MODULATORS OF PHARMACOKINETIC PROPERTIES OF THERAPEUTICS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application Ser. No. 60/903,228, entitled "Modulators of Pharmacokinetic Properties of Therapeutics", filed February 23, 2007, and U.S. Provisional Application Ser. No. 60/958,716, entitled "Modulators of Pharmacokinetic Properties of Therapeutics", filed July 6, 2007. The contents of these provisional applications are herein incorporated by reference in their entirety for all purposes.

FIELD OF THE INVENTION

This application relates generally to compounds and pharmaceutical compositions which modify, *e.g.*, improve, the pharmacokinetics of a co-administered drug, and methods of modifying, *e.g.*, improving, the pharmacokinetics of a drug by co-administration of the compounds with the drug.

BACKGROUND OF THE INVENTION

Oxidative metabolism by cytochrome P450 enzymes is one of the primary mechanisms of drug metabolism. It can be difficult to maintain therapeutically effective blood plasma levels of drugs which are rapidly metabolized by cytochrome P450 enzymes. Accordingly, the blood plasma levels of drugs which are susceptible to cytochrome P450 enzyme degradation can be maintained or

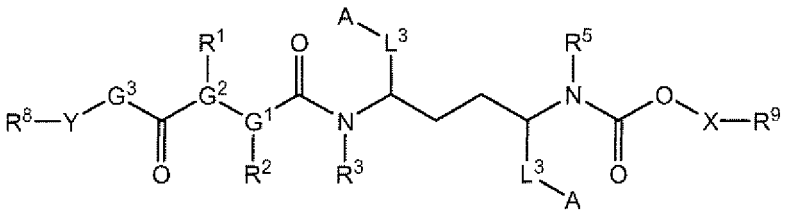
enhanced by co-administration of cytochrome P450 inhibitors, thereby improving the pharmacokinetics of the drug.

While certain drugs are known to inhibit cytochrome P450 enzymes, more and/or improved inhibitors for cytochrome P450 monooxygenase are desirable. Particularly, it would be desirable to have cytochrome P450 monooxygenase inhibitors which do not have appreciable biological activity other than cytochrome P450 inhibition. Such inhibitors can be useful for minimizing undesirable biological activity, *e.g.*, side effects. In addition, it would be desirable to have P450 monooxygenase inhibitors that lack significant or have a reduced level of protease inhibitor activity. Such inhibitors could be useful for enhancing the effectiveness of antiretroviral drugs, while minimizing the possibility of eliciting viral resistance, especially against protease inhibitors.

SUMMARY OF THE INVENTION

One aspect of the present application is directed to compounds and pharmaceutical compositions which modify, *e.g.*, improve, the pharmacokinetics of a co-administered drug, *e.g.*, by inhibiting cytochrome P450 monooxygenase.

In one embodiment, the present application provides for compounds having a structure according to Formula IV,



Formula IV

or a pharmaceutically acceptable salt, solvate, and/or ester thereof, wherein,

each L^3 is independently an alkylene or substituted alkylene;

each A is independently an aryl or substituted aryl;

X is heterocyclylalkyl;

Y is heterocyclylalkyl or alkyl;

G^1 and G^2 are independently CH or N, with the proviso that G^1 and G^2 are different;

G^3 is $-NR^7-$ or $-O-$;

R^1, R^3, R^5, and R^7 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

R^2 is independently selected from the group consisting of substituted alkyl, alkoxyalkyl, hydroxyalkyl, trialkylsiloxyalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-$N(R^a)$-C(O)-alkyl, -alkylene-NR^a-C(O)-$N(R^a)_2$, -alkylene-NR^a-C(=N-R^b)-$N(R^a)_2$, -alkylene-C(=N-R^b)-$N(R^a)_2$, -alkylene-C(O)-OH, -alkylene-C(O)-Oalkyl, and -alkylene-C(O)-$N(R^c)_2$;

R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, and –CN;

each R^a is independently selected from the group consisting of H, alkyl, and substituted alkyl;

R^b is selected from the group consisting of H, alkyl, substituted alkyl, CN, and –$S(O_2)$-alkyl; and

each R^c is independently selected from the group consisting of H, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, –$S(O_2)$-alkyl, –$S(O_2)$-aryl, and substituted –$S(O_2)$-aryl.

In another embodiment, the present application provides for a pharmaceutical composition comprising a compound of Formula I, and a pharmaceutically acceptable carrier or excipient.

In another embodiment, the present application provides for a pharmaceutical composition comprising a compound of Formula I, at least one

additional therapeutic agent, and a pharmaceutically acceptable carrier or exipient.

In another embodiment, the present application provides for a method for improving the pharmacokinetics of a drug, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In another embodiment, the present application provides for a method for inhibiting cytochrome P450 monooxygenase in a patient comprising administering to a patient in need thereof an amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase.

In another embodiment, the present application provides for a method for treating a viral infection, *e.g.*, HIV, comprising administering to a patient in need thereof a therapeutically effective amount of a compound of Formula I, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are metabolized by cytochrome P450 monooxygenase, and are suitable for treating a viral infection, *e.g.*, HIV.

In another embodiment, the present application provides for a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of Formula I, or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional active agent which is metabolized by cytochrome P450 monooxygenase.

DETAILED DESCRIPTION

Reference will now be made in detail to certain claims of the invention, examples of which are illustrated in the accompanying structures and formulas. While the invention will be described in conjunction with the enumerated claims, it will be understood that they are not intended to limit the invention to those claims. On the contrary, the invention is intended to cover all alternatives, modifications, and equivalents, which may be included within the scope of the present invention as defined by the claims.

All documents cited herein are each incorporated by reference in their entirety for all purposes.

Definitions

Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

As used herein, "a compound of the invention" or "a compound of formula (I)" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, ester or stereoisomer thereof, or a physiologically functional derivative thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of formula (number)" means a compound of that formula and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof.

"Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e*, C_1-C_{20} alkyl), 1 to 10 carbon atoms (*i.e.*, C_1-C_{10} alkyl), or 1 to 6 carbon atoms (*i.e.*, C_1-C_6

alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH_3), ethyl (Et, -CH_2CH_3), 1-propyl (n-Pr, n-propyl, -$CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, -$CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, -$CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, -$CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, -$CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, -$C(CH_3)_3$), 1-pentyl (n-pentyl, -$CH_2CH_2CH_2CH_2CH_3$), 2-pentyl (-$CH(CH_3)CH_2CH_2CH_3$), 3-pentyl (-$CH(CH_2CH_3)_2$), 2-methyl-2-butyl (-$C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl (-$CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl (-$CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl (-$CH_2CH(CH_3)CH_2CH_3$), 1-hexyl (-$CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl (-$CH(CH_3)CH_2CH_2CH_2CH_3$), 3-hexyl (-$CH(CH_2CH_3)(CH_2CH_2CH_3)$), 2-methyl-2-pentyl (-$C(CH_3)_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-$CH(CH_3)CH(CH_3)CH_2CH_3$), 4-methyl-2-pentyl (-$CH(CH_3)CH_2CH(CH_3)_2$), 3-methyl-3-pentyl (-$C(CH_3)(CH_2CH_3)_2$), 2-methyl-3-pentyl (-$CH(CH_2CH_3)CH(CH_3)_2$), 2,3-dimethyl-2-butyl (-$C(CH_3)_2CH(CH_3)_2$), 3,3-dimethyl-2-butyl (-$CH(CH_3)C(CH_3)_3$, and octyl (-$(CH_2)_7CH_3$).

"Alkoxy" means a group having the formula –O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} alkoxy), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} alkoxy), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CH_3 or –OMe), ethoxy (-OCH_2CH_3 or -OEt), t-butoxy (-O-$C(CH_3)_3$ or –OtBu) and the like.

"Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.*, C_1-C_{20} haloalkyl), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} haloalkyl), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkyl). Examples of suitable haloalkyl groups include, but are not limited

to, $-CF_3$, $-CHF_2$, $-CFH_2$, $-CH_2CF_3$, and the like.

"Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C_2-C_{20} alkenyl), 2 to 12 carbon atoms (*i.e.*, C_2-C_{12} alkenyl), or 2 to 6 carbon atoms (*i.e.*, C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl ($-CH=CH_2$), allyl ($-CH_2CH=CH_2$), cyclopentenyl ($-C_5H_7$), and 5-hexenyl ($-CH_2CH_2CH_2CH_2CH=CH_2$).

"Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C_2-C_{20} alkynyl), 2 to 12 carbon atoms (*i.e.*, C_2-C_{12} alkyne,), or 2 to 6 carbon atoms (*i.e.*, C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic ($-C\equiv CH$), propargyl ($-CH_2C\equiv CH$), and the like.

"Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene ($-CH_2-$), 1,1-ethyl ($-CH(CH_3)-$), 1,2-ethyl ($-CH_2CH_2-$), 1,1-propyl ($-CH(CH_2CH_3)-$), 1,2-propyl ($-CH_2CH(CH_3)-$), 1,3-propyl ($-CH_2CH_2CH_2-$), 1,4-butyl ($-CH_2CH_2CH_2CH_2-$), and the like.

"Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10

carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

"Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

"Amino" means an –NH_2 or a –NR_2 group in which the "R" groups are independently H, alkyl, haloalkyl, hydroxylalkyl, carbocyclyl (substituted or unsubstituted, including saturated or partially unsaturated cycloalkyl and aryl groups), heterocyclyl (substituted or unsubstituted, including saturated or unsaturated heterocycloalkyl and heteroaryl groups), arylalkyl (substituted or unsubstituted) or arylalkyl (substituted or unsubstituted) groups. Non-limiting examples of amino groups include –NH_2, -NH(alkyl), NH(haloalkyl), -NH(carbocyclyl), -NH(heterocyclyl), -N(alkyl)$_2$, -N(carbocyclyl)$_2$, -N(heterocyclyl)$_2$, -N(alkyl)(carbocyclyl), -N(alkyl)(heterocyclyl), -N(carbocyclyl)(heterocyclyl), etc., wherein alkyl, carbocyclyl, and heterocyclyl can be substituted or unsubstituted and as defined and described herein. "Substituted" or "protected" amino means an aminoalkyl as described and defined herein in which a H of the amino group is replaced with e.g., acyl groups, for example conventional amine protecting groups such as 9-Fluorenylmethyl carbamate ("Fmoc"), *t*-Butyl carbamate ("Boc"), Benzyl carbamate ("Cbz"), acetyl, trifluoracetyl, -C(O)-amino, phthalimidyl, triphenylmethyl, *p*-Toluenesulfonyl ("Tosyl"), methylsulfonyl ("mesyl"), etc.

"Aminoalkyl" means an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an amino radical as defined and described herein. Non-limiting examples of aminoalkyl include –CH_2-NH_2, -CH_2CH_2-NH_2, -$CH_2CH_2CH_2$-NH_2, -$CH_2CH_2CH_2CH_2$-NH_2, -$CH_2CH(CH_3)$-NH_2, -$CH_2CH_2CH(CH_3)$-NH_2, –CH_2-$NH(CH_3)$, -CH_2CH_2-$NH(CH_3)$, -$CH_2CH_2CH_2$-$NH(CH_3)$, -$CH_2CH_2CH_2CH_2$-$NH(CH_3)$, -$CH_2CH(CH_3)$-$NH(CH_3)$, -$CH_2CH_2CH(CH_3)$-$NH(CH_3)$, –CH_2-$N(CH_3)_2$, -CH_2CH_2-$N(CH_3)_2$, -$CH_2CH_2CH_2$-$N(CH_3)_2$, -$CH_2CH_2CH_2CH_2$-$N(CH_3)_2$, -$CH_2CH(CH_3)$-$N(CH_3)_2$, -$CH_2CH_2CH(CH_3)$-$N(CH_3)_2$, –CH_2-$NH(CH_2CH_3)$, -CH_2CH_2-$NH(CH_2CH_3)$, -$CH_2CH_2CH_2$-$NH(CH_2CH_3)$, -$CH_2CH_2CH_2CH_2$-$NH(CH_2CH_3)$, -$CH_2CH(CH_3)$-$NH(CH_2CH_3)$, -$CH_2CH_2CH(CH_3)$-$NH(CH_2CH_3)$, –CH_2-$N(CH_2CH_3)_2$, -CH_2CH_2-$N(CH_2CH_3)_2$, -$CH_2CH_2CH_2$-$N(CH_2CH_3)_2$, -$CH_2CH_2CH_2CH_2$-$N(CH_2CH_3)_2$, -$CH_2CH(CH_3)$-$N(CH_2CH_3)_2$, -$CH_2CH_2CH(CH_3)$-$N(CH_2CH_3)_2$, etc. "Substituted" or "protected" aminoalkyl means an aminoalkyl as described and defined herein in which the H of the amino group is replaced with e.g., acyl groups, for example conventional amine protecting groups such as 9-Fluorenylmethyl carbamate ("Fmoc"), *t*-Butyl carbamate ("Boc"), Benzyl carbamate ("Cbz"), acetyl, -C(O)-amino, trifluoracetyl, phthalimidyl, triphenylmethyl, *p*-Toluenesulfonyl ("Tosyl"), methylsulfonyl ("mesyl"), etc.

"Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

"Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is

replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkenyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

"Arylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkynyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, heterocyclyl, heteroaryl, carbocyclyl, etc. , for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical

substituents include, but are not limited to, -X, -R, $-O^-$, =O, -OR, -SR, $-S^-$, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$, -NHC(=O)R, $-NHS(=O)_2R$, -C(=O)R, -C(=O)NRR $-S(=O)_2O^-$, $-S(=O)_2OH$, $-S(=O)_2R$, $-OS(=O)_2OR$, $-S(=O)_2NR$, -S(=O)R, $-OP(=O)(OR)_2$, $-P(=O)(OR)_2$, $-P(=O)(O^-)_2$, $-P(=O)(OH)_2$, $-P(O)(OR)(O^-)$, -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, $-C(O)O^-$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(=NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. When the number of carbon atoms is designated for a substituted group, the number of carbon atoms refers to the group, not the substituent (unless otherwise indicated). For example, a C_{1-4} substituted alkyl refers to a C_{1-4} alkyl, which can be substituted with groups having more the, e.g., 4 carbon atoms.

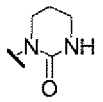
The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I which have such stability are contemplated as falling within the scope of the present invention.

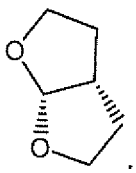
"Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., -OCH_3, etc.), an amine (e.g., -$NHCH_3$, -$N(CH_3)_2$, etc.), or a thioalkyl group (e.g., -SCH_3). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., -CH_2CH_2-O-CH_3, etc.), an alkyl amine (e.g., -CH_2NHCH_3, -$CH_2N(CH_3)_2$, etc.), or a thioalkyl ether (e.g.,-CH_2-S-CH_3). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., -CH_2CH_2-OH), an aminoalkyl group (e.g., -CH_2NH_2), or an alkyl thiol group (e.g., -CH_2CH_2-SH). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C_1-C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

"Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and *J. Am. Chem. Soc.* (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more (*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings (i.e., heterocycloalkyls), partially unsaturated rings, and aromatic rings (*i.e.*, heteroaromatic rings). Substituted heterocyclyls include, for

example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a

pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

"Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl-CH_2-, heterocyclyl-$CH(CH_3)$-, heterocyclyl-CH_2CH_2-, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by

means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkyl group comprises 2 to 20 carbon atoms, *e.g.*, the alkyl portion of the heterocyclylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

"Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkenyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms.

"Heterocyclylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.*, a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclyl

alkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkynyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclylalkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms.

"Heteroaryl" refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those listed in the definition of "heterocyclyl", including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

"Carbocycle" or "carbocyclyl" refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloakenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl.

Non-limiting examples of bicyclo carbocycles includes naphthyl.

"Arylheteroalkyl" refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-
O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

"Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl
include -CH_2-pyridinyl, -CH_2-pyrrolyl, -CH_2-oxazolyl, -CH_2-indolyl, -CH_2-isoindolyl, -CH_2-purinyl, -CH_2-furanyl, -CH_2-thienyl, -CH_2-benzofuranyl, -CH_2-benzothiophenyl, -CH_2-carbazolyl, -CH_2-imidazolyl, -CH_2-thiazolyl, -CH_2-isoxazolyl, -CH_2-pyrazolyl, -CH_2-isothiazolyl, -CH_2-quinolyl, -CH_2-isoquinolyl, -CH_2-pyridazyl, -CH_2-pyrimidyl, -CH_2-pyrazyl, -$CH(CH_3)$-pyridinyl, -$CH(CH_3)$-pyrrolyl, -$CH(CH_3)$-oxazolyl, -$CH(CH_3)$-indolyl, -$CH(CH_3)$-isoindolyl, -$CH(CH_3)$-purinyl, -$CH(CH_3)$-furanyl, -$CH(CH_3)$-thienyl, -$CH(CH_3)$-benzofuranyl, -$CH(CH_3)$-benzothiophenyl, -$CH(CH_3)$-carbazolyl, -$CH(CH_3)$-imidazolyl, -$CH(CH_3)$-thiazolyl, -$CH(CH_3)$-isoxazolyl, -$CH(CH_3)$-pyrazolyl, -$CH(CH_3)$-isothiazolyl, -$CH(CH_3)$-quinolyl, -$CH(CH_3)$-isoquinolyl, -$CH(CH_3)$-pyridazyl, -$CH(CH_3)$-pyrimidyl, -$CH(CH_3)$-pyrazyl, etc.

The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (e.g., an optionally substituted aryl group) refers to a moiety having 0, 1, 2, or more substituents.

"Ac" means acetyl (-C(O)CH_3).

"Ac_2O" means acetic anhydride.

"DCM" means dichloromethane (CH_2Cl_2).

"DIBAL" means diisobutylaluminum hydride.

"DMAP" means dimethylaminopyridine.

