,

and R^7 is H.

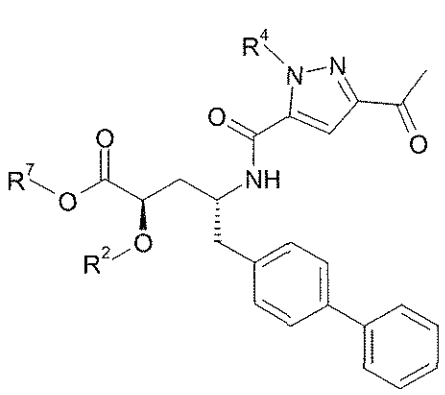
10. The compound of Claim 1, of the formula IX:



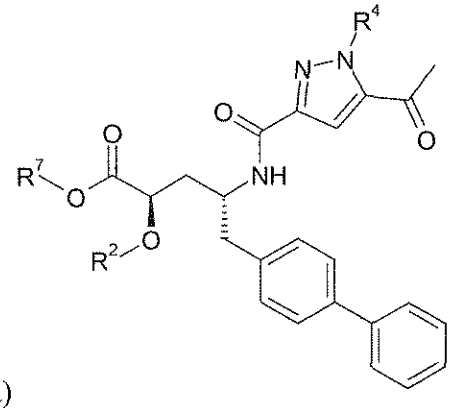
(IX)

where R^2 is H and R^7 is selected from $-CH_2OC(O)OCH_2CH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$.

11. The compound of Claim 1, of the formula Xa or Xb:



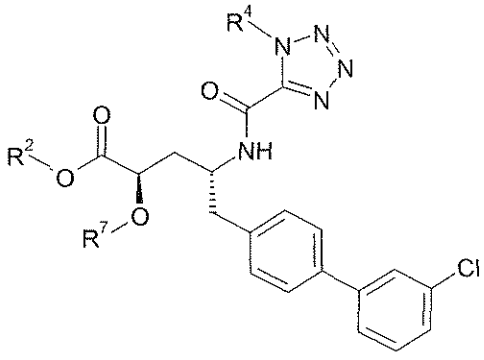
(Xa)



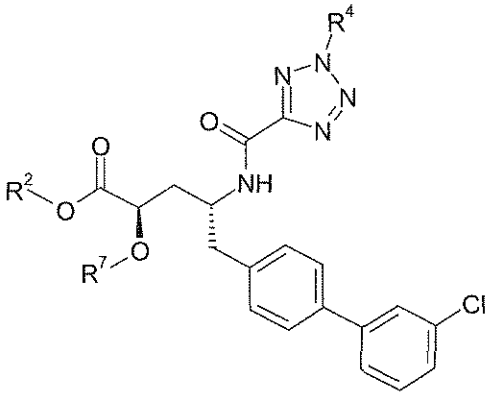
(Xb)

where R^2 is H, R^4 is $-CH_2OP(O)(OH)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$.

12. The compound of Claim 1, of the formula XIa or XIb:



(XIa)

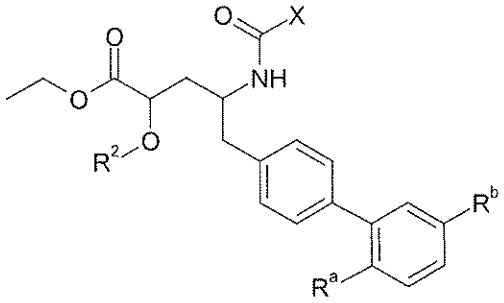


(XIb)

where R^2, R^4, and R^7 are H; or R^2 and R^4 are H, and R^7 is $-CH_2OC(O)OCH_2CH_3$.

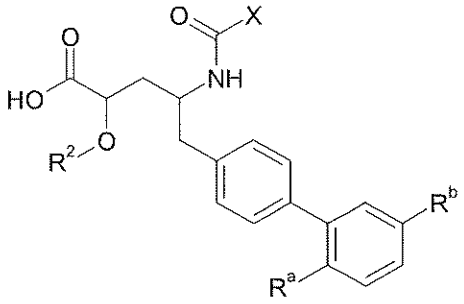
13. A process for preparing a compound as claimed in any one of Claims 1 to 12, comprising the step of:

(a) reacting a compound of formula



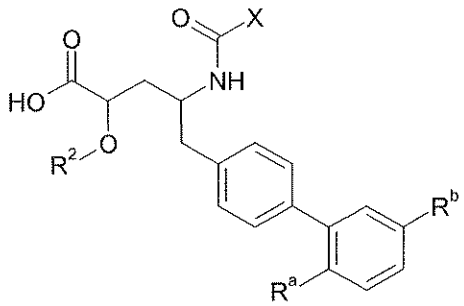
with a compound of formula HO-R^7 in a transesterification reaction; or

(b) reacting a compound of formula



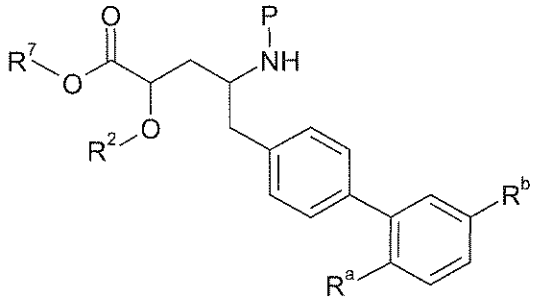
with a compound of formula L-R^7 in a nucleophilic substitution reaction, where L is a leaving group; or

(c) reacting a compound of formula



with a compound of formula L-R^2 in a nucleophilic substitution reaction, where L is a leaving group; or

(d) reacting a compound of formula



with a compound of formula HOOC-X in a coupling reaction, where P is H or an amino-

protecting group;

to produce a compound of formula XII.

14. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in any one of Claims 1 to 12, optionally together with an additional therapeutic agent.

15. The pharmaceutical composition of Claim 14, wherein the additional therapeutic agent is an AT_1 receptor antagonist.

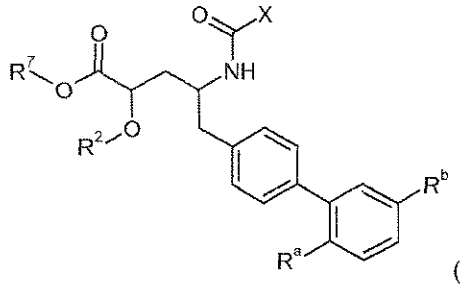
16. A compound as claimed in any one of Claims 1 to 12, for use in therapy.

17. A compound as claimed in Claim 16, for use in treating hypertension, heart failure, or renal disease.

CLAIMS

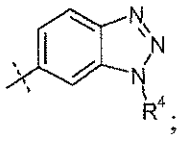
WHAT IS CLAIMED IS:

1. A compound of formula XII:

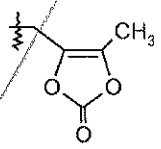


(XII)

where:

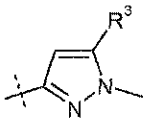
(i) R^a is H; R^b is Cl; X is ; and

R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and



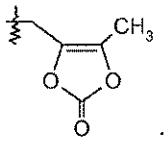
;

or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ii) R^a is H; R^b is Cl; X is ; and

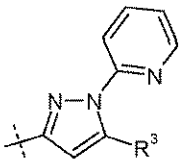
R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$,

$-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

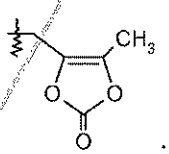


;

or R^3 is selected from $-OC(O)CH_2CH_3$, $-OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

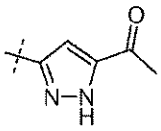
(iii) R^a is H; R^b is Cl; X is  ; and

R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

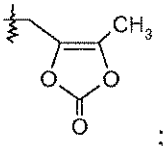


;

or R^2 is H, R^3 is selected from $-OC(O)CH_2CH_3$, $-OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

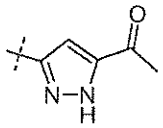
(iv) R^a is F; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

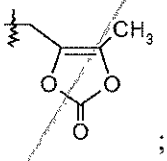


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

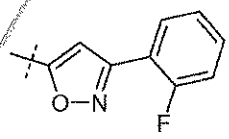
(v) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, -CH_2CH_3, -CH_2CF_3, -$(CH_2)_2CF_3$, -$CH_2CF_2CH_3$, -$CH_2CF_2CF_3$, -$C(CH_3)(CF_3)_2$, -$CH(CH_2CH_3)CF_3$, -$CH(CH_3)CF_2CF_3$, -$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -CHR^{c}OC(O)-C_{1-4}alkyl, -CHR^{c}OC(O)O-C_{2-4}alkyl, -CHR^{c}OC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -CH_2OC(O)CHR^d-NH_2, -CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}alkyl, benzyl, and

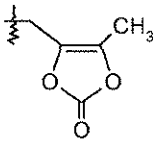


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

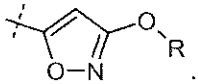
(vi) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, -CH_2CH_3, -CH_2CF_3, -$(CH_2)_2CF_3$, -$CH_2CF_2CH_3$, -$CH_2CF_2CF_3$, -$C(CH_3)(CF_3)_2$, -$CH(CH_2CH_3)CF_3$, -$CH(CH_3)CF_2CF_3$, -$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -CHR^{c}OC(O)-C_{1-4}alkyl, -CHR^{c}OC(O)O-C_{2-4}alkyl, -CHR^{c}OC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -CH_2OC(O)CHR^d-NH_2, -CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}alkyl, benzyl, and

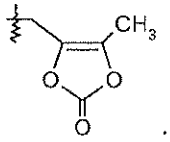


;

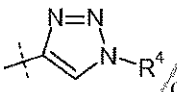
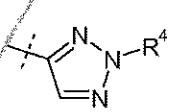
or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

(vii) R^a is H; R^b is Cl; X is  ; R is H or $-CH_3$; and

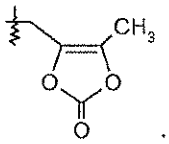
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

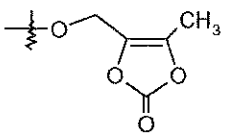
or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(viii) R^a is F; R^b is Cl; X is  or  ; and

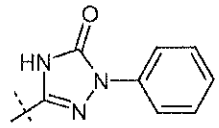
R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

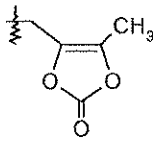
or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and

 ,

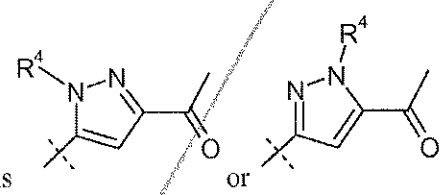
and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ix) R^a is H; R^b is Cl; X is  ; and

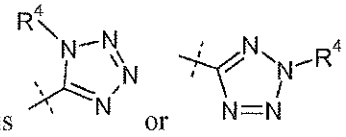
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(x) R^a is H; R^b is H; X is  ; and

R^2 and R^4 are H, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$; or

(xi) R^a is H; R^b is Cl; X is  ; and

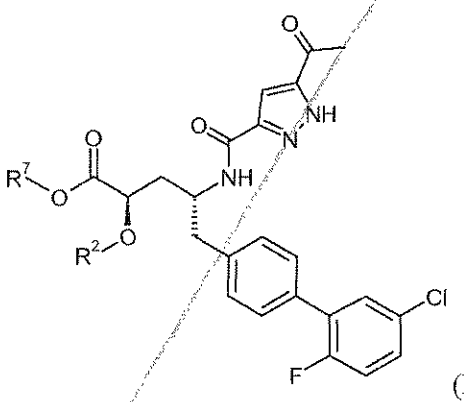
R^2 and R^4 are H, and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$,

-$(CH_2)_{2-3}OH$, -$CH_2CH(NH_2)COOCH_3$, -$(CH_2)_2OCH_3$, -$CH_2OC(O)CH_3$, -$CH_2OC(O)(CH_2)_2CH_3$, -$CHR^cOC(O)O$-C_{2-4}alkyl, -$CHR^cOC(O)O$-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, -$CH_2OC(O)CHR^d$-NH_2, -$CH_2OC(O)CHR^d$-$NHC(O)O$-C_{1-6}alkyl, and benzyl; or R^2 is H, R^4 is selected from -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$ and -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from -$C(O)$-C_{1-6}alkyl, -$C(O)CHR^d$-NH_2, -$C(O)CHR^d$-$NHC(O)O$-C_{1-6}alkyl, and -$P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is -$CH_2OP(O)(OR^e)_2$ or -$CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is -CH_2CH_3; or R^2 is -$C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is -CH_2CH_3;

where each R^c is independently H or -C_{1-3}alkyl; each R^d is independently H, -CH_3, -$CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, -C_{1-6}alkyl, or phenyl;

or a pharmaceutically acceptable salt thereof.