"EDC" means 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide.

"Et" means ethyl.

"EtOAc" means ethylacetate.

"HOBt" means N-hydroxybenzotriazole.

"Me" means methyl (-CH_3).

"MeOH" means methanol.

"MeCN" means acetonitrile.

"Pr" means propyl.

"i-Pr" means isopropyl (-$CH(CH_3)_2$).

"i-PrOH" means isopropanol.

"rt" means room temperature.

"TFA" means trifluoroacetic acid.

"THF" means tetrahydrofuran.

The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

"Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

"Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John

Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides, and the like.

Ether- and Ester-forming protecting groups

Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

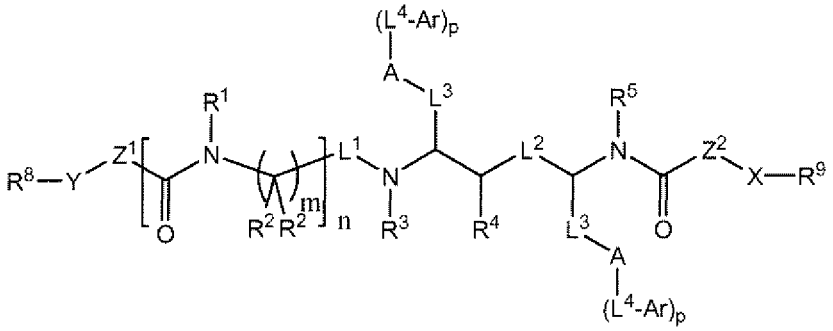
Metabolites of the Compounds of the Invention

Also falling within the scope of this invention are the in vivo metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the invention includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., C^{14} or H^{3}) compound of the invention, administering it parenterally in a detectable dose (e.g., greater than

about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no anti-infective activity of their own.

Compounds of Formula I

In one embodiment, the present application provides compounds according to Formula I,



Formula I

or a pharmaceutically acceptable salt, solvate, and/or ester thereof, wherein,

L^1 is selected from the group consisting of $-C(R^6)_2-$, -C(O)-, $-S(O_2)-$, $-N(R^7)-C(O)-$, and -O-C(O)-;

L^2 is a covalent bond, $-C(R^6)_2-$ or -C(O)-;

each L^3 is independently a covalent bond, an alkylene, or substituted alkylene;

each L^4 is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, -CH_2-O-, and -NH-;

each A is independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl,

with the proviso that when A is H, p is 0;

Z^1 and Z^2 are each independently -O- or -N(R^7)-;

Y and X are independently selected from the group consisting of heterocyclyl and heterocyclylalkyl;

each Ar is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^1, R^3, and R^5 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

each R^2 is independently selected from the group consisting of H, alkyl, substituted alkyl, alkoxyalkyl, hydroxyalkyl, arylheteroalkyl, substituted arylheteroalkyl, arylalkyl, substituted arylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-C(O)-OH, -alkylene-C(O)-Oalkyl, -alkylene-C(O)amino, -alkylene-C(O)-alkyl;

R^4 and R^6 are independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl;

each R^7 is independently selected from the group consisting of H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, and substituted heterocyclyl;

R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, and -CN;

m is 1 or 2;

n is 0 or 1; and

each p is independently 0 or 1.

In another embodiment of the compounds of Formula I, n is 1.

In another embodiment of the compounds of Formula I, n is 0.

In another embodiment of the compounds of Formula I, n is 1 and L^2 is -$CH(R^6)$-, wherein R^6 is selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl.

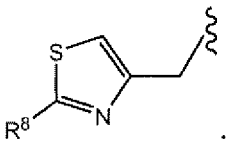
In another embodiment of the compounds of Formula I, n is 1 and L^2 is –CH_2-.

In another embodiment of the compounds of Formula I, n is 1 and L^2 is -C(O)-.

In another embodiment of the compounds of Formula I, n is 1 and Y is heterocyclylalkyl.

In another embodiment of the compounds of Formula I, n is 1 and Y-R^8 is –CH_2-(substituted heteroaryl).

In another embodiment of the compounds of Formula I, n is 1 and Y-R^8 is



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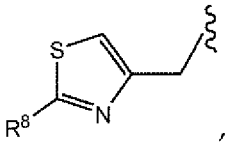
In another embodiment of the compounds of Formula I, n is 1 and Y-R^8 is



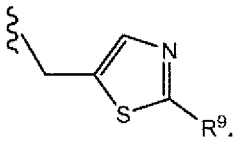
,

wherein R^8 is alkyl, for example 2-propyl.

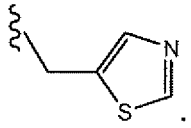
In another embodiment of the compounds of Formula I, n is 1 and X is heterocyclylalkyl.

In another embodiment of the compounds of Formula I, n is 1 and X is –CH_2-heteroaryl.

In another embodiment of the compounds of Formula I, n is 1 and X-R^9 is



In another embodiment of the compounds of Formula I, n is 1 and X-R^9 is



In another embodiment of the compounds of Formula I, n is 1 and Z^1 is –N(R^7)-.

In another embodiment of the compounds of Formula I, n is 1 and Z^1 is –N(alkyl)- or –N(carbocyclyl)-.

In another embodiment of the compounds of Formula I, n is 1 and Z^1 is –N(CH_3)- or –N(cyclopropyl)-.

In another embodiment of the compounds of Formula I, n is 1 and Z^1 is –NH-.

In another embodiment of the compounds of Formula I, n is 1 and each A is independently aryl or substituted aryl.

In another embodiment of the compounds of Formula I, n is 1 and each A is phenyl.

In another embodiment of the compounds of Formula I, n is 1 and each A is phenyl and each p is 0.

In another embodiment of the compounds of Formula I, n is 1 and R^2 is H, alkyl, substituted alkyl, or heteroalkyl.

In another embodiment of the compounds of Formula I, n is 1 and R^2 is 2-propyl, methyl, -CH_2-O-benzyl, –CH(CH_3)(O-t-Bu) , or -CH(CH_3)(OH).

In another embodiment of the compounds of Formula I, L^1 is -C(O)-;

each A is independently aryl, substituted aryl, alkyl, or substituted alkyl;

R^1 is H or alkyl;

each R^2 is independently H, alkyl, substituted alkyl, or heteroalkyl;

R^3, R^4, R^5, and R^6 are each H;

each R^7 is independently H, alkyl, or carbocyclyl;

R^8 is H or alkyl;

R^9 is H;

X and Y are both heterocyclylalkyl;

Z^2 is –O-; and

p is 0.

In another embodiment of the compounds of Formula I, each A is phenyl;

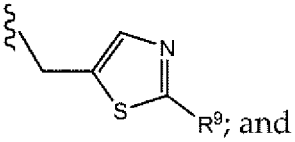
R^1 is H or $–CH_3$;

each R^2 is H, methyl, ethyl, 2-propyl, $-CH_2$-O-benzyl, $-CH(CH_3)$-OH, or $-CH(CH_3)$(O-t-Bu);

each R^7 is H, methyl or cyclopropyl;

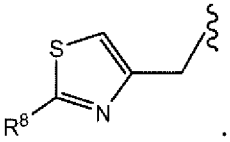
R^8 is H or 2-propyl;

X is



; and

Y is



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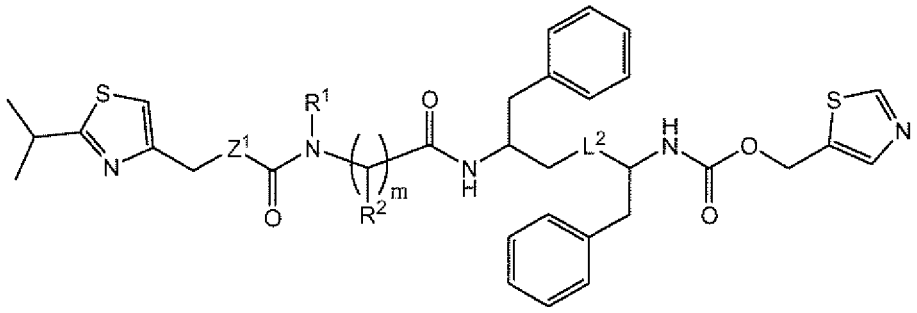
In another embodiment, the compounds of Formula I have the following general Formula IA:



Formula IA.

In another embodiment of the compounds of Formula IA, Z^1 is -N(R^7)-. In a particular embodiment, R^7 is H. In another particular embodiment, R^7 is alkyl, for example any of the alkyl groups disclosed herein. In another particular embodiment, R^7 is heteroalkyl, for example any of the heteroalkyl groups disclosed herein. In another particular embodiment, R^7 is substituted or unsubstituted carbocyclyl, wherein for example, said carbocyclyl is any of the carbocyclyl groups disclosed herein. In another particular embodiment, R^7 is substituted or unsubstituted heterocyclyl, wherein for example, said heterocyclyl is any of the heterocyclyl groups disclosed herein.

In another embodiment of the compounds of Formula IA, Z^1 is -O-.

In another embodiment of the compounds of Formula IA, L^2 is -C(R^6)$_2$-, wherein each R^6 is H.

In another embodiment of the compounds of Formula IA, L^2 is -C(R^6)$_2$-, wherein each R^6 is independently H or alkyl, and said alkyl includes any alkyl disclosed herein.

In another embodiment of the compounds of Formula IA, L^2 is -C(R^6)$_2$-, wherein one R^6 is H and the other R^6 is alkyl, wherein said alkyl includes any alkyl disclosed herein.

In another embodiment of the compounds of Formula IA, m is 1 and R^2 is H.

In another embodiment of the compounds of Formula IA, m is 1 and R^2 is alkyl, wherein said alkyl includes any alkyl disclosed herein.

In another embodiment of the compounds of Formula IA, m is 1 and R^2 is i-propyl.

In another embodiment of the compounds of Formula IA, m is 1 and R^2 is i-butyl.

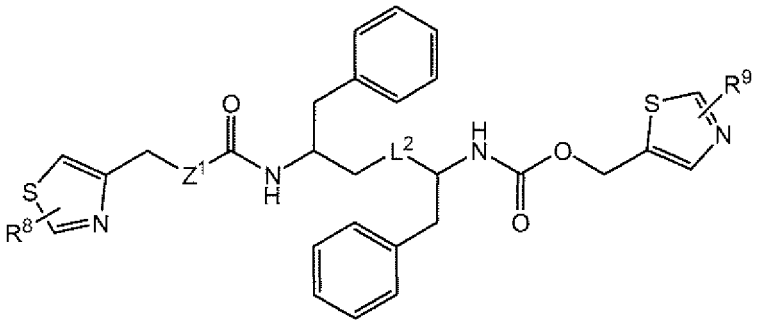
In another embodiment of the compounds of Formula IA, m is 1 and R^2 is ethyl.

In another embodiment of the compounds of Formula IA, m is 1 and R^2 is methyl.

In another embodiment of the compounds of Formula IA, m is 2 and each R^2 is independently selected from H and alkyl.

In another embodiment of the compounds of Formula IA, m is 2 and each R^2 is H.

In another embodiment, the compounds of Formula I have the following general Formula IB:



Formula IB.

In another embodiment of the compounds of Formula IB, Z^1 is -N(R^7)-. In a particular embodiment, R^7 is H. In another particular embodiment, R^7 is alkyl, for example any of the alkyl groups disclosed herein. In another particular embodiment, R^7 is heteroalkyl, for example any of the heteroalkyl groups disclosed herein. In another particular embodiment, R^7 is substituted or

unsubstituted carbocyclyl, wherein for example, said carbocyclyl is any of the carbocyclyl groups disclosed herein. In another particular embodiment, R^7 is substituted or unsubstituted heterocyclyl, wherein for example, said heterocyclyl is any of the heterocyclyl groups disclosed herein.

In another embodiment of the compounds of Formula IB, Z^1 is -O-.

In another embodiment of the compounds of Formula IB, L^2 is $-C(R^6)_2-$, wherein each R^6 is H.

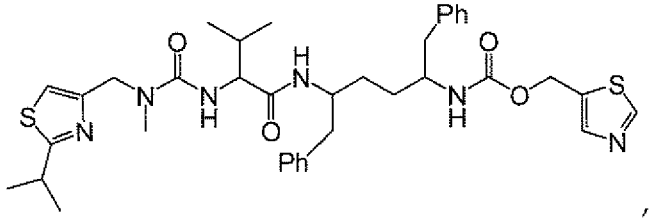
In another embodiment of the compounds of Formula IB, L^2 is $-C(R^6)_2-$, wherein each R^6 is independently H or alkyl, and said alkyl includes any alkyl disclosed herein.

In another embodiment of the compounds of Formula IB, L^2 is $-C(R^6)_2-$, wherein one R^6 is H and the other R^6 is alkyl, wherein said alkyl includes any alkyl disclosed herein.

In another embodiment of the compounds of Formula IB, R^8 and R^9 are both H.

In another embodiment of the compounds of Formula IB, R^8 and R^9 are independently selected from H and alkyl, wherein said alkyl includes any alkyl disclosed herein.

In another embodiment, the compounds of Formula I have one of the following structures:



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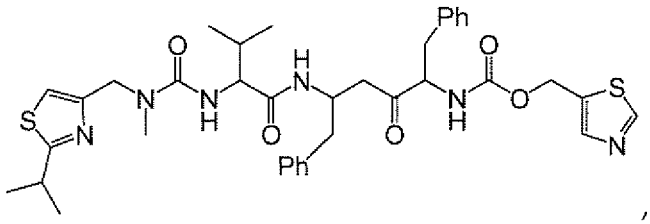

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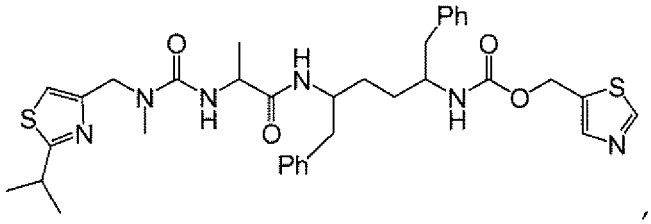

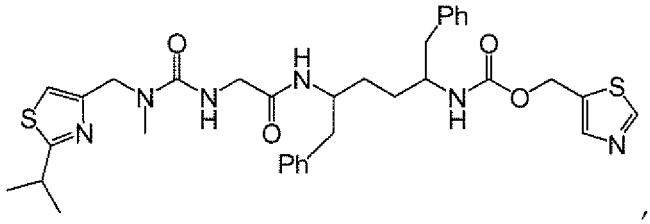

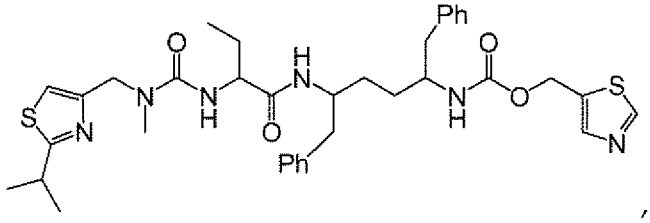

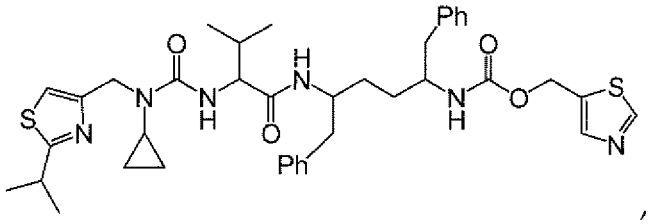

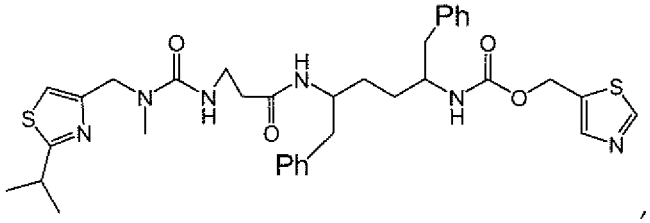

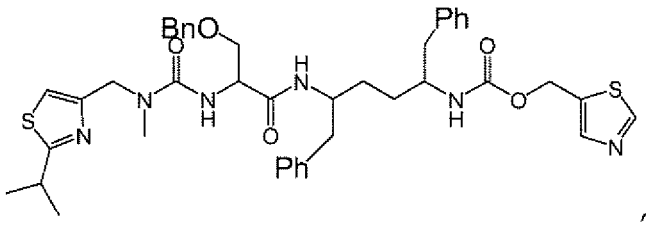

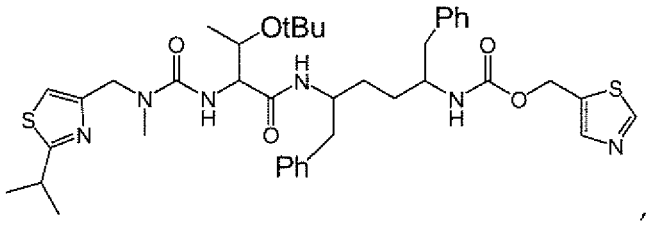

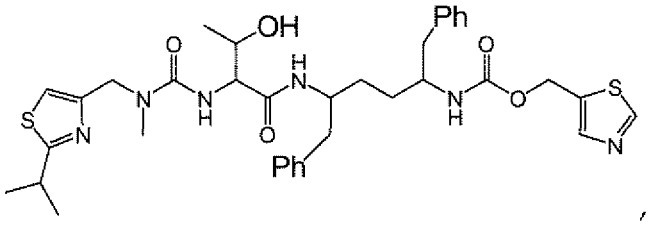

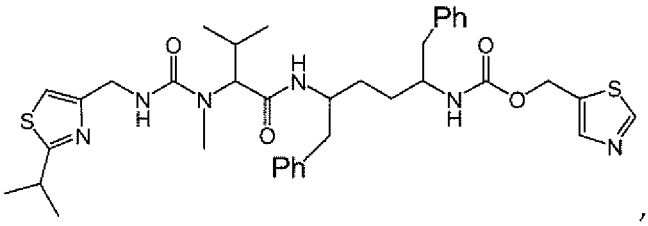

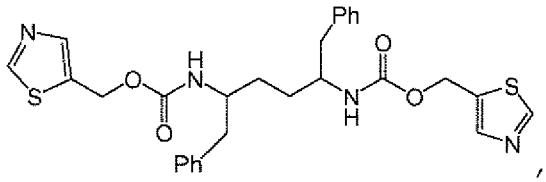

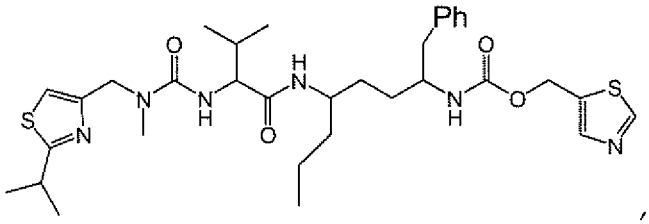

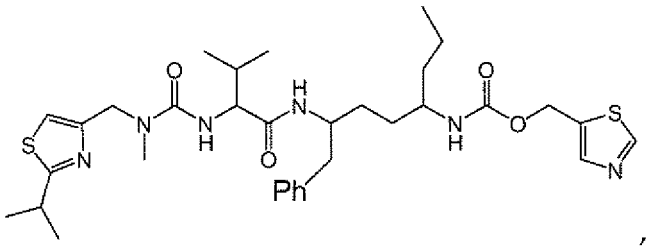

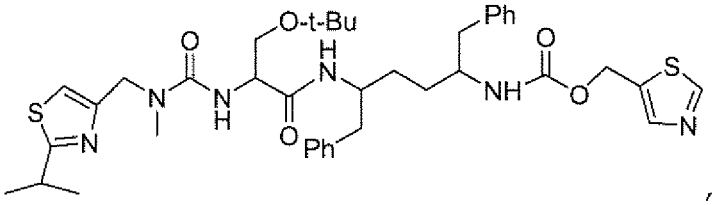

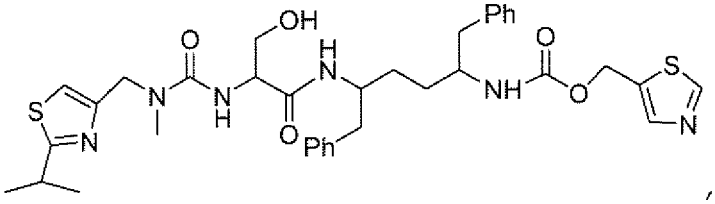

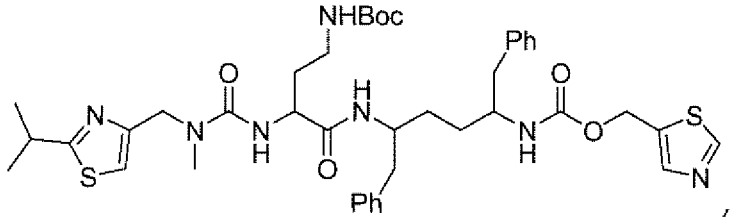

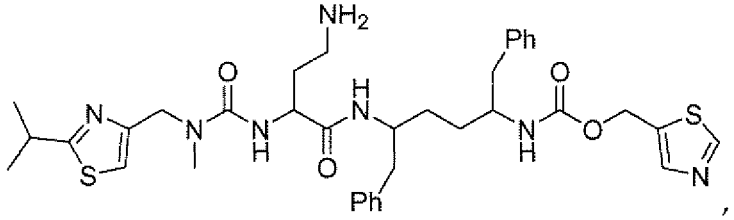

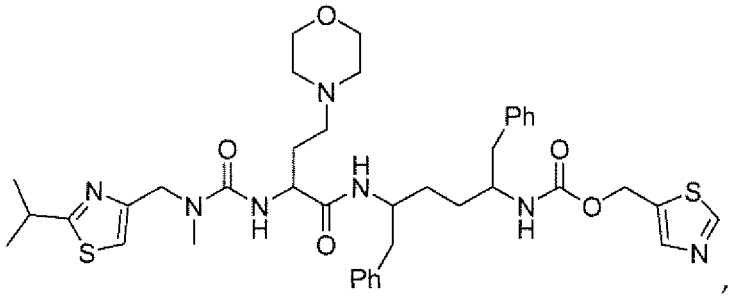

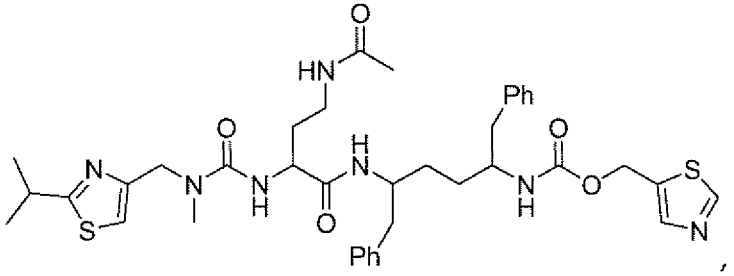

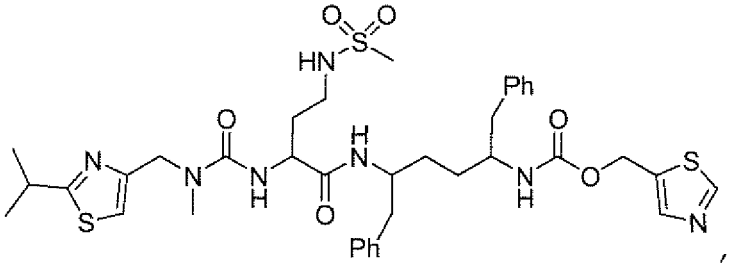

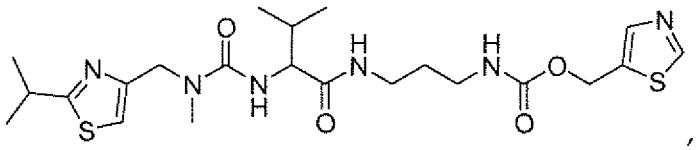

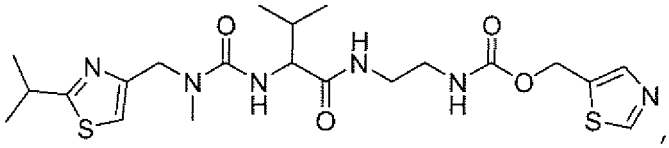

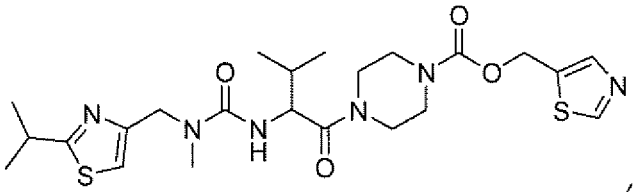

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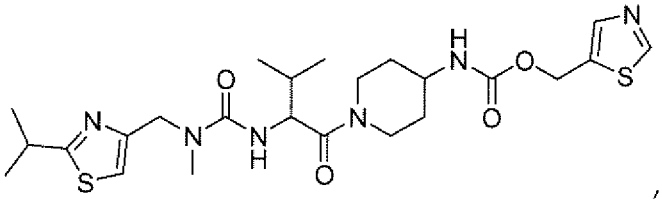

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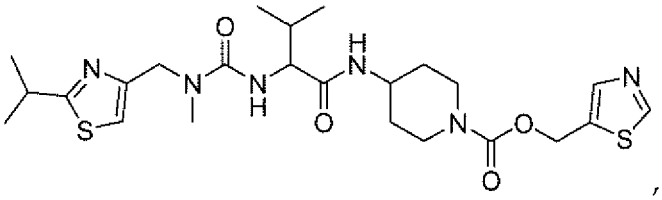

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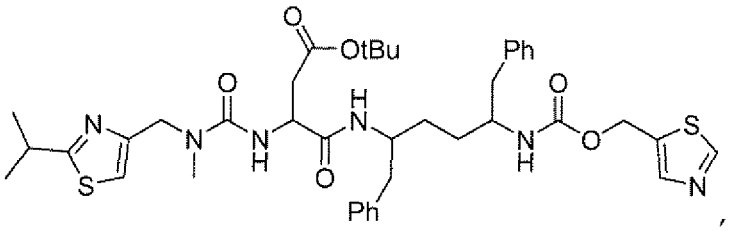

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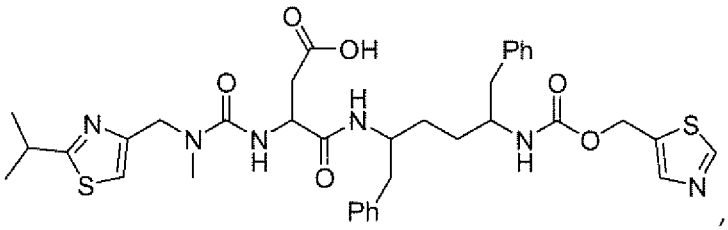

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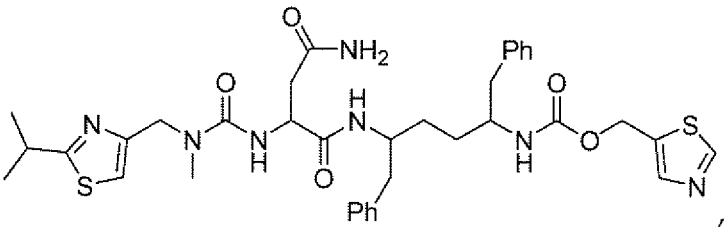

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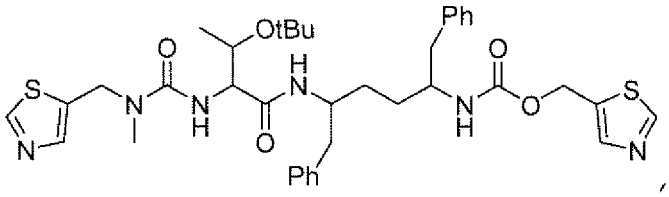

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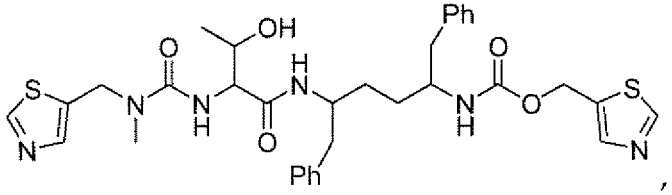