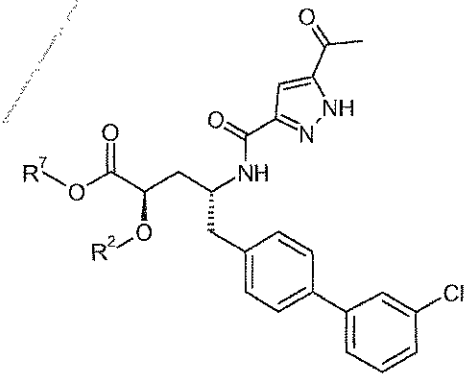
2. The compound of Claim 1, of the formula IV:



(IV).

3. The compound of Claim 2, where R^2 is H and R^7 is selected from H and -CH_2CH_3.

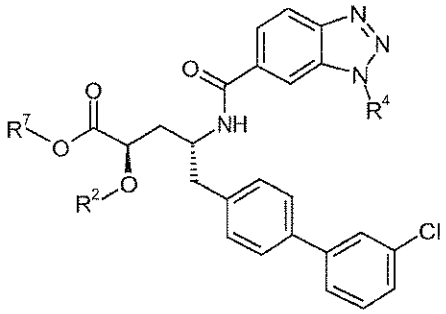
4. The compound of Claim 1, of formula V:



(V).

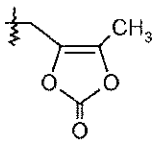
5. The compound of Claim 4, where R^2 is H and R^7 is selected from H and -CH_2CH_3.

6. The compound of Claim 1, of the formula I:



(I).

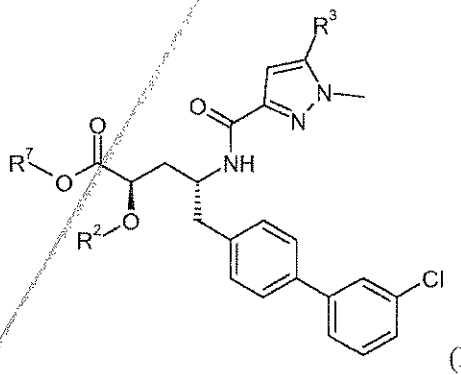
7. The compound of Claim 6, where R^2 is H, R^4 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, benzyl, and



;

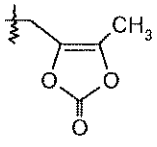
or R^2 is H, R^4 is $-OCH_2OC(O)CH_3$ and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is H, R^4 is selected from $-OCH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and $-OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and R^7 is H; or R^2 is H, R^4 is -O-benzyl and R^7 is H.

8. The compound of Claim 1, of the formula II:



(II).

9. The compound of Claim 8, where R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_2CF_3$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, benzyl, and



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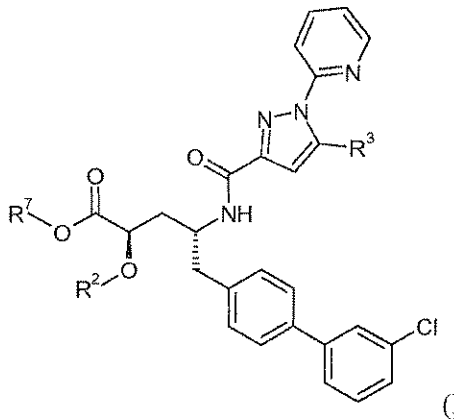
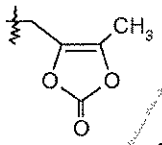
10. The compound of Claim 1, of the formula III:



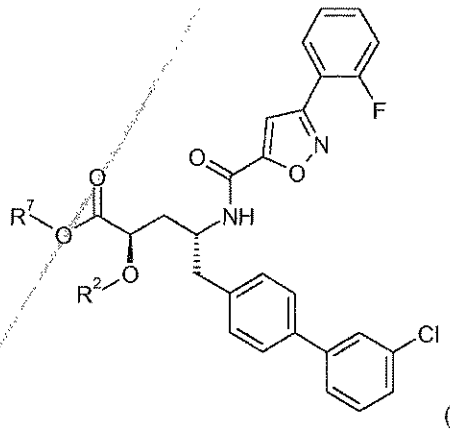
(III).

11. The compound of Claim 10, where R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and



where R^d is $-CH(CH_3)_2$; or R^2 is H, R^3 is $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^3 is -OH, and R^7 is H.

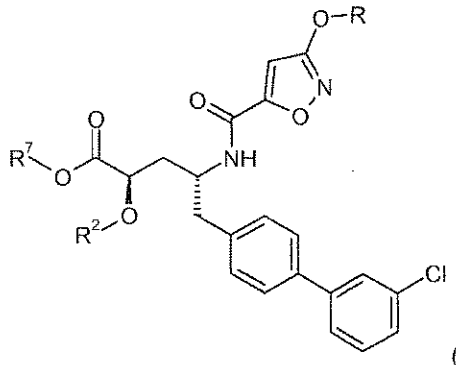
12. The compound of Claim 1, of the formula VI:



(VI).

13. The compound of Claim 12, where R^2 is H and R^7 is selected from H, $-CH_2OC(O)CH_3$, $-CH_2OC(O)OCH_2CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, and $-C(O)CH[CH(CH_3)_2]$-NHC(O)OCH_3.

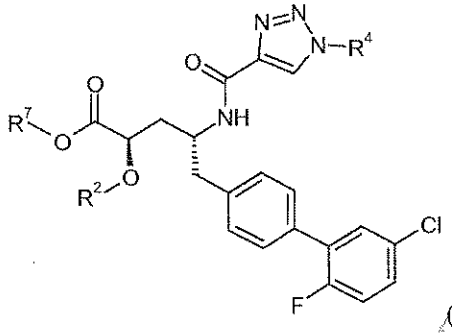
14. The compound of Claim 1, of the formula VII:



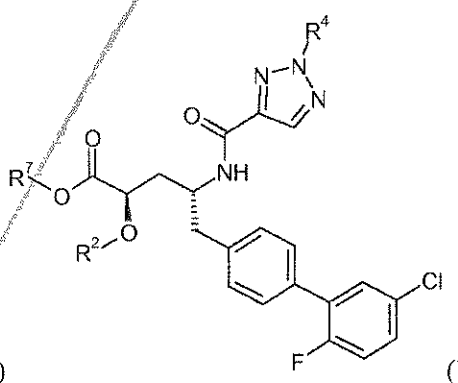
(VII).

15. The compound of Claim 14, where R is -CH_3, R^2 is H, and R^7 is selected from -$CH_2OC(O)CH_3$, -$CH_2OC(O)OCH(CH_3)_2$, -$CH_2OC(O)OCH_2CH_3$, and -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$.

16. The compound of Claim 1, of the formula VIIIa or VIIIb:

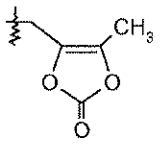


(VIIIa)



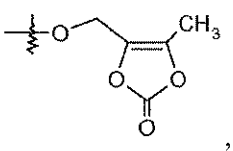
(VIIIb).

17. The compound of Claim 16, where R^2 is H, R^4 is -OH and R^7 is selected from -$CH_2CF_2CF_3$, -$CH_2OC(O)CH_3$, -$CH_2OC(O)(CH_2)_2CH_3$, -$CH_2OC(O)OCH_2CH_3$, -$CH_2OC(O)OCH(CH_3)_2$, -$CH(CH_3)OC(O)O$-cyclohexyl, -$CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and



;

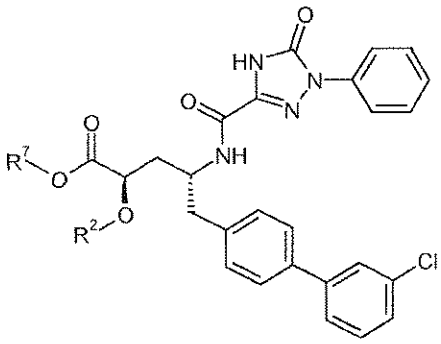
or R^2 is H, R^4 is selected from -$OCH_2OC(O)(CH_2)_2CH_3$, -$OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, -$OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and



,

and R^7 is H.

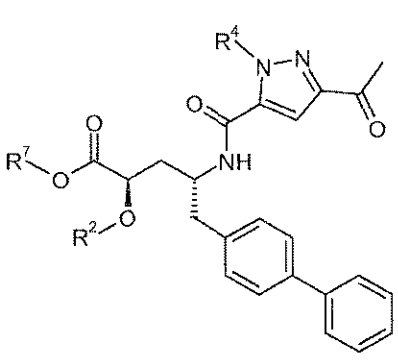
18. The compound of Claim 1, of the formula IX:



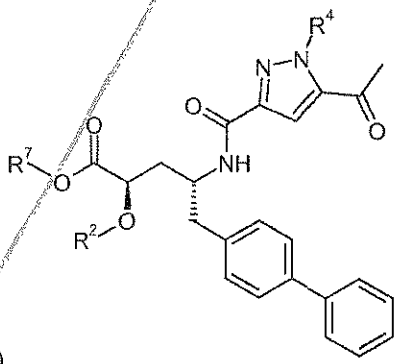
(IX).

19. The compound of Claim 18, where R^2 is H and R^7 is selected from $-CH_2OC(O)OCH_2CH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$.

20. The compound of Claim 1, of the formula Xa or Xb:



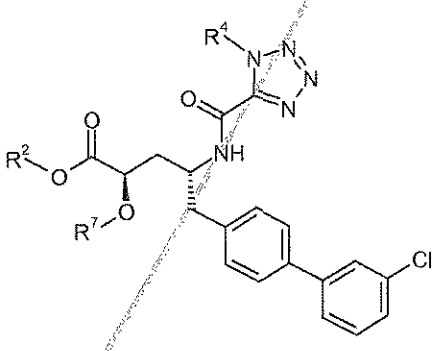
(Xa)



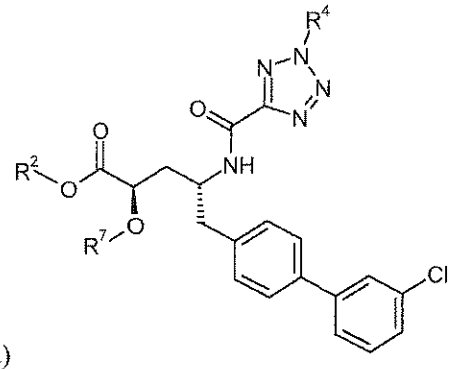
(Xb).

21. The compound of Claim 20, where R^2 is H, R^4 is $-CH_2OP(O)(OH)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$.

22. The compound of Claim 1, of the formula XIa or XIb:



(XIa)

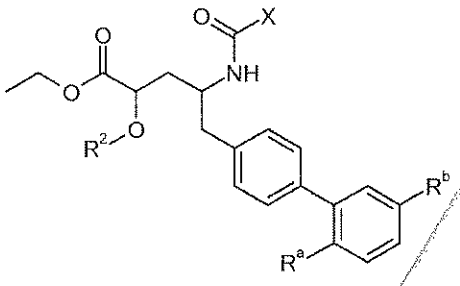


(XIb).