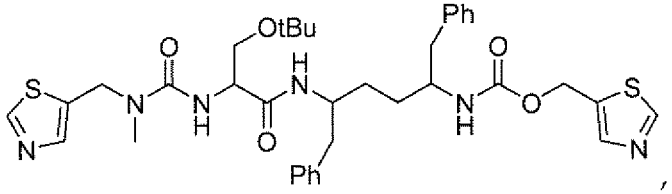

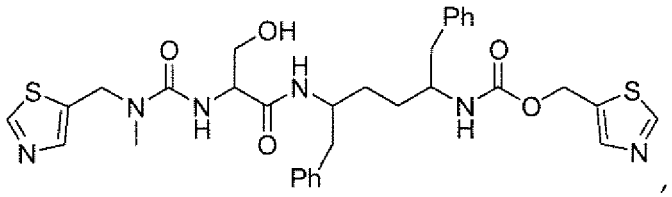

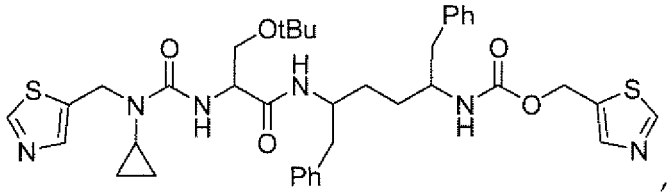

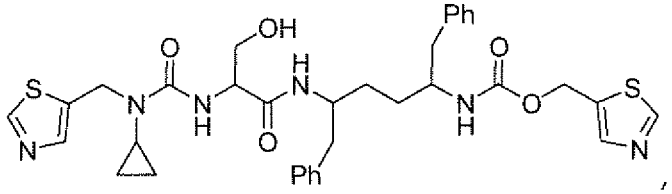

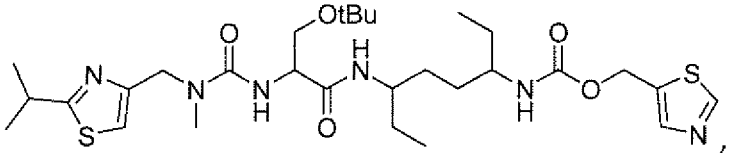

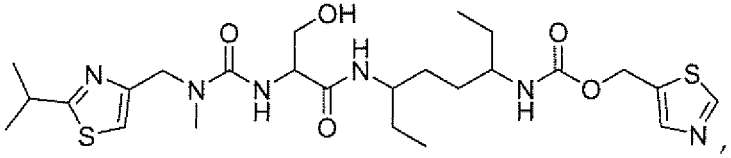

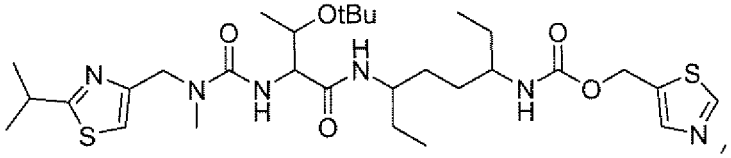

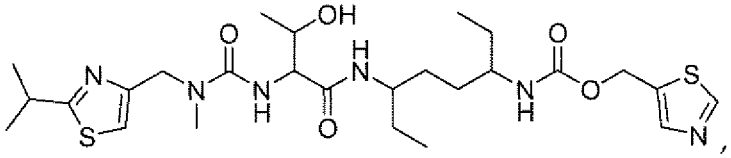

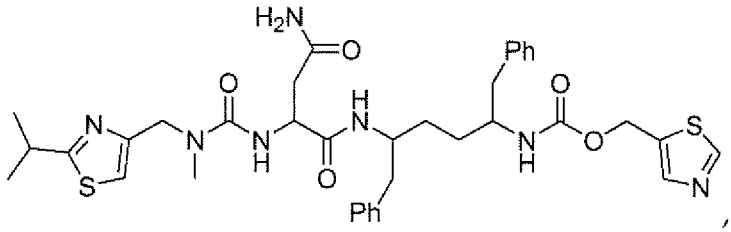

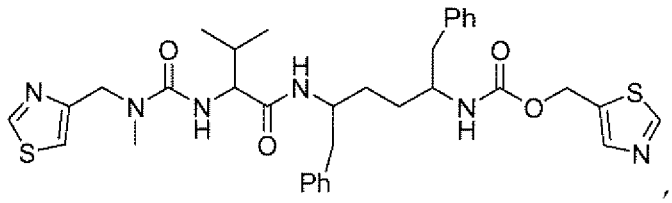

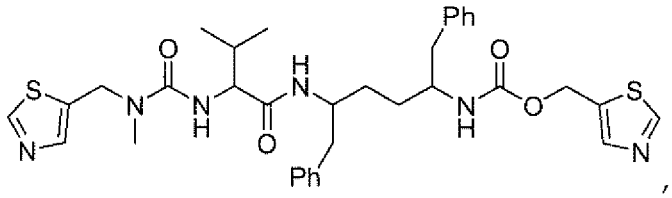

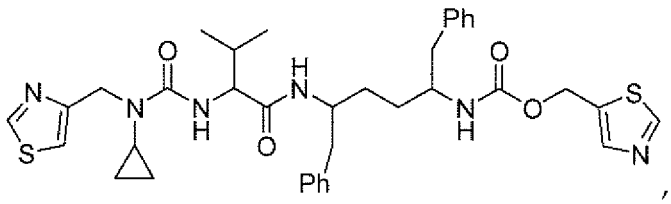

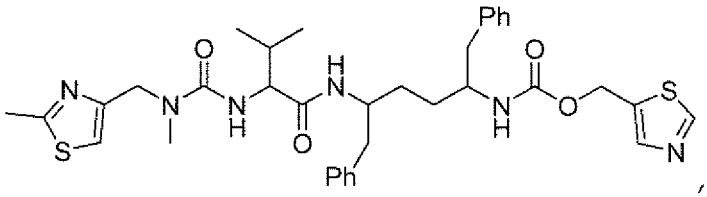

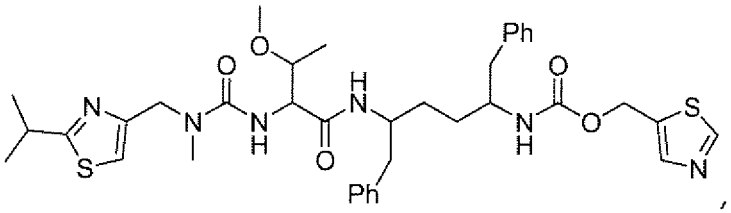

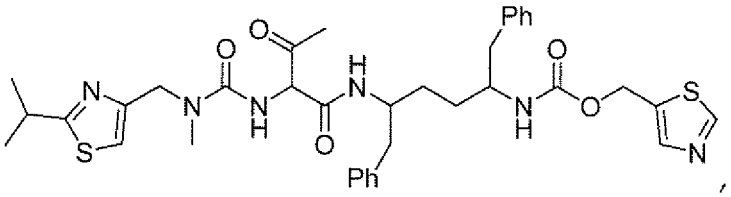

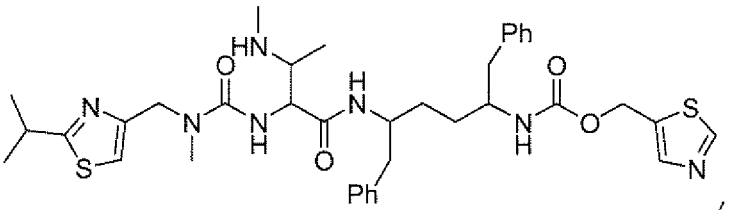

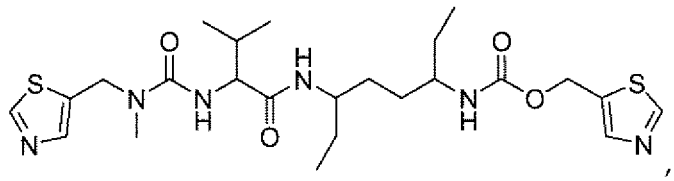

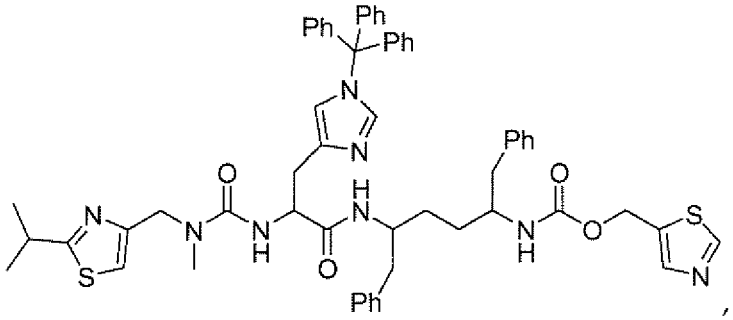

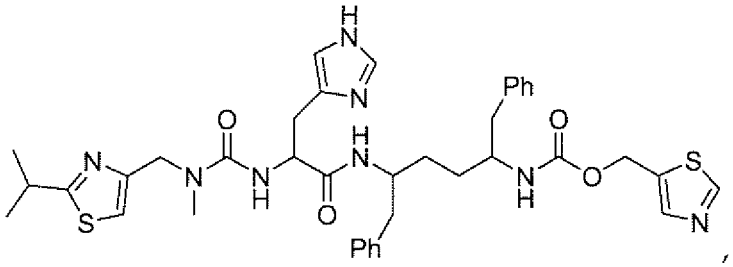

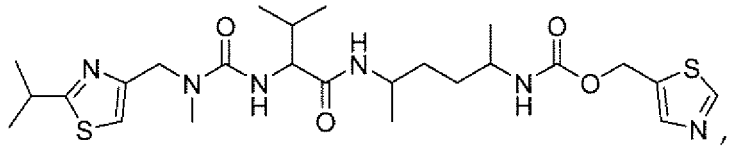

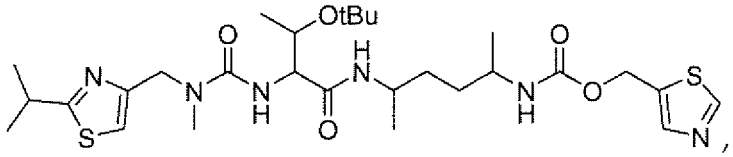

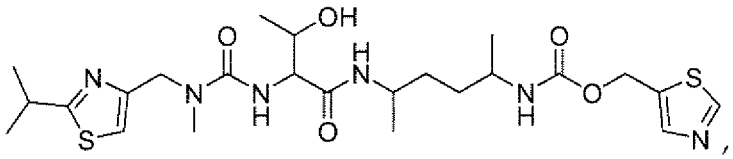

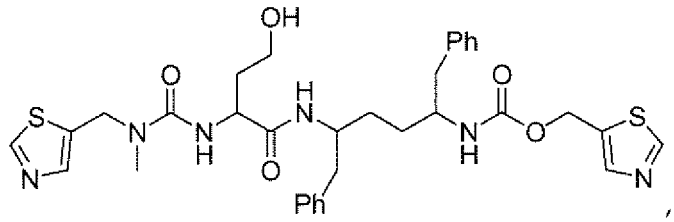

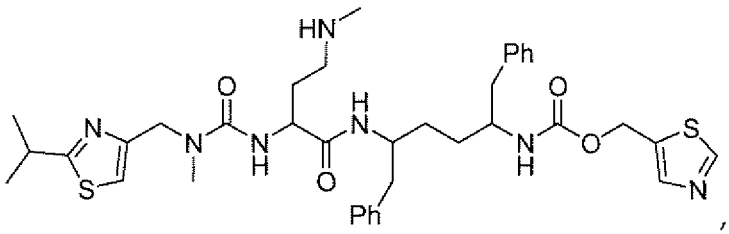

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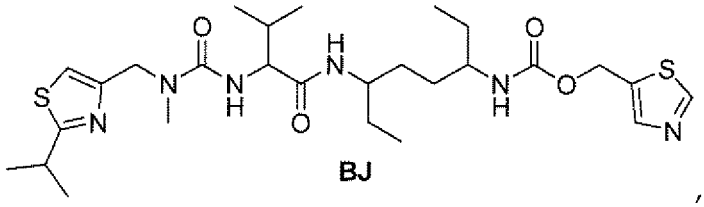

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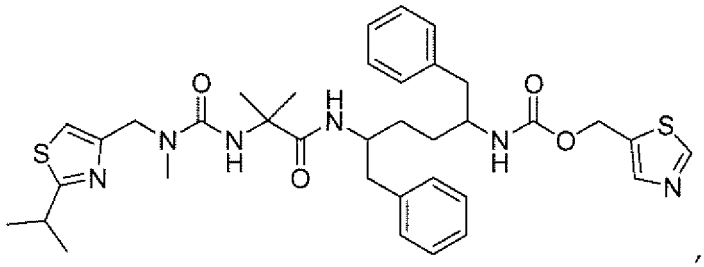

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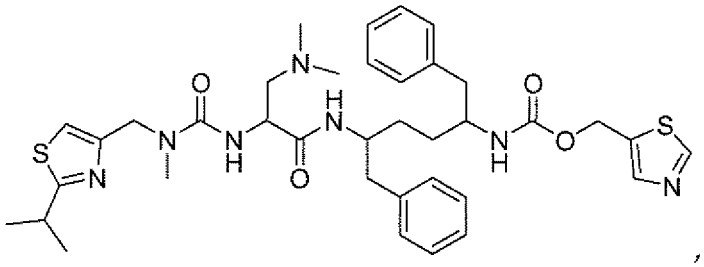

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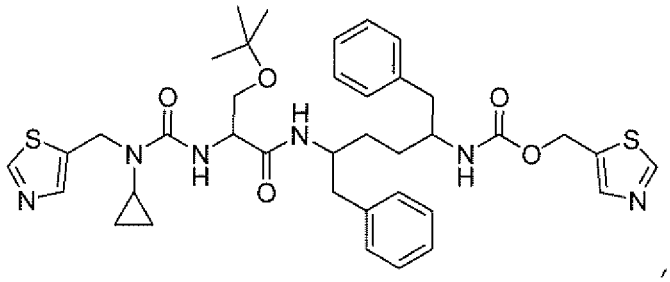

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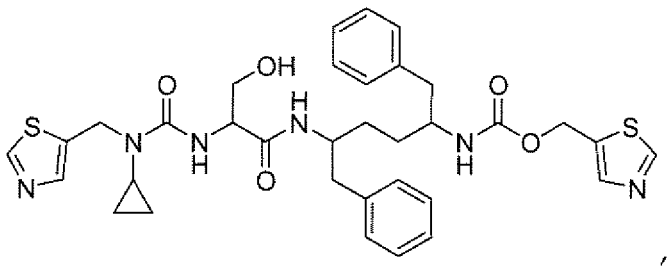

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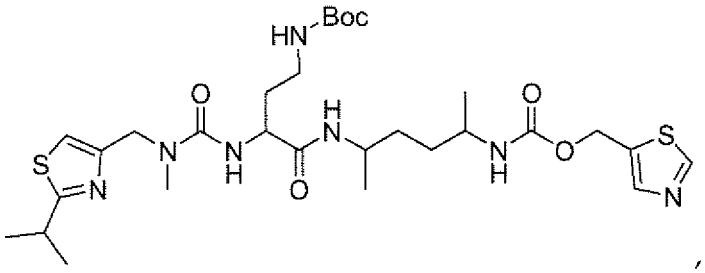

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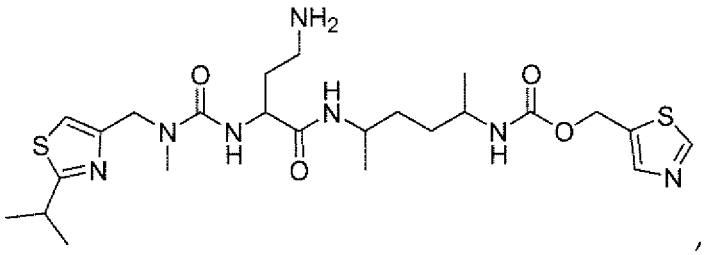

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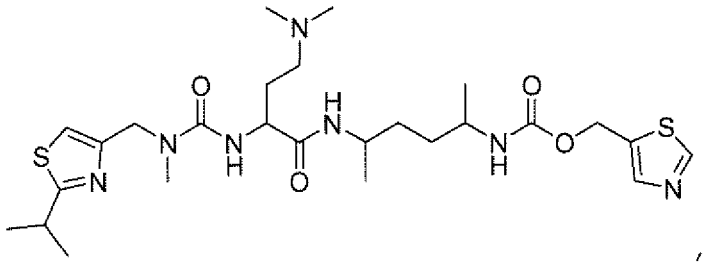

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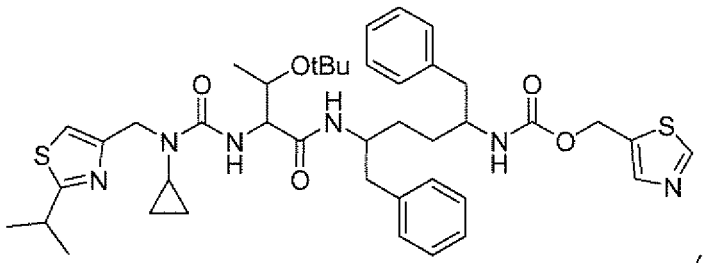

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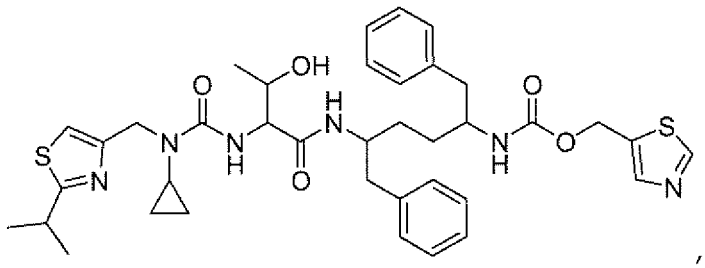

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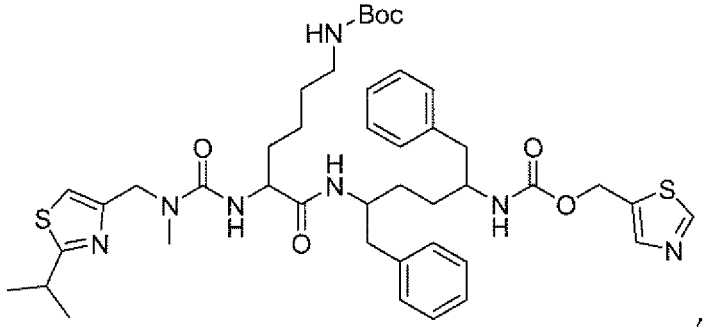

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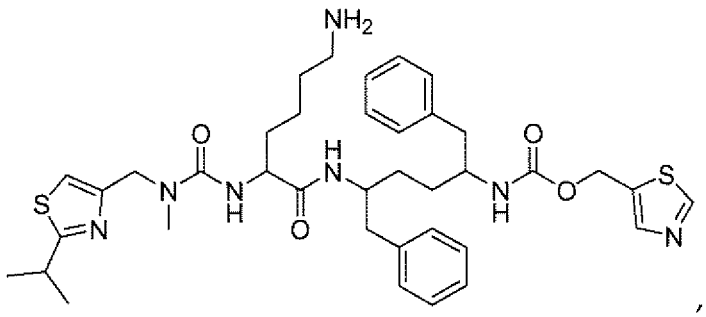

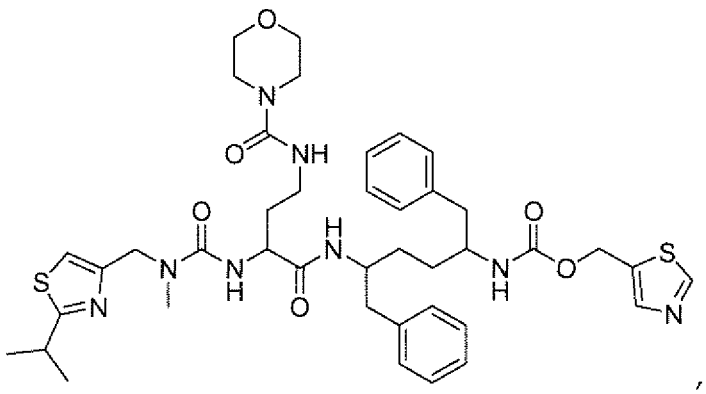

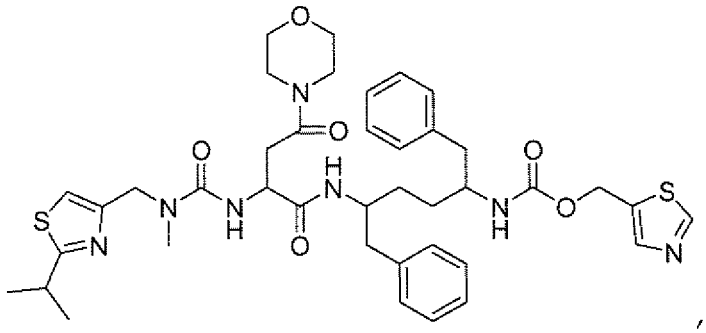

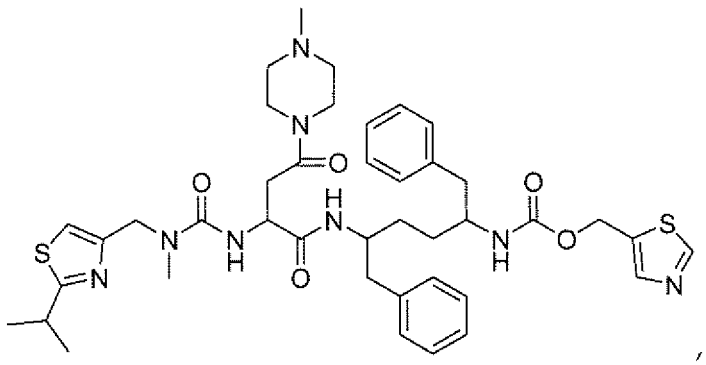

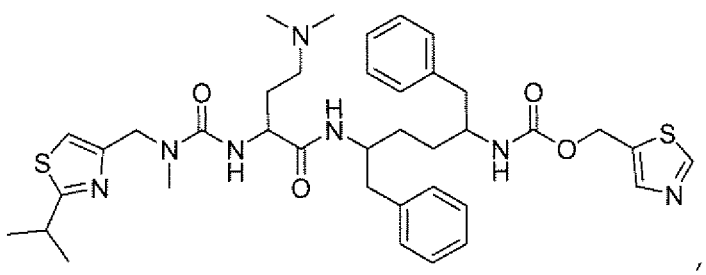

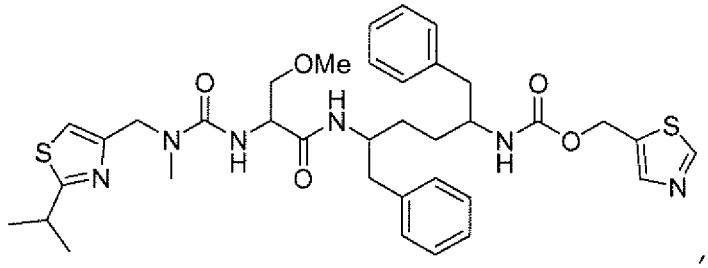

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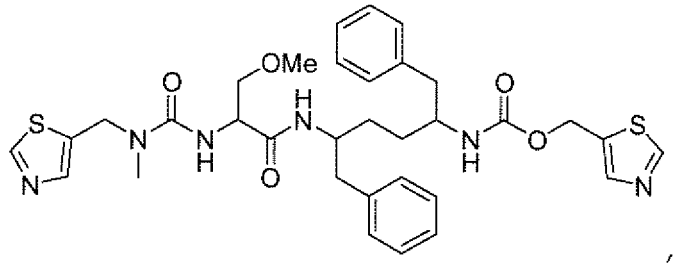

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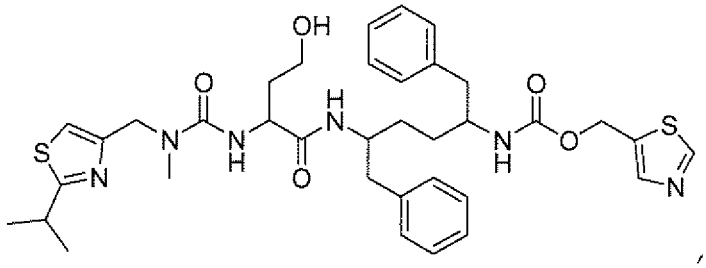

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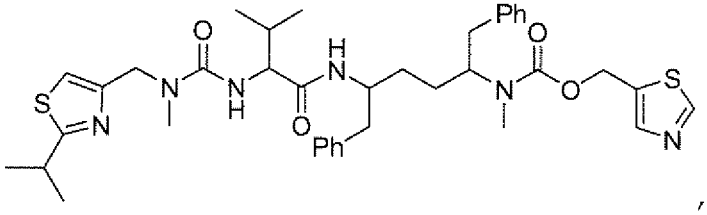