23. The compound of Claim 22, where R^2, R^4, and R^7 are H; or R^2 and R^4 are H, and R^7 is $-CH_2OC(O)OCH_2CH_3$.

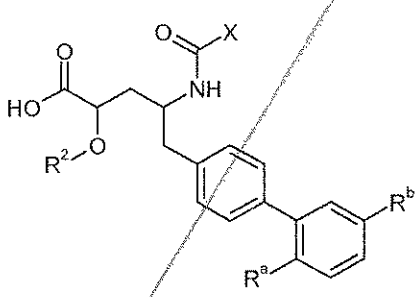
24. A process for preparing a compound as claimed in any one of Claims 1 to 23, comprising the step of:

(a) reacting a compound of formula



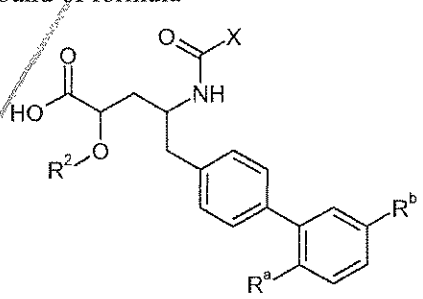
with a compound of formula HO-R^7 in a transesterification reaction; or

(b) reacting a compound of formula



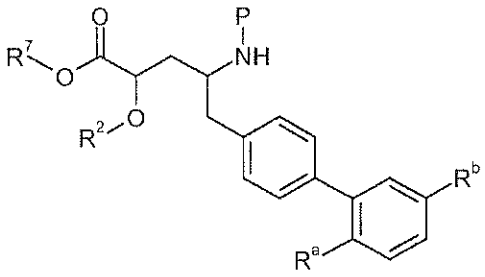
with a compound of formula L-R^7 in a nucleophilic substitution reaction, where L is a leaving group; or

(c) reacting a compound of formula



with a compound of formula L-R^2 in a nucleophilic substitution reaction, where L is a leaving group; or

(d) reacting a compound of formula



with a compound of formula HOOC-X in a coupling reaction, where P is H or an amino-protecting group;

to produce a compound of formula XII.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in any one of Claims 1 to 23.

26. The pharmaceutical composition of Claim 25, further comprising a therapeutic agent selected from adenosine receptor antagonists, α-adrenergic receptor antagonists, β_1-adrenergic receptor antagonists, β_2-adrenergic receptor agonists, dual-acting β-adrenergic receptor antagonist/α_1-receptor antagonists, advanced glycation end product breakers, aldosterone antagonists, aldosterone synthase inhibitors, aminopeptidase N inhibitors, 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, AT_1 receptor antagonists and dual-acting AT_1 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 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 guanylate cyclase stimulators and activators, tricyclic antidepressants, vasopressin receptor antagonists, and combinations thereof.

27. The pharmaceutical composition of Claim 26, wherein the therapeutic agent is an

AT_1 receptor antagonist.

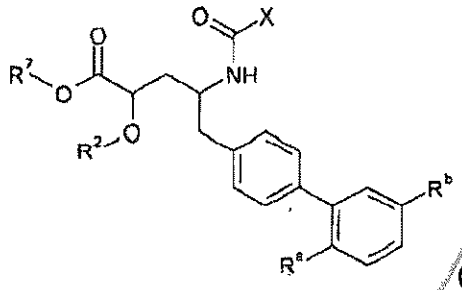
28. A compound as claimed in any one of Claims 1 to 23, for use in therapy.

29. A compound as claimed in Claim 28, for use in treating hypertension, heart failure, or renal disease.

30. The use of a compound as claimed in any one of Claims 1 to 23, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.

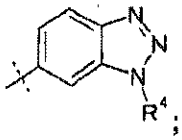
AMENDED CLAIMS
received by the International Bureau on 10.October 2013 (10.10.2013)

1. A compound of formula XII:

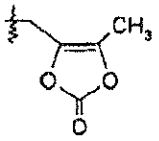


(XII)

where:

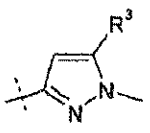
(i) R^a is H; R^b is Cl; X is ; and

R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and



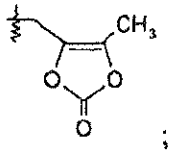
;

or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ii) R^a is H; R^b is Cl; X is ; and

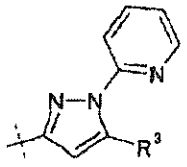
R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$,

$-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

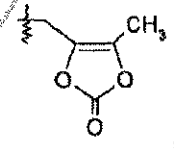


;

or R^3 is selected from $-OC(O)CH_2CH_3$, $-OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

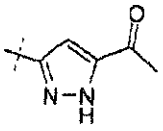
(iii) R^a is H; R^b is Cl; X is  ; and

R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

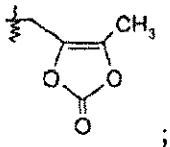


;

or R^2 is H, R^3 is selected from $-OC(O)CH_2CH_3$, $-OC(O)CH_2CH(CH_3)_2$, -OC(O)-phenyl, $-OCH_2OC(O)CHR^d-NH_2$, and $-OCH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^3 is -OH, and R^7 is H; or

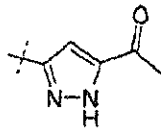
(iv) R^a is F; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

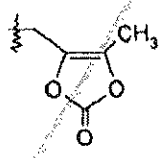


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

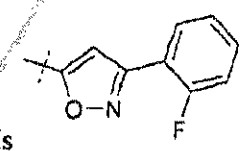
(v) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, -CHR^{c}OC(O)-C_{1-4}alkyl, -CHR^{c}OC(O)O-C_{2-4}alkyl, -CHR^{c}OC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d$-NH_2, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

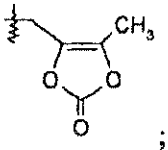


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

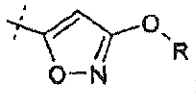
(vi) R^a is H; R^b is Cl; X is  ; and

R^2 is H and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, -CHR^{c}OC(O)-C_{1-4}alkyl, -CHR^{c}OC(O)O-C_{2-4}alkyl, -CHR^{c}OC(O)O-cyclohexyl, -C_{2-4}alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d$-NH_2, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and

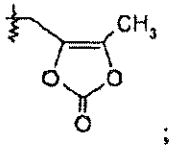


;

or R^2 is selected from -C(O)-C_{1-6}alkyl, -C(O)CHR^d-NH_2, -C(O)CHR^d-NHC(O)O-C_{1-6}alkyl, and -P(O)(OR^e)$_2$, and R^7 is H; or

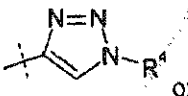
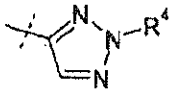
(vii) R^a is H; R^b is Cl; X is  ; R is H or $-CH_3$; and

R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

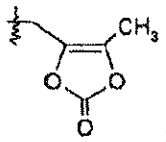


;

or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

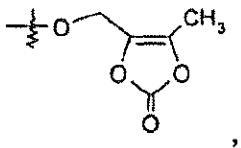
(viii) R^a is F; R^b is Cl; X is  or  ; and