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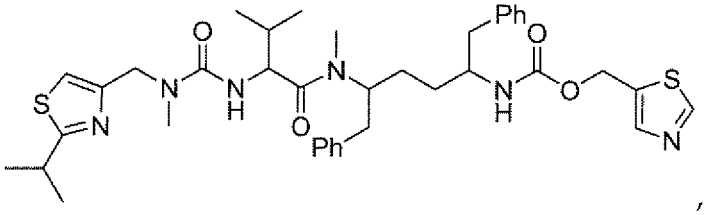

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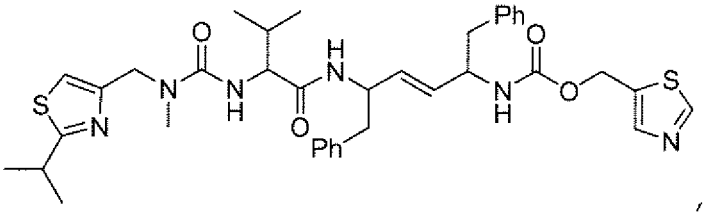

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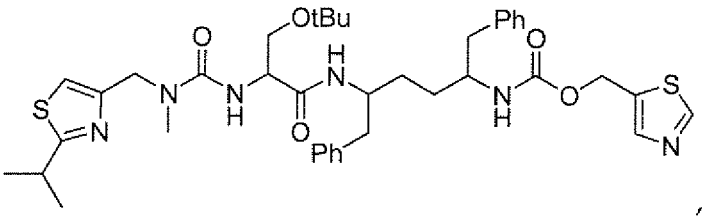

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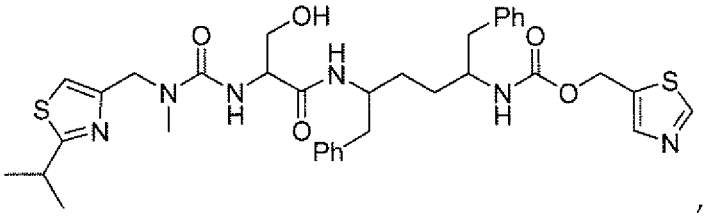

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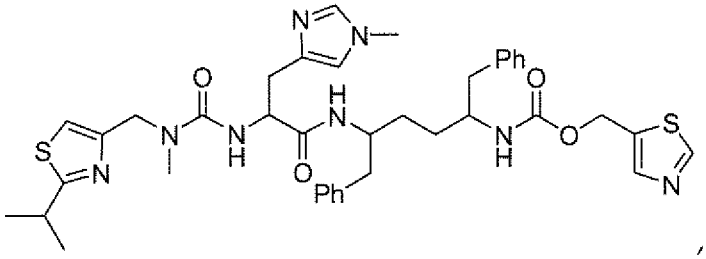

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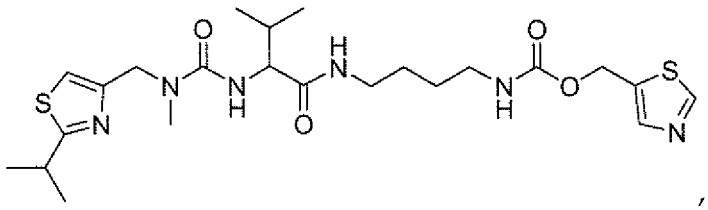

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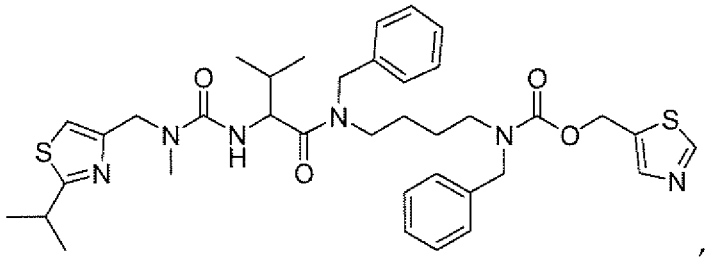

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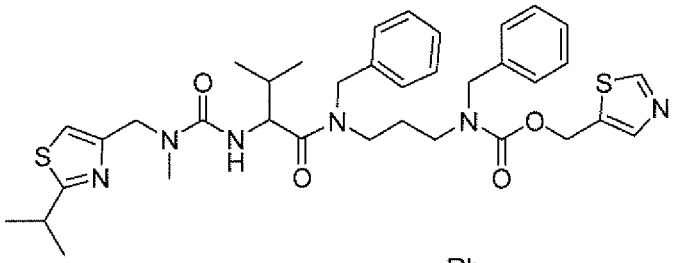

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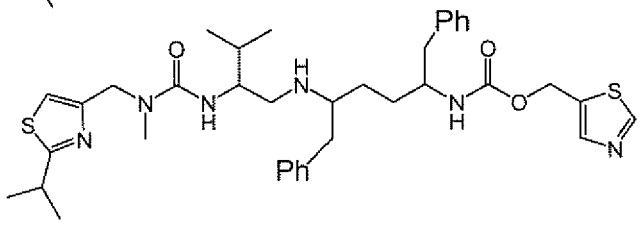

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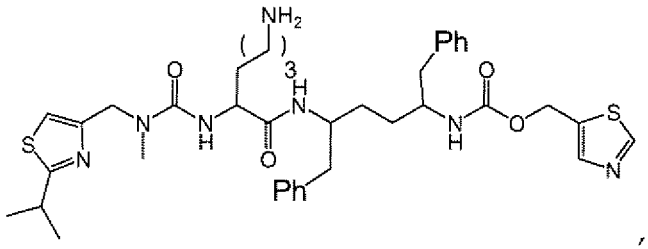

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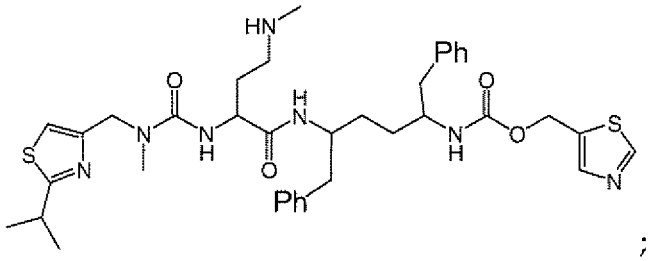

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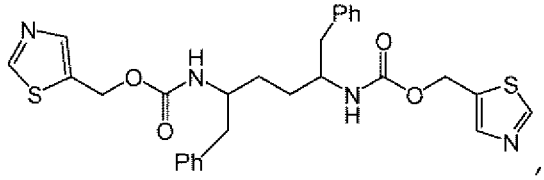
including stereoisomers or mixtures of stereoisomers thereof. One skilled in the art will recognize that stereoisomers or mixtures of stereoisomers of the compounds of the present application include enantiomers, diastereomers, and other stereoisomers. For example, for:



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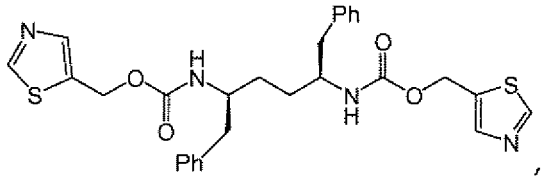
contemplated stereoisomers include at least:



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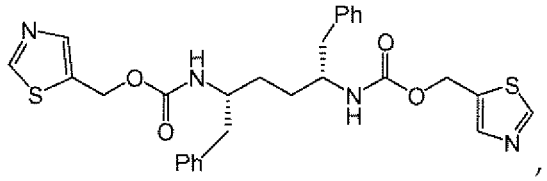

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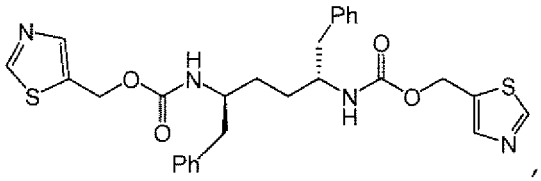

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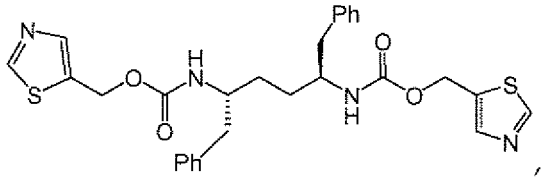

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as well as mixtures of two or more of these stereoisomers.

In still another embodiment of the compounds of Formula I, L^1 is -$C(R^6)_2$-, -C(O)-, -$S(O_2)$-, -$N(R^7)$-C(O)-, or -O-C(O)-. When L^1 is –$C(R^6)_2$-, each R^6 is independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl, wherein alkyl, substituted alkyl, and heteroalkyl are as defined and exemplified herein. Non-limiting examples of –$C(R^6)_2$- include -CH_2-, -CH(alkyl)-, -CH(substituted alkyl)-, -CH(heteroalkyl)-, -$C(alkyl)_2$-, -C(substituted $alkyl)_2$-, -$C(heteroalkyl)_2$-, -C(alkyl)(substituted alkyl)-, -C(heteroalkyl)(substituted alkyl)-, and -C(alkyl)(heteroalkyl)-, wherein alkyl, substituted alkyl, and heteroalkyl are as defined and exemplified herein. When L^1 is -$N(R^7)$-C(O)-, R^7 is H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl are as defined and exemplified herein.

In still another embodiment of the compounds of Formula I, L^2 is -$C(R^6)_2$- or -C(O)-. When L^2 is -$C(R^6)_2$-, each R^6 is independently selected from H, alkyl, substituted alkyl or heteroalkyl, where each alkyl, substituted alkyl, or heteroalkyl can include any of the alkyl, substituted alkyl, or heteroalkyl groups defined or disclosed herein. Non-limiting examples of -$C(R^6)_2$- include –CH_2-, -$CH(CH_3)$-, -$CH(-CH_2CH_3)$-, -$CH(-CH_2CH_2CH_3)$-, -$CH(-CH(CH_3)_2)$-, -$CH(-CH_2CH_2CH_2CH_3)$-, -$CH(-CH_2CH(CH_3)_2)$-, -$CH(-CH(CH_3)CH_2CH_3)$-, -$CH(-C(CH_3)_3)$-, -$C(CH_3)_2$-, -$CH(OCH_3)$-, -$CH(CH_2OH)$-, -$CH(CH_2CH_2OH)$-, etc.

In still another embodiment of the compounds of Formula I, each L^3 is independently a covalent bond, an alkylene or substituted alkylene. When any L^3 is an alkylene, non-limiting examples of alkylene includes any of the alkylenes defined or disclosed herein. When any L^3 is a substituted alkylene, non-limiting examples of substituted alkylene includes any of the substituted alkylenes defined

or disclosed herein. For example, substituted alkylenes include alkylenes substituted with one or more -OH group, alkylenes substituted with one or more ether group, e.g., a -O-Bn group, alkylenes substituted with one or more halogen, or alkylenes substituted with combinations of two or more substituents (e.g., -OH and halogen, halogen and ether, etc.).

In still another embodiment of the compounds of Formula I, each L^3 is the same, i.e., each L^3 is the same alkylene or substituted alkylene group.

In still another embodiment of the compounds of Formula I, each L^3 is different, i.e., one L^3 is an alkylene and the other L^3 is a substituted alkylene, one L^3 is an alkylene and the other L^3 is a different alkylene, or one L^3 is a substituted alkylene, and the other L^3 is a different substituted alkylene.

In still another embodiment of the compounds of Formula I, each L^4 is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, -CH_2-O-, and -NH-. When L^4 is alkylene, said alkylene includes any alkylene defined or exemplified herein. When L^4 is substituted alkylene, said substituent includes any alkylene defined or exemplified herein, substituted by one or more substituents as defined herein.

In still another embodiment of the compounds of Formula I, both L^4 groups are the same, i.e. both L^4 groups are a covalent bond, both are -O-, both are -CH_2-O-, (wherein the CH_2 group is attached to either the "A" moiety or the "Ar" moiety of Formula I), both are a substituted or unsubstituted alkylene, or both are –NH-.

In still another embodiment of the compounds of Formula I, each L^4 is different. For example, one L^4 is a covalent bond and the other L^4 is –O-, one L^4 is a covalent bond and the other L^4 is -CH_2-O- (wherein the CH_2 group is attached to either the "A" moiety or the "Ar" moiety of Formula I), one L^4 is a covalent bond and the other L^4 is –NH-, one L^4 is a –O- and the other L^4 is -CH_2-O- (wherein the

CH_2 group is attached to either the "A" moiety or the "Ar" moiety of Formula I), one L^4 is –O- and the other L^4 is –NH-, one L^4 is -CH_2-O- (wherein the CH_2 group is attached to either the "A" moiety or the "Ar" moiety of Formula I) and the other L^4 is –NH-, one L4 is a covalent bond and the other L^4 is a substituted or unsubstituted alkylene, one L^4 is a substituted alkylene and the other L^4 is a unsubstituted alkylene, one L^4 is a substituted or unsubstituted alkene and the other L^4 is –O-, one L^4 is a substituted or unsubstituted alkylene and the other L^4 is -CH_2-O- (wherein the CH_2 group is attached to either the "A" moiety or the "Ar" moiety of Formula I), or one L^4 is substituted or unsubstituted alkylene and the other L^4 is -NH-.

In still another embodiment of the compounds of Formula I, each A is independently H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclyl, or substituted heterocyclyl, with the proviso that when A is H, p is 0. When any A is alkyl, said alkyl includes any alkyl defined or exemplified herein. When any A is substituted alkyl, said alkyl includes any alkyl defined or exemplified herein substituted with one or more of any substituent defined or exemplified herein. When any A is aryl, said aryl includes any aryl defined or exemplified herein. When any A is substituted aryl, said aryl includes any aryl defined or exemplified herein substituted with one or more of any substituent defined or exemplified herein. When any A is heterocyclyl, said heterocyclyl includes any heterocyclyl defined or exemplified herein. When any A is substituted heterocyclyl, said heterocyclyl is any heterocyclyl defined or exemplified herein substituted with one or more of any substituent defined or exemplified herein.

In still another embodiment of the compounds of Formula I, each A is H and each p is 0.

In still another embodiment of the compounds of Formula I, each A is substituted or unsubstituted alkyl, wherein alkyl is any alkyl defined or

exemplified herein, and, when present, the substituents on said alkyl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, each A is substituted or unsubstituted aryl, wherein aryl is any aryl defined or exemplified herein, and, when present, the substituents on said aryl include one or more of any substituents defined or exemplified herein. In a particular embodiment, A is phenyl.

In still another embodiment of the compounds of Formula I, each A is substituted or unsubstituted heterocyclyl, wherein heterocyclyl is any heterocyclyl defined or exemplified herein, and, when present, the substituents on said heterocyclyl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, one A is H and the other A is substituted or unsubstituted alkyl, wherein alkyl is any alkyl defined or exemplified herein, and, when present, the substituent on said alkyl includes one or more of any substituent defined or exemplified herein.

In still another embodiment of the compounds of Formula I, one A is H and the other A is substituted or unsubstituted aryl, wherein aryl is any aryl defined or exemplified herein, and the substituents on said aryl are any substituents defined and exemplified herein. In a particular embodiment, one A is phenyl.

In still another embodiment of the compounds of Formula I, one A is H and the other A is substituted or unsubstituted heterocyclyl, wherein heterocyclyl is any heterocyclyl defined or exemplified herein, and, when present, the substituents on said heterocyclyl include one or more of any substituent defined or exemplified herein.

In still another embodiment of the compounds of Formula I, one A is substituted or unsubstituted alkyl, and the other A is substituted or unsubstituted aryl, wherein alkyl and aryl are any alkyl or aryl defined or exemplified herein, and, when present, the substituents on said alkyl or aryl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, one A is substituted or unsubstituted alkyl, and the other A is substituted or unsubstituted heterocyclyl, wherein alkyl and heterocyclyl are any alkyl or heterocyclyl defined or exemplified herein, and, when present, the substituents on said alkyl or heterocyclyl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, one A is substituted or unsubstituted aryl, and the other A is substituted or unsubstituted heterocyclyl, wherein aryl and heterocyclyl are any aryl or heterocyclyl defined or exemplified herein, and, when present, the substituents on said aryl or heterocyclyl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, Z^1 is -O- or -$N(R^7)$-. When Z^1 is -$N(R^7)$-, R^7 is H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl are any alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl defined or exemplified herein.

In still another embodiment of the compounds of Formula I, Z^2 is -O- or -$N(R^7)$-. When Z^2 is -$N(R^7)$-, R^7 is H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl,

wherein alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl are any alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl defined or exemplified herein.

In still another embodiment of the compounds of Formula I, Z^1 and Z^2 are the same, e.g., Z^1 and Z^2 are both -O-, or Z^1 and Z^2 are both -N(R^7)-, where R^7 is H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl are any alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl defined or exemplified herein.

In still another embodiment of the compounds of Formula I, Z^1 and Z^2 are different, e.g. Z^1 is –O- and Z^2 is -N(R^7)-, Z^1 is -N(R^7)- and Z^2 is –O-, or Z^1 and Z^2 are both -N(R^7)- but in Z^1 the R^7 is different from the R^7 in Z^2. When either Z^1 of Z^2 is -N(R^7)-, R^7 is H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl, wherein alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl are any alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, or substituted heterocyclyl defined or exemplified herein.

In still another embodiment of the compounds of Formula I, Y is heterocyclyl or heterocyclylalkyl, wherein heterocyclyl and heterocyclylalkyl are any heterocyclyl or heterocyclylalkyl defined or exemplified herein. In a particular embodiment, Y is heterocyclylalkyl, e.g. thiazolylmethyl (-CH_2-thiazolyl).