R^2 is H, R^4 is -OH, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and



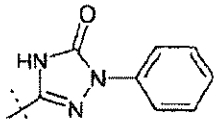
;

or R^2 is H, R^4 is selected from -O-benzyl, $-OCHR^cOC(O)-C_{1-4}$alkyl, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and

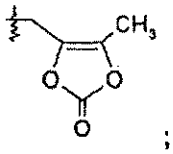


,

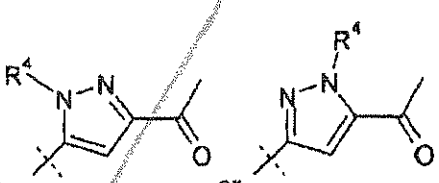
and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is -OH, and R^7 is H; or

(ix) R^a is H; R^b is Cl; X is  ; and

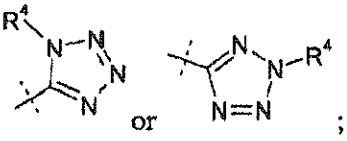
R^2 is H and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, benzyl, and

 ;

or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, and R^7 is H; or

(x) R^a is H; R^b is H; X is  ; and

R^2 and R^4 are H, and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-CHR^cOC(O)-C_{1-4}$alkyl, $-CHR^cOC(O)O-C_{2-4}$alkyl, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}$alkylene-$N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}$alkyl, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}$alkyl, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$; or

(xi) R^a is H; R^b is Cl; X is  ; and

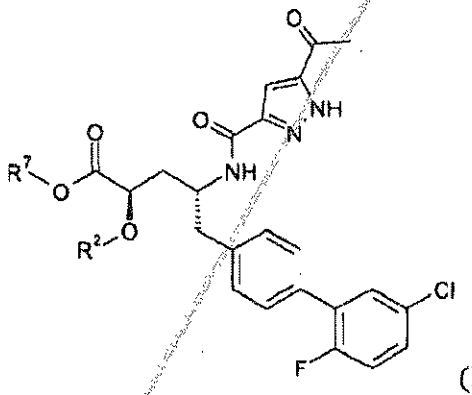
R^2 and R^4 are H, and R^7 is selected from H, $-CH_2CH_3$, $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CH_3$, $-CH_2CF_2CF_3$, $-C(CH_3)(CF_3)_2$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$,

$-(CH_2)_{2-3}OH$, $-CH_2CH(NH_2)COOCH_3$, $-(CH_2)_2OCH_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CHR^cOC(O)O-C_{2-4}alkyl$, $-CHR^cOC(O)O$-cyclohexyl, $-C_{2-4}alkylene-N(CH_3)_2$, $-CH_2OC(O)CHR^d-NH_2$, $-CH_2OC(O)CHR^d-NHC(O)O-C_{1-6}alkyl$, and benzyl; or R^2 is H, R^4 is selected from $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is selected from $-C(O)-C_{1-6}alkyl$, $-C(O)CHR^d-NH_2$, $-C(O)CHR^d-NHC(O)O-C_{1-6}alkyl$, and $-P(O)(OR^e)_2$, R^4 is H, and R^7 is H; or R^2 is H, R^4 is $-CH_2OP(O)(OR^e)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$;

where each R^c is independently H or $-C_{1-3}alkyl$; each R^d is independently H, $-CH_3$, $-CH(CH_3)_2$, phenyl, or benzyl; and each R^e is independently H, $-C_{1-6}alkyl$, or phenyl;

or a pharmaceutically acceptable salt thereof.

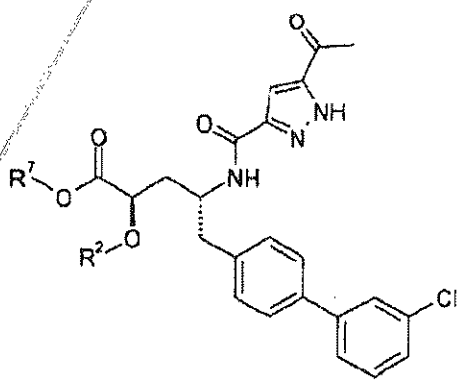
2. The compound of Claim 1, of the formula IV:



(IV).

3. The compound of Claim 2, where R^2 is H and R^7 is selected from H and $-CH_2CH_3$.

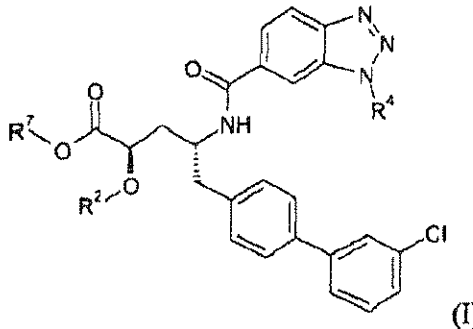
4. The compound of Claim 1, of formula V:



(V).

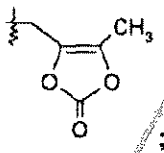
5. The compound of Claim 4, where R^2 is H and R^7 is selected from H and $-CH_2CH_3$.

6. The compound of Claim 1, of the formula I:



(I).

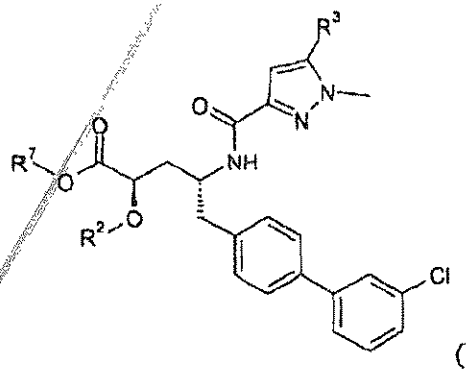
7. The compound of Claim 6, where R^2 is H, R^4 is -OH and R^7 is selected from $-CH_2CF_3$, $-(CH_2)_2CF_3$, $-CH_2CF_2CF_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-CH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, benzyl, and



;

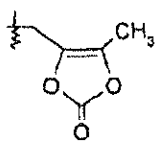
or R^2 is H, R^4 is $-OCH_2OC(O)CH_3$ and R^7 is selected from H and $-CH_2OC(O)CH_3$; or R^2 is H, R^4 is selected from $-OCH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and $-OCH_2OC(O)CH[CH(CH_3)_2]$-$NHC(O)OCH_3$, and R^7 is H; or R^2 is H, R^4 is -O-benzyl and R^7 is H.