In still another embodiment of the compounds of Formula I, X is heterocyclyl or heterocyclylalkyl, wherein heterocyclyl and heterocyclylalkyl are any heterocyclyl or heterocyclylalkyl defined or exemplified herein. In a particular embodiment, X is heterocyclylalkyl, e.g. thiazolylmethyl.

In still another embodiment of the compounds of Formula I, X and Y are different, e.g., X and Y are different heterocyclyls, X and Y are different heterocyclylalkyls, X is heterocyclyl and Y is heterocyclylalkyl, or X is heterocyclylalkyl and Y is heterocyclyl, wherein heterocyclyl and heterocyclylalkyl are any heterocyclyl or heterocyclylalkyl defined or exemplified herein.

In still another embodiment of the compounds of Formula I, X and Y are the same. In a particular embodiment both X and Y are heterocyclylalkyls, e.g. thiazolylmethyl.

In still another embodiment of the compounds of Formula I, each Ar is aryl, substituted aryl, heteroaryl, or substituted heteroaryl, wherein the aryl or heteroaryl are any aryl or heteroaryl defined or exemplified herein, and, when present, the substituents on the aryl or heteroaryl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, each Ar is the same, e.g., each Ar is an aryl such as phenyl.

In still another embodiment of the compounds of Formula I, each Ar is different, e.g. one Ar is a substituted or unsubstituted aryl and the other Ar is a substituted or unsubstituted heteroaryl, each Ar is a different substituted or unsubstituted aryl, or each Ar is a different substituted or unsubstituted heteroaryl, wherein aryl and heteroaryl are any aryl or heteroaryl defined or exemplified herein, and, when present, the substituents on the aryl or heteroaryl include one or more of any substituents defined or exemplified herein.

In still another embodiment of the compounds of Formula I, R^1, R^3, and R^5 are each independently H, alkyl, or substituted alkyl, wherein alkyl and substituted alkyl include any of the alkyl or substituted alkyls defined or disclosed herein.

In still another embodiment of the compounds of Formula I, R^1, R^3, and R^5 are each the same. In a particular embodiment R^1, R^3, and R^5 are each H. in another particular embodiment R^1, R^3, and R^5 are each alkyl, e.g. one of the alkyl groups defined or disclosed herein.

In still another embodiment of the compounds of Formula I, R^1, R^3, and R^5 are each different.

In still another embodiment of the compounds of Formula I, one of R^1, R^3, and R^5 is different from the other two groups.

In still another embodiment of the compounds of Formula I, n and m are both 1, and each R^2 is independently H, alkyl, substituted alkyl, arylheteroalkyl, arylalkyl, or heterocyclylalkyl, wherein alkyl, substituted alkyl, arylheteroalkyl, aryl alkyl, or heterocyclylalkyl is any alkyl, substituted alkyl, arylheteroalkyl, aryl alkyl, or heterocyclylalkyl defined or disclosed herein.

In still another embodiment of the compounds of Formula I, n and m are both 1, and R^2 is H.

In still another embodiment of the compounds of Formula I, n is 1, m is 2, and R^2 is H.

In still another embodiment of the compounds of Formula I, n and m are both 1, and at least one R^2 is alkyl. In a particular embodiment at least one R^2 is methyl. In another particular embodiment at least one R^2 is ethyl. In another particular embodiment at least one R^2 is i-propyl. In another particular embodiment at least one R^2 is t-butyl. In another particular embodiment, one R^2 is H, and the other R^2 is methyl. In another particular embodiment, one R^2 is H, and

the other R^2 is ethyl. In another particular embodiment, one R^2 is H, and the other R^2 is i-propyl. In another particular embodiment, one R^2 is H, and the other R^2 is t-butyl.

In still another embodiment of the compounds of Formula I, n and m are both 1, and R^2 is substituted alkyl. In a particular embodiment at least one R^2 is –$CH(CH_3)OH$ or –$CH(CH_3)O$(t-Bu)

In still another embodiment of the compounds of Formula I, n and m are both 1, and at least one R^2 is arylheteroalkyl. In particular embodiment n and m are both 1, and at least one R^2 is selected from the group consisting of H, methyl, ethyl, benzyl-O-CH_2-, i-propyl, -$CH(CH_3)$OBn, -$CH_2CH(CH_3)$-O-tBu, -$CH(CH_3)OH$, -CH_2OH, -CH_2OtBu, -$CH_2CH_2NH_2$, -CH_2CH_2NH-P (where P is a protecting group such as Boc, Ac, methanesulfonyl, etc.), -CH_2CH_2-morpholine, -$CH_2C(O)OH$, -$CH_2C(O)$OtBu, and -$CH_2C(O)$-NH_2.

In still another embodiment of the compounds of Formula I, n and m are both 1, and at least one R^2 is arylheteroalkyl. In particular embodiment n and m are both 1, one R^2 is H and one R^2 is selected from the group consisting of H, methyl, ethyl, benzyl-O-CH_2-, i-propyl, -$CH(CH_3)$OBn, -$CH_2CH(CH_3)$-O-tBu, -$CH(CH_3)OH$, -CH_2OH, -CH_2OtBu, -$CH_2CH_2NH_2$, -CH_2CH_2NH-P (where P is a protecting group such as Boc, Ac, methanesulfonyl, etc.), -CH_2CH_2-morpholine, -$CH_2C(O)OH$, -$CH_2C(O)$OtBu, and -$CH_2C(O)$-NH_2.

In still another embodiment of the compounds of Formula I, R^4 is H, alkyl, substituted alkyl, and heteroalkyl, wherein alkyl, substituted alkyl, and heteroalkyl are any alkyl, substituted alkyl, or heteroalkyl defined or disclosed herein. A particular embodiment, R^4 is H.

In still another embodiment of the compounds of Formula I, R^6 is H, alkyl, substituted alkyl, and heteroalkyl, wherein alkyl, substituted alkyl, and

heteroalkyl are any alkyl, substituted alkyl, or heteroalkyl defined or disclosed herein. A particular embodiment, R^6 is H.

In still another embodiment of the compounds of Formula I, R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, and -CN, wherein when R^8 or R^9 are alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, or substituted heterocyclyl, said alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, or substituted heterocyclyl are any such groups defined or disclosed herein.

In still another embodiment of the compounds of Formula I, R^8 and R^9 are the same. In a particular embodiment R^8 and R^9 are both H.

In still another embodiment of the compounds of Formula I, R^8 and R^9 are different. In a particular embodiment R^8 is alkyl and R^9 is H. in another particular embodiment, R^8 is i-propyl and R^9 is H.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an –alkylene-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an –alkylene-aryl-alkylene-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-aryl-alkylene-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and

heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl, and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-alkylene-heteroaryl group, wherein said alkylene and heteroaryl moieties are any alkylene and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-alkylene-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl, and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-O-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-CH_2-O-aryl group, wherein said

alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-OCH_2-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-NH-aryl group, wherein said alkylene and aryl moieties are any alkylene and aryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-O-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-CH_2-O-heterocyclyl group,

wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-aryl-OCH_2-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-aryl-NH-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-heterocyclyl-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-heterocyclyl-O-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene

and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-CH_2-O-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-OCH_2-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-NH-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-O-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-CH_2-O-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-OCH_2-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-NH-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heterocyclyl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-aryl-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl

moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-O-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-CH_2-O-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-OCH_2-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-aryl-NH-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an –alkylene-heteroaryl-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-O-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-CH_2-O-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-OCH_2-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-NH-aryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl

moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-O-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heterocyclyl-CH_2-O-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-OCH_2-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an -alkylene-heteroaryl-NH-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the alkylene and/or aryl and/or heteroaryl with one or more of any substituents defined or exemplified herein.

In yet another embodiment of the compounds of Formula I, at least one of the -L^3-A-(L^4-Ar)$_p$ moieties is an alkyl group.

In yet another embodiment of the compounds of Formula I, both of the -L^3-A-(L^4-Ar)$_p$ moieties are alkyl groups, wherein the alkyl groups are the same or different.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and X and Y are both -CH_2-heterocyclyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and Y is –CH_2-heterocyclyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and X is –CH_2-heterocyclyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and Y is –CH_2-thiazolyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and X is –CH_2-thiazolyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl and X and Y are both -CH_2-thiazolyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, and n and m are both 1.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_1-C_6 alkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_1-C_6 hydroxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_2-C_{10} alkoxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_7-C_{14} arylalkyloxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_1-C_6 aminoalkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a C_1-C_6 aminoalkyl substituted on the nitrogen with an amine protecting group selected from acyl, alkylsulfonyl, arylsulfonyl, heterocyclylacyl, and benzyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and at least one R^2 is a substituted or unsubstituted heterocyclylalkyl.

In yet another embodiment of the compounds of Formula I, both -L^3-A-(L^4-Ar)$_p$ moieties are –CH_2-phenyl, X and Y are both -CH_2-thiazolyl, n and m are both 1, and L^2 is –CH_2-.

In yet another embodiment of the compounds of Formula I, at least one -L^3-A-(L^4-Ar)$_p$ moiety is–CH_2-phenyl-CH_2-phenyl.

In yet another embodiment of the compounds of Formula I, at least one -L^3-A-(L^4-Ar)$_p$ moiety is–CH_2- heteroaryl-CH_2-phenyl.

In yet another embodiment of the compounds of Formula I, at least one -L^3-A-(L^4-Ar)$_p$ moiety is–CH_2-phenyl-CH_2-heteroaryl.

In yet another embodiment of the compounds of Formula I, at least one -L^3-A-(L^4-Ar)$_p$ moiety is–CH_2- heteroaryl-CH_2-heteroaryl.

In yet another embodiment of the compounds of Formula I, X and Y are both heterocyclylalkyl.

In yet another embodiment of the compounds of Formula I, X and Y are both heteroarylalkyl.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, and both –L^3-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both –L^3-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, and L^2 is –CH_2-.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both –L^3-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is –CH_2-, and m and n are both 1.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both –L^3-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is –CH_2-, m and n are both 1, and R^1 is H.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both –L^3-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is –CH_2-, m and n are both 1, R^1 is H, and Z^1 is -N(alkyl)-.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, and Z^1 is -N(CH_3)-.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, and Z^2 is –O-.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(CH_3)-, and Z^2 is –O-.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, Z^2 is –O-, and Y is substituted or unsubstituted $-CH_2$-4-thiazole.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, Z^2 is –O-, and R^8-Y is $-CH_2$-(2-alkyl-4-thiazole).

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, and R^8-Y is $-CH_2$-(2-iPr-4-thiazole).

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2$-, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, Z^2 is –O-, Y is substituted or unsubstituted $-CH_2$-4-thiazole, and X is substituted or unsubstituted $-CH_2$-5-thiazole.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, Z^2 is –O-, Y is substituted or unsubstituted $-CH_2$-4-thiazole, and X is unsubstituted $-CH_2$-5-thiazole.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), and X is unsubstituted $-CH_2$-5-thiazole.

In another embodiment of the compounds of Formula I, each R^2 is independently H or hydroxyalkyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or heterocyclylalkyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is a 5- or 6-membered ring having at least one ring nitrogen atom.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is a 6-membered ring having at least one ring nitrogen atom.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is a 6-membered ring having at least one ring nitrogen atom, where the $-CH_2-$ moiety thereof is bonded to the ring nitrogen atom.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholinyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is selected from

the group consisting of piperadyl, piperazyl, and morpholinyl, and the $-CH_2-$ moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or aminoalkyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or aminoalkyl substituted with an amine protecting group selected from the group consisting of acetyl, alkylsulfonyl, Boc, Cbz, and Fmoc.

In another embodiment of the compounds of Formula I, each R^2 is independently H or ethylacetamide ($-CH_2CH_2NHC(O)CH_3$).

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-$(L^4$-Ar$)_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted $-CH_2$-5-thiazole, and R^2 is independently H or hydroxyalkyl.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-$(L^4$-Ar$)_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted $-CH_2$-5-thiazole, and one R^2 is H and the other R^2 is hydroxyalkyl.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-$(L^4$-Ar$)_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted $-CH_2$-5-thiazole, and one R^2 is H and the other R^2 is hydroxymethyl.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-$(L^4$-Ar$)_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted $-CH_2$-5-thiazole, and each R^2 is independently H or $-CH_2-$

heterocyclyl, wherein said heterocyclyl is a 5- or 6-membered ring having at least one ring nitrogen atom.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted -CH_2-5-thiazole, and each R^2 is independently H or $-CH_2$-heterocyclyl, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholinyl, and the $-CH_2$- moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted -CH_2-5-thiazole, and one R^2 is H and the other R^2 is $-CH_2$-heterocyclyl, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholinyl, and the $-CH_2$- moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted -CH_2-5-thiazole, and each R^2 is independently H or aminoalkyl substituted with an amine protecting group selected from the group consisting of acetyl, alkylsulfonyl, Boc, Cbz, and Fmoc.

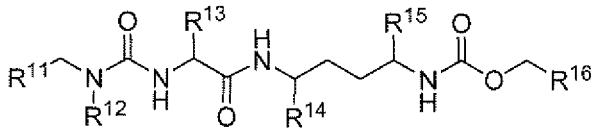
In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted -CH_2-5-thiazole, and one R^2 is H and the other R^2 is aminoalkyl

substituted with an amine protecting group selected from the group consisting of acetyl, alkylsulfonyl, Boc, Cbz, and Fmoc.

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(H)-, Z^2 is –O-, R^8-Y is $-CH_2$-(2-iPr-4-thiazole), X is unsubstituted -CH_2-5-thiazole, and one R^2 is H and the other R^2 is ethylacetamide (-$CH_2CH_2NHC(O)CH_3$).

In another embodiment of the compounds of Formula I, L^1 is -C(O)-, R^4 is H, both $-L^3$-A-(L^4-Ar)$_p$ groups are substituted or unsubstituted benzyl, L^2 is $-CH_2-$, m and n are both 1, R^1 is H, Z^1 is -N(alkyl)-, Z^2 is –O-, and Y is substituted or unsubstituted $-CH_2$-thiazole.

In still another embodiment, the compounds of Formula I, or pharmaceutically acceptable salts, solvates, esters, or stereoisomers thereof, have the structure shown in Formula IIA:



Formula IIA

wherein R^{11} and R^{16} are each independently heterocyclyl or substituted heterocyclyl; and R^{12}, R^{13}, R^{14}, and R^{15} are each independently H, -C_{1-4} alkyl or -C_{1-4} substituted alkyl.

In still another embodiment of the compounds of Formula IIA, R^{13} is H, -C_{1-4} alkyl, -$(CH_2)_{0-1}CR^{17}R^{18}OR^{19}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$, -$(CH_2)_{1-3}C(O)R^{22}$, -$(CH_2)_{1-3}S(O)_2R^{22}$ or -$(CH_2)_{1-3}$-R^{23}; R^{14} and R^{15} are each independently H, -C_{1-4} alkyl or arylalkyl; R^{17} and R^{18} are each independently H or -C_{1-3} alkyl; R^{19} is H, -C_{1-4} alkyl or arylalkyl; R^{20} and R^{21} are each independently H, -C_{1-3} alkyl, -$C(O)R^{17}$ or -$S(O)_2R^{17}$; or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form an unsubstituted or substituted 5-6

membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O; R^{22} is H, -C_{1-3} alkyl, -OR^{19} or -$NR^{20}R^{21}$; and R^{23} is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O.

In still another embodiment of the compounds of Formula IIA, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$, or -$(CH_2)_{1-3}$-$R^{23}$ wherein R^{20} and R^{21} form a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O or R^{23} is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O, and the 5-6 membered heterocyclyl ring is optionally substituted with a C_{1-2} alkyl.

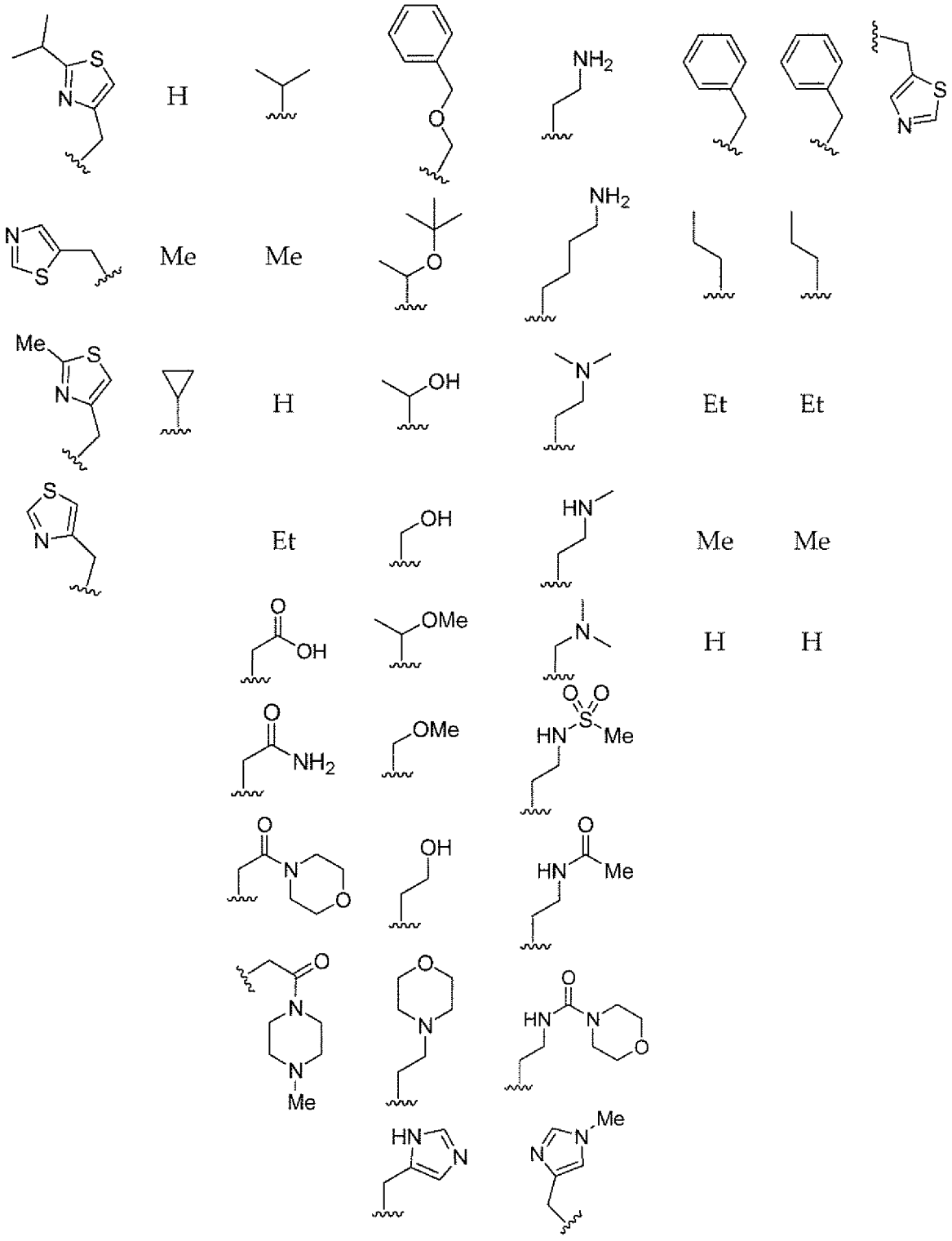
In still another embodiment of the compounds of Formula IIA, R^{13} is -$(CH_2)_{0-1}CR^{17}R^{18}OR^{19}$. In a particular embodiment, R^{13} is a C_{1-2} hydroxyalkyl or a C_{1-6} alkoxyalkyl group.