8. The compound of Claim 1, of the formula II:



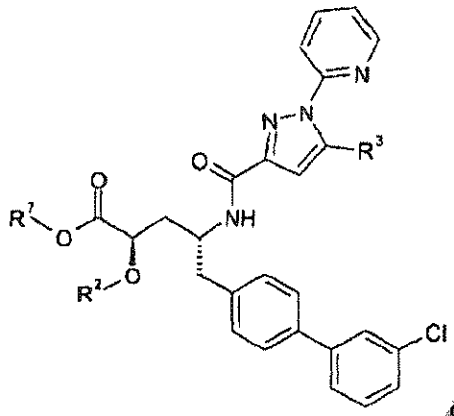
(II).

9. The compound of Claim 8, where R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CF_2CF_3$, $-CH(CH_2CH_3)CF_3$, $-CH(CH_3)CF_2CF_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, benzyl, and



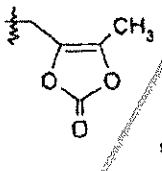
.

10. The compound of Claim 1, of the formula III:



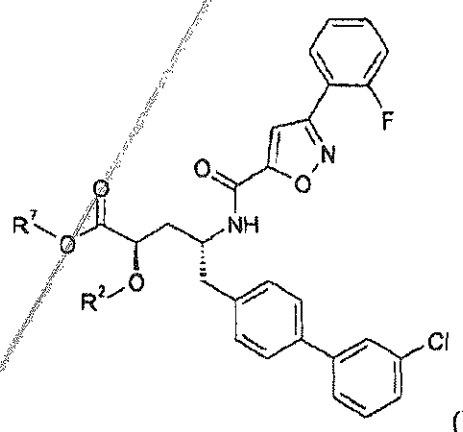
(III).

11. The compound of Claim 10, where R^2 is H, R^3 is -OH and R^7 is selected from $-CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-CH_2OC(O)CHR^d$-NHC(O)O-C_{1-6}alkyl, benzyl, and



where R^d is $-CH(CH_3)_2$; or R^2 is H, R^3 is $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is H; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^3 is -OH, and R^7 is H.

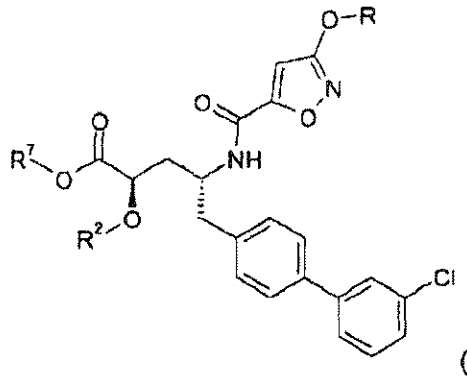
12. The compound of Claim 1, of the formula VI:



(VI).

13. The compound of Claim 12, where R^2 is H and R^7 is selected from H, $-CH_2OC(O)CH_3$, $-CH_2OC(O)OCH_2CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, and $-C(O)CH[CH(CH_3)_2]$-NHC(O)OCH_3.

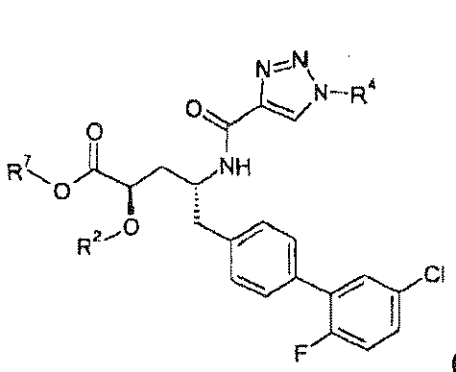
14. The compound of Claim 1, of the formula VII:



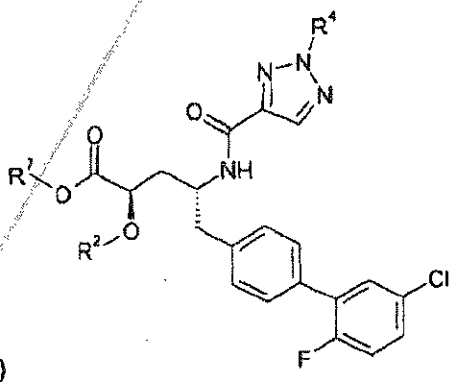
(VII).

15. The compound of Claim 14, where R is $-CH_3$, R^2 is H, and R^7 is selected from $-CH_2OC(O)CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, $-CH_2OC(O)OCH_2CH_3$, and $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$.

16. The compound of Claim 1, of the formula VIIIa or VIIIb:

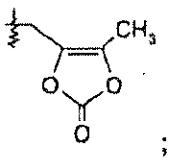


(VIIIa)



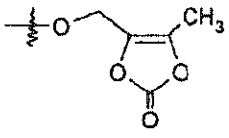
(VIIIb).

17. The compound of Claim 16, where R^2 is H, R^4 is -OH and R^7 is selected from $-CH_2CF_2CF_3$, $-CH_2OC(O)CH_3$, $-CH_2OC(O)(CH_2)_2CH_3$, $-CH_2OC(O)OCH_2CH_3$, $-CH_2OC(O)OCH(CH_3)_2$, $-CH(CH_3)OC(O)O$-cyclohexyl, $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$, and



;

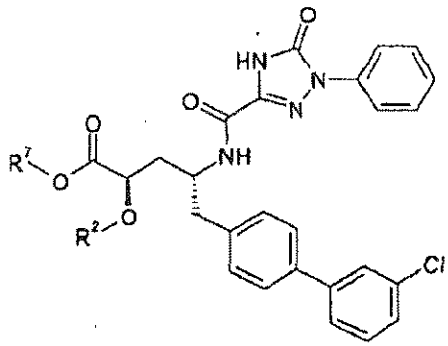
or R^2 is H, R^4 is selected from $-OCH_2OC(O)(CH_2)_2CH_3$, $-OCH_2OC(O)CH[CH(CH_3)_2]NH_2$, $-OCH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$, and



,

and R^7 is H.