In still another embodiment of the compounds of Formula IIA, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$. In a particular embodiment, R^{13} is a C_{1-4}alkylene-NH_2 group, C_{1-4}alkylene-NHP (wherein P is a protecting group such as Boc, Fmoc, Cbz, Ac, trifluoroacetyl, toluenesulfony group, benzyl, etc.), or C_{1-4}alkylene-$N(alkyl)_2$ group.

In still another embodiment of the compounds of Formula IIA, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$. In a particular embodiment, R^{13} is a C_{1-4}alkylene-$C(O)NH_2$ group or C_{1-4}alkylene-$C(O)N(alkyl)_2$ group.

In still another embodiment of the compounds of Formula IIA, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, and R^{16} are each independently selected from the groups shown in the Table, below:

R^{11}	R^{12}	R^{13}	R^{14}	R^{15}	R^{16}



In still another embodiment of the compounds of Formula IIA, R^{11} is substituted or unsubstituted heterocyclyl, R^{12} is alkyl, R^{13} is substituted or

unsubstituted heterocyclylalkyl, R^{14} and R^{15} are each independently substituted or unsubstituted arylalkyl, and R^{16} is substituted or unsubstituted heterocyclyl.

In still another embodiment of the compounds of Formula IIA, R^{11} is substituted heterocyclyl, R^{12} is alkyl, R^{13} is unsubstituted heterocyclylalkyl, R^{14} and R^{15} are both unsubstituted arylalkyl, and R^{16} is unsubstituted heterocyclyl.

In still another embodiment of the compounds of Formula IIA, R^{11} is substituted or unsubstituted heterocyclyl, R^{12} is alkyl, R^{13} is hydroxyalkyl, R^{14} and R^{15} are each independently substituted or unsubstituted arylalkyl, and R^{16} is substituted or unsubstituted heterocyclyl.

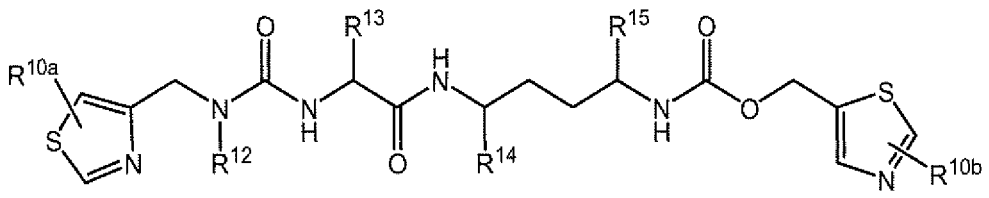
In still another embodiment of the compounds of Formula IIA, R^{11} is substituted heterocyclyl, R^{12} is alkyl, R^{13} is hydroxyalkyl, R^{14} and R^{15} are both unsubstituted arylalkyl, and R^{16} is unsubstituted heterocyclyl.

In still another embodiment of the compounds of Formula IIA, R^{11} is substituted or unsubstituted heterocyclyl, R^{12} is alkyl, R^{13} is protected or unprotected aminoalkyl, R^{14} and R^{15} are each independently substituted or unsubstituted arylalkyl, and R^{16} is substituted or unsubstituted heterocyclyl.

In still another embodiment of the compounds of Formula IIA, R^{11} is substituted heterocyclyl, R^{12} is alkyl, R^{13} is protected aminoalkyl, R^{14} and R^{15} are both unsubstituted arylalkyl, and R^{16} is unsubstituted heterocyclyl.

In still another embodiment of the compounds of Formula IIA, R^{11} is substituted heterocyclyl, R^{12} is alkyl, R^{13} is acylated aminoalkyl, R^{14} and R^{15} are both unsubstituted arylalkyl, and R^{16} is unsubstituted heterocyclyl.

In another embodiment, the compounds of Formula I, or pharmaceutically acceptable salts, solvates, stereoisomers and/or esters thereof, have the following structure IIB:

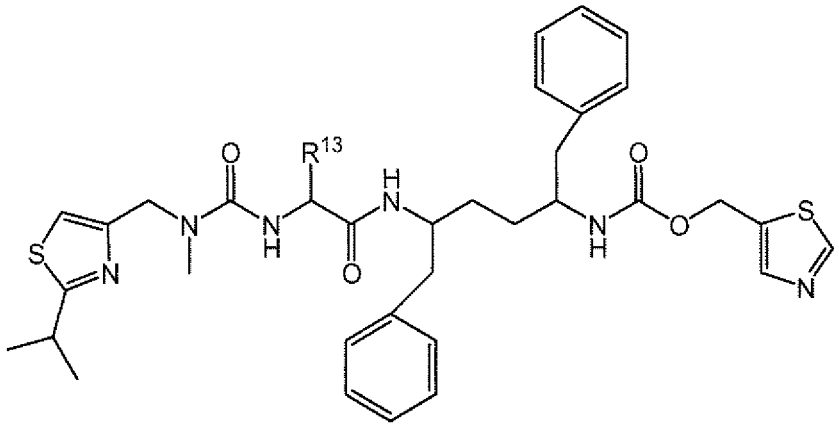


Formula IIB

R^{10a} and R^{10b} are each independently H or -C_{1-4} alkyl; R^{12} is H or -CH_3; R^{13} is H, -C_{1-4} alkyl, -$(CH_2)_{0-1}CR^{17}R^{18}OR^{19}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)NR^{20}R^{21}$, -$(CH_2)_{1-3}C(O)R^{22}$, -$(CH_2)_{1-3}S(O)_2R^{22}$ or -$(CH_2)_{1-3}$-R^{23}; R^{14} and R^{15} are each independently H, -C_{1-4} alkyl or arylalkyl; R^{17} and R^{18} are each independently H or -C_{1-3} alkyl; R^{19} is H, -C_{1-4} alkyl or arylalkyl; R^{20} and R^{21} are each independently H, -C_{1-3} alkyl, -$C(O)R^{17}$ or -$S(O)_2R^{17}$; or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O; R^{22} is H, -C_{1-3}alkyl, -OR^{19} or -$NR^{20}R^{21}$; and R^{23} is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O.

In still another embodiment of the compounds of Formula IIB, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$, or -$(CH_2)_{1-3}$-$R^{23}$ wherein R^{20} and R^{21} form a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O or R^{23} is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O, and the 5-6 membered heterocyclyl ring is optionally substituted with a C_{1-2} alkyl.

In another embodiment, the compounds of Formula I, or pharmaceutically acceptable salts, solvates, stereoisomers and/or esters thereof, have the following structure IIC:



Formula IIC

wherein: R^{13} is H, -C_{1-4} alkyl, -$(CH_2)_{0-1}CR^{17}R^{18}OR^{19}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$ $NR^{20}R^{21}$, -$(CH_2)_{1-3}C(O)R^{22}$ or -$(CH_2)_{1-3}$-R^{23}; R^{17} and R^{18} are each independently H or C_{1-3} alkyl; R^{19} is H, -C_{1-4} alkyl or arylalkyl; R^{20} and R^{21} are each independently H, -C_{1-3} alkyl, -$C(O)R^{17}$ or -$S(O)_2R^{17}$; or R^{20} and R^{21}, taken together with the nitrogen atom to which they are attached, form a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O; R^{22} is H, -C_{1-3}alkyl, -OR^{19} or -$NR^{20}R^{21}$; and R^{23} is a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O.

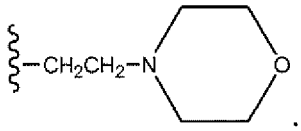
In still another embodiment of the compounds of Formula IIC, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$, -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$, or -$(CH_2)_{1-3}$-$R^{23}$ wherein R^{20} and R^{21} form a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O or R^{23} is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O, and the 5-6 membered heterocyclyl ring is optionally substituted with a C_{1-2} alkyl.

In still another embodiment of the compounds of Formula IIC, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$. In a particular embodiment, R^{13} is a C_{1-4}alkylene-NH_2 group, C_{1-4}alkylene-NHP (wherein P is a protecting group such as Boc, Fmoc, Cbz,

Ac, trifluoroacetyl, toluenesulfony group, benzyl, etc.), or C_{1-4}alkylene-N(alkyl)$_2$ group.

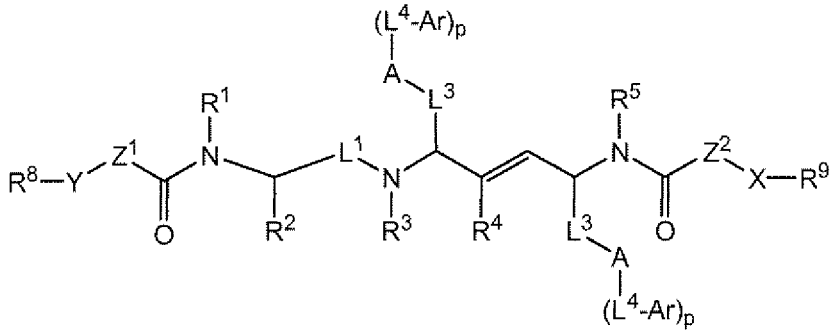
In still another embodiment of the compounds of Formula IIC, R^{13} is -$(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)$-$NR^{20}R^{21}$. In a particular embodiment, R^{13} is a C_{1-4}alkylene-C(O)NH_2 group or C_{1-4}alkylene-C(O)N(alkyl)$_2$ group.

In still another embodiment of the compounds of Formula IIC, R^{13} is -CH_2OH, -$CH_2CH_2NHC(O)CH_3$ or



.

In another embodiment, the compounds of of the present invention, or pharmaceutically acceptable salts, solvates, stereoisomers and/or esters thereof, have the following structure IID:



Formula IID

wherein,

L^1 is selected from the group consisting of $-C(R^6)_2$-, -C(O)-, $-S(O_2)$-, $-N(R^7)$-C(O)-, and -O-C(O)-;

each L^3 is independently a covalent bond, an alkylene, or substituted alkylene;

each L^4 is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, $-CH_2$-O-, and -NH-;

each A is independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl,

with the proviso that when A is H, p is 0;

Z^1 and Z^2 are each independently -O- or -N(R^7)-;

Y and X are independently selected from the group consisting of heterocyclyl and heterocyclylalkyl;

each Ar is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted heteroaryl;

R^1, R^3, and R^5 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

R^2 is independently selected from the group consisting of H, alkyl, substituted alkyl, alkoxyalkyl, hydroxyalkyl, arylheteroalkyl, substituted arylheteroalkyl, arylalkyl, substituted arylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-C(O)-OH, -alkylene-C(O)-Oalkyl, -alkylene-C(O)amino, -alkylene-C(O)-alkyl;

R^4 and R^6 are independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl;

each R^7 is independently selected from the group consisting of H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, and substituted heterocyclyl;

R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, and -CN; and

each p is independently 0 or 1.

In another embodiment of the compounds of Formula IID, L^1 is -C(R^6)$_2$-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-.

In another embodiment of the compounds of Formula IID, each L^3 is alkylene.

In another embodiment of the compounds of Formula IID, each L^3 is –CH_2-.

In another embodiment of the compounds of Formula IID, each A is aryl or substituted aryl.

In another embodiment of the compounds of Formula IID, each A is phenyl or substituted phenyl.

In another embodiment of the compounds of Formula IID, X is heterocyclylalkyl.

In another embodiment of the compounds of Formula IID, X is thiazolylmethyl.

In another embodiment of the compounds of Formula IID, Y is heterocyclylalkyl.

In another embodiment of the compounds of Formula IID, Y is thiazolylmethyl.

In another embodiment of the compounds of Formula IID, Z^1 is $-N(R^7)-$.

In another embodiment of the compounds of Formula IID, Z^1 is -NH-.

In another embodiment of the compounds of Formula IID, Z^1 is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, Z^1 is $-N(CH_3)-$.

In another embodiment of the compounds of Formula IID, Z^2 is -O-.

In another embodiment of the compounds of Formula IID, L^1 is $-C(R^6)_2-$ and X and Y are heterocyclylalkyl.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and X and Y are heterocyclylalkyl.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and X and Y are thiazolylmethyl.

In another embodiment of the compounds of Formula IID, L^1 is $-C(R^6)_2-$ and Z^1 is $-N(R^7)-$.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and Z^1 is $-N(R^7)-$.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and Z^1 is -NH-.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and Z^1 is –N(alkyl)-.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$ and Z^1 is $–N(CH_3)-$.

In another embodiment of the compounds of Formula IID, L^1 is $-C(R^6)_2-$ and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, each L^3 is alkylene and each A is aryl or substituted aryl.

In another embodiment of the compounds of Formula IID, each L^3 is $–CH_2-$ and each A is aryl or substituted aryl.

In another embodiment of the compounds of Formula IID, each L^3-A is benzyl or substituted benzyl.

In another embodiment of the compounds of Formula IID, X and Y are heterocyclylalkyl and Z^1 is $-N(R^7)-$.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z^1 is $-N(R^7)-$.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z^1 is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z^1 is $-N(CH_3)-$.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z^1 is -NH-.

In another embodiment of the compounds of Formula IID, X and Y are heterocyclylalkyl and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, Z^1 is -N(R^7)- and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, Z^1 is -N(alkyl)- and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, Z^1 is -N(CH_3)- and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, Z^1 is -NH- and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, L^1 is -C(R^6)$_2$-, X and Y are heterocyclylalkyl, and Z^1 is -N(R^7)-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-, X and Y are heterocyclylalkyl, and Z^1 is -N(R^7)-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-, X and Y are thiazolylmethyl, and Z^1 is -N(R^7)-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-, X and Y are thiazolylmethyl, and Z^1 is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-, X and Y are thiazolylmethyl, and Z^1 is -N(CH_3)-.

In another embodiment of the compounds of Formula IID, L^1 is -CH_2-, X and Y are thiazolylmethyl, and Z^1 is -NH-.

In another embodiment of the compounds of Formula IID, L^1 is -C(R^6)$_2$-; X and Y are heterocyclylalkyl; and Z^2 is –O-.

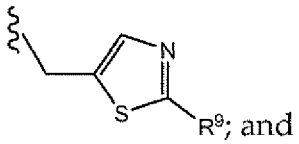
In another embodiment of the compounds of Formula IID, L^1 is -CH_2-; X and Y are heterocyclylalkyl; and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$; X and Y are thiazolylmethyl; and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, L^1 is $-C(R^6)_2-$; each L^3 is alkylene; each A is aryl or substituted aryl; X and Y are heterocyclylalkyl; Z^1 is $-N(R^7)-$; and Z^2 is –O-.

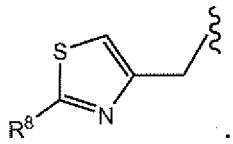
In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$; each L^3-A is benzyl or substituted benzyl; X and Y are thiazolylmethyl; Z^1 is $-N(CH_3)-$; and Z^2 is –O-.

In another embodiment of the compounds of Formula IID, L^1 is $-CH_2-$; each L^3-A is benzyl or substituted benzyl; Z^1 is $-N(CH_3)-$; Z^2 is –O-; X is



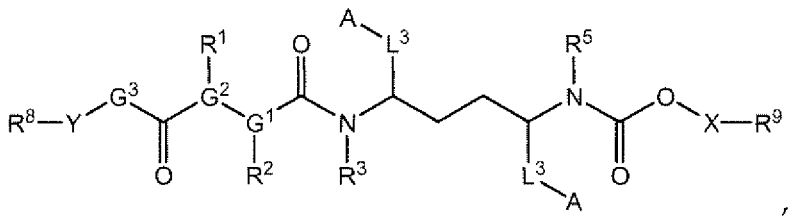
; and

Y is



.