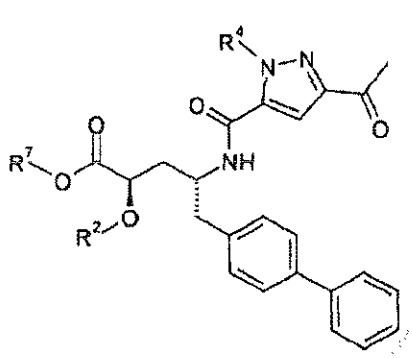
18. The compound of Claim 1, of the formula IX:



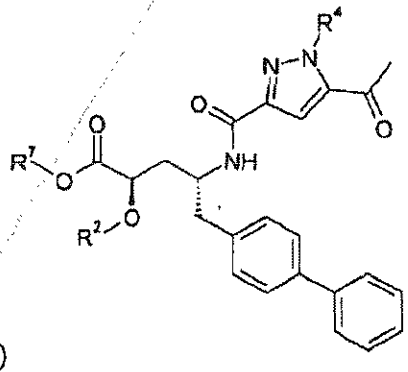
(IX).

19. The compound of Claim 18, where R^2 is H and R^7 is selected from $-CH_2OC(O)OCH_2CH_3$ and $-CH_2OC(O)CH[CH(CH_3)_2]-NHC(O)OCH_3$.

20. The compound of Claim 1, of the formula Xa or Xb:



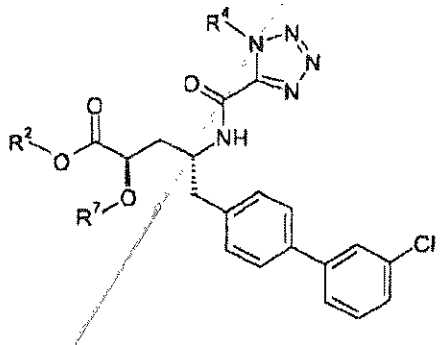
(Xa)



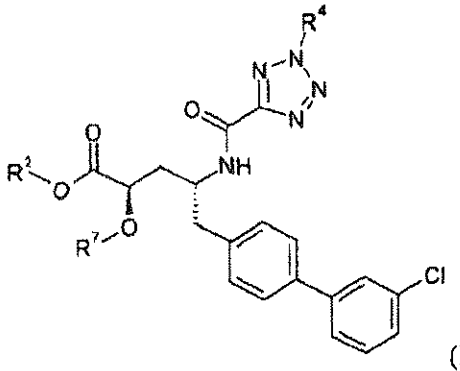
(Xb).

21. The compound of Claim 20, where R^2 is H, R^4 is $-CH_2OP(O)(OH)_2$ or $-CH_2OC(O)CH[CH(CH_3)_2]NH_2$, and R^7 is $-CH_2CH_3$; or R^2 is $-C(O)CH[CH(CH_3)_2]NH_2$, R^4 is H, and R^7 is $-CH_2CH_3$.

22. The compound of Claim 1, of the formula XIa or XIb:



(XIa)

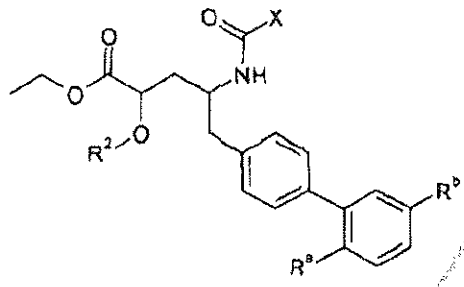


(XIb).

23. The compound of Claim 22, where R^2, R^4, and R^7 are H; or R^2 and R^4 are H, and R^7 is $-CH_2OC(O)OCH_2CH_3$.

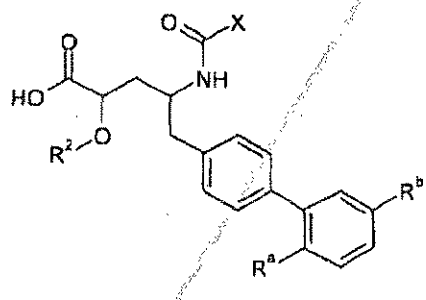
24. A process for preparing a compound as claimed in any one of Claims 1 to 23, comprising the step of:

(a) reacting a compound of formula



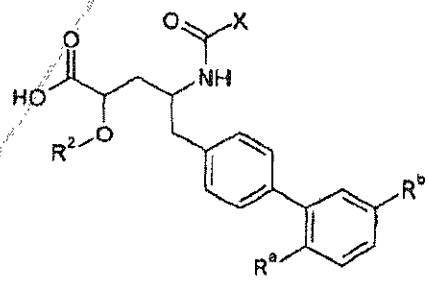
with a compound of formula HO-R^7 in a transesterification reaction; or

(b) reacting a compound of formula



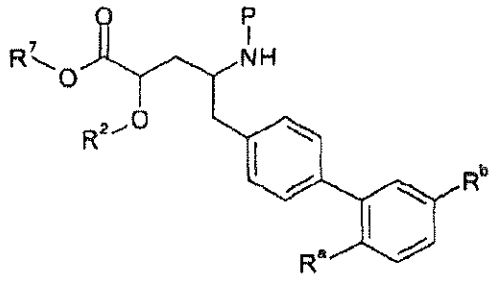
with a compound of formula L-R^7 in a nucleophilic substitution reaction, where L is a leaving group; or

(c) reacting a compound of formula



with a compound of formula L-R^2 in a nucleophilic substitution reaction, where L is a leaving group; or

(d) reacting a compound of formula



with a compound of formula HOOC-X in a coupling reaction, where P is H or an amino-protecting group;

to produce a compound of formula XII.

25. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound as claimed in any one of Claims 1 to 23.

26. The pharmaceutical composition of Claim 25, further comprising a therapeutic agent selected from adenosine receptor antagonists, α_1-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, AT_1 receptor antagonists and dual-acting AT_1 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 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 guanylate cyclase stimulators and activators, tricyclic antidepressants, vasopressin receptor antagonists, and combinations thereof.

27. The pharmaceutical composition of Claim 26, wherein the therapeutic agent is an

AT_1 receptor antagonist.

28. A compound as claimed in any one of Claims 1 to 23, for use in therapy.

29. A compound as claimed in Claim 28, for use in treating hypertension, heart failure, or renal disease.

30. The use of a compound as claimed in any one of Claims 1 to 23, for the manufacture of a medicament for treating hypertension, heart failure, or renal disease.