In another embodiment, the compounds of of the present invention, or pharmaceutically acceptable salts, solvates, stereoisomers and/or esters thereof, have the following structure IV:



,

wherein,

each L^3 is independently an alkylene or substituted alkylene;

each A is independently an aryl or substituted aryl;

X is heterocyclylalkyl;

Y is heterocyclylalkyl or alkyl;

G^1 and G^2 are independently CH or N, with the proviso that G^1 and G^2 are different;

G^3 is $-NR^7-$ or $-O-$;

R^1, R^3, R^5, and R^7 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

R^2 is independently selected from the group consisting of substituted alkyl, alkoxyalkyl, hydroxyalkyl, trialkylsiloxyalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-$N(R^a)$-C(O)-alkyl, -alkylene-NR^a-$C(O)$-$N(R^a)_2$, -alkylene-NR^a-$C(=N-R^b)$-$N(R^a)_2$, -alkylene-$C(=N-R^b)$-$N(R^a)_2$, -alkylene-C(O)-OH, -alkylene-C(O)-Oalkyl, and -alkylene-$C(O)$-$N(R^c)_2$;

R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, and –CN;

each R^a is independently selected from the group consisting of H, alkyl, and substituted alkyl;

R^b is selected from the group consisting of H, alkyl, substituted alkyl, CN, and $-S(O_2)$-alkyl; and

each R^c is independently selected from the group consisting of H, alkyl, substituted alkyl, heterocyclyl, and $-S(O_2)$-alkyl.

In some embodiments of the compounds of Formula IV, each L^3 is alkylene, for example any of those described herein, e.g. $-CH_2-$ and each A is phenyl. In a particular embodiment, both $-L^3$-A moieties are benzyl.

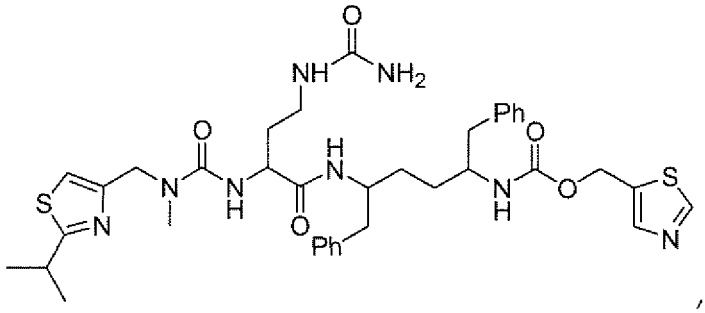
In some embodiments of the compounds of Formula IV, X and Y are both heteroaryl (for example, any heteroaryl described herein). In a particular embodiment, both X and Y are thiazolyl.

In some embodiments of the compounds of Formula IV, G^1 is CH, and G^2 is N. In a particular embodiment, G^2 is N and R^1 is H. In another particular

embodiment, G^2 is N, R^1 is H, and G^3 is NR^7. In yet another particular embodiment, G^2 is N, R^1 is H, and G^3 is NCH_3.

In some embodiments of the compounds of Formula IV, R^2 is substituted or unsubstituted aminoalkyl. In a particular embodiment, R^2 is substituted or unsubstituted aminoalkyl, G^2 is N and R^1 is H, and both X and Y are thiazolyl. In another particular embodiment, R^2 is $-CH_2CH_2-NHR^d$, wherein R^d is selected from the group consisting of H, haloalkyl, $-C(O)-N(R^a)_2$, $-C(=N-R^b)-N(R^a)_2$, hydroxyalkyl, $-C(N(R^a)_2)=CHNO_2$, -C(O)-alkyl, G^2 is N and R^1 is H, and both X and Y are thiazolyl. In still another particular embodiment, R^2 is $-CH_2CH_2-NH-C(O)$-alkyl.

In specific embodiments, the compounds of Formula IV have the following structures:



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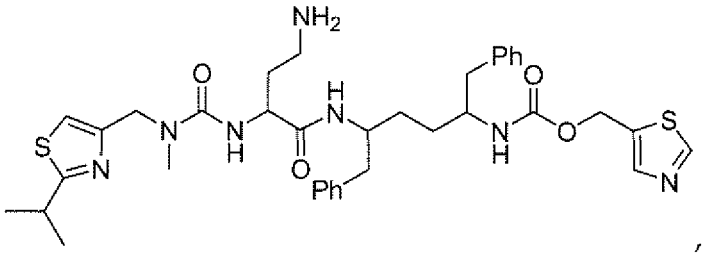

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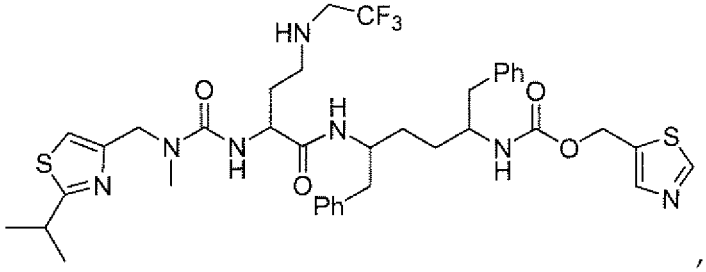

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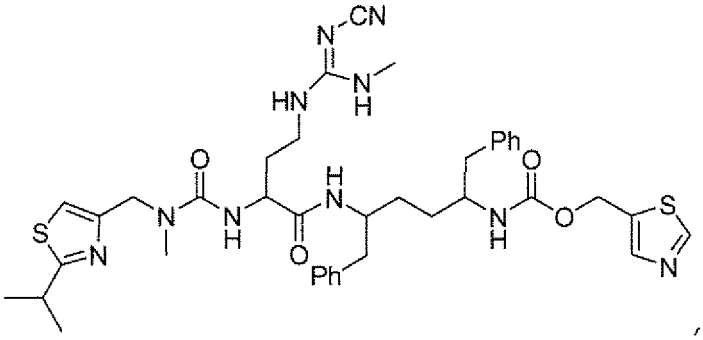

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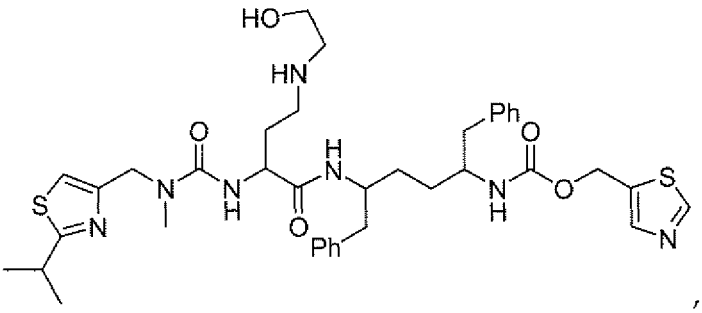

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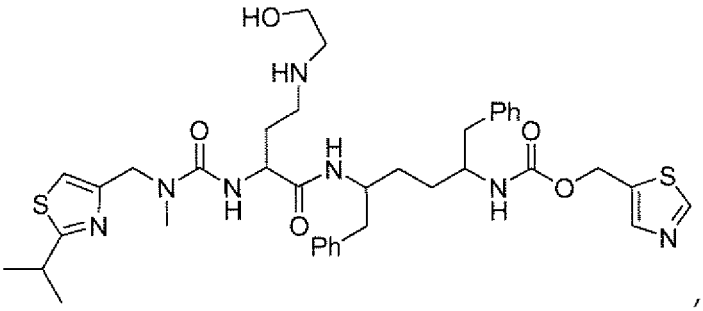

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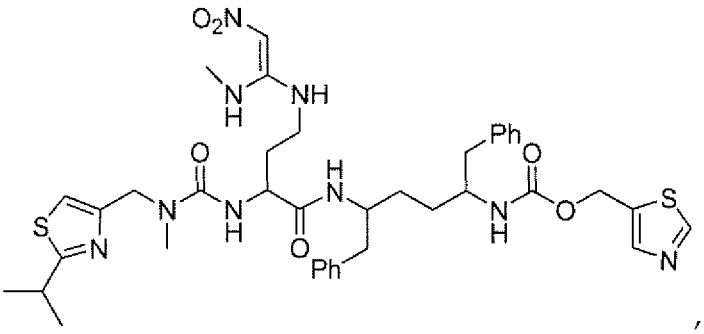

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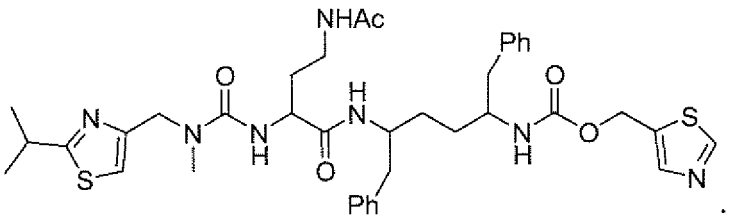
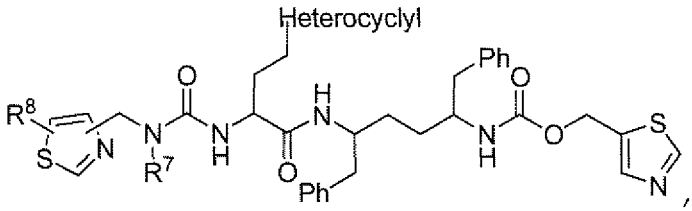


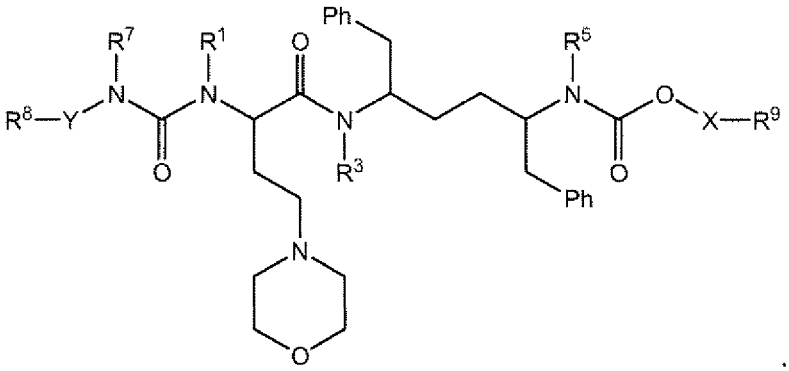
.

In other embodiments, the compounds of Formula IV have the following general formula:



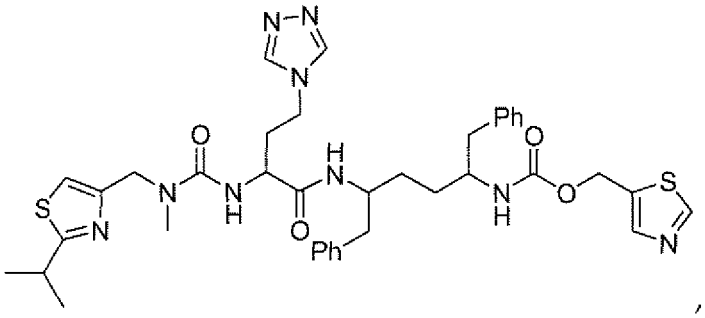
, wherein said "Heterocyclyl" is substituted or unsubstituted. In a particular embodiment, said "Heterocyclyl" is a substituted or unsubstituted heteroaryl, for example, and of the heteroaryls described herein. In other embodiments, said "Heterocyclyl" is a substituted or unsubstituted heterocycloalkyl, including any heterocycloalkyl described herein. In a particular embodiment, the heterocyclyl is unsubstituted morpholinyl. In a more specific particular embodiment, the heterocyclyl is unsubstituted morpholinyl and R^8 is alkyl.

In other embodiments, the compounds of Formula IV have the following general formula:



. In a particular embodiment of the compounds of the above general formula, X and Y are both heteroarylalkyl.

In other specific embodiments, the compounds of Formula IV have the following structures:



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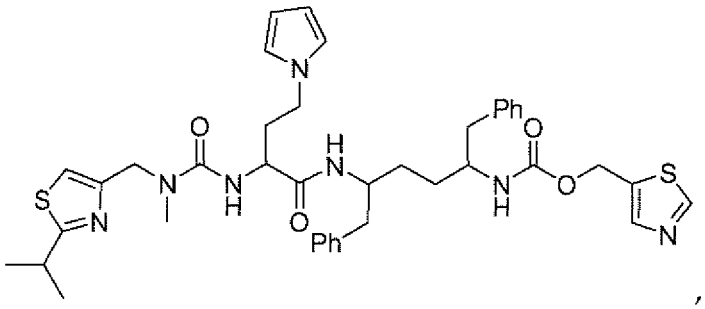

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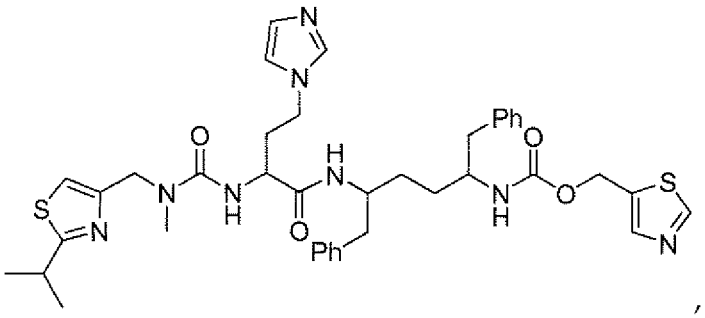

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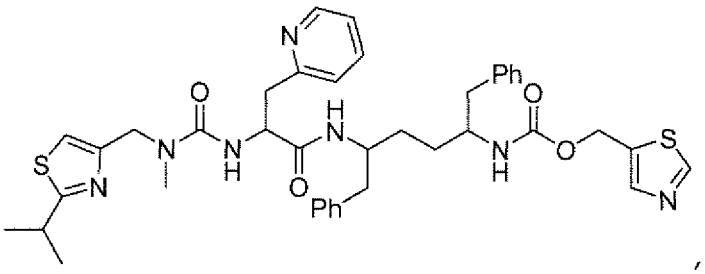

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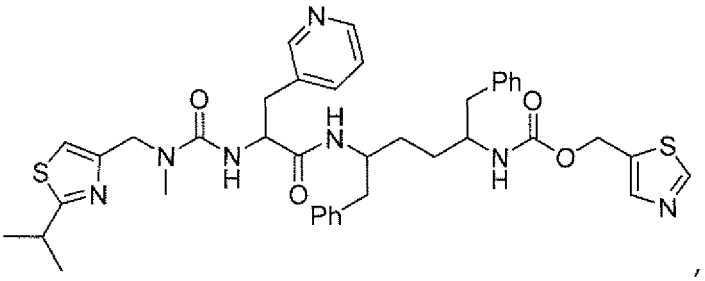

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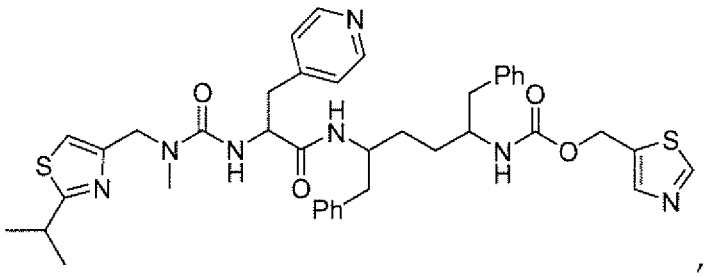

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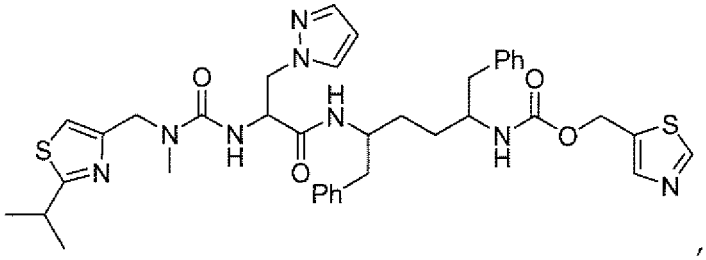

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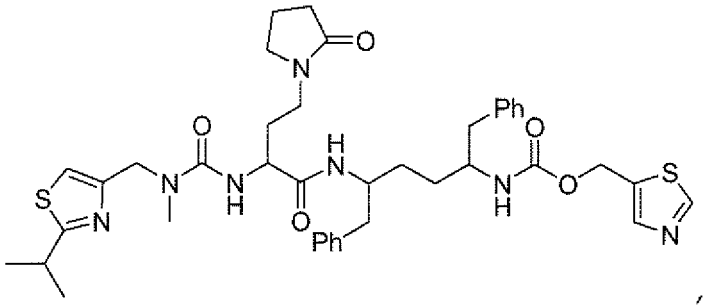

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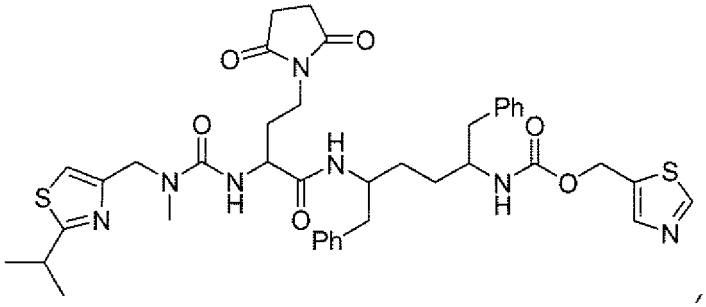

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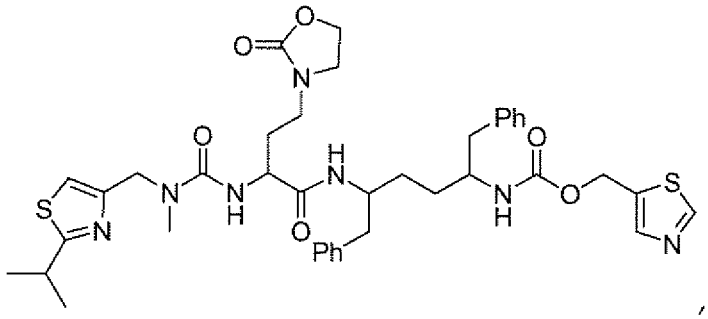

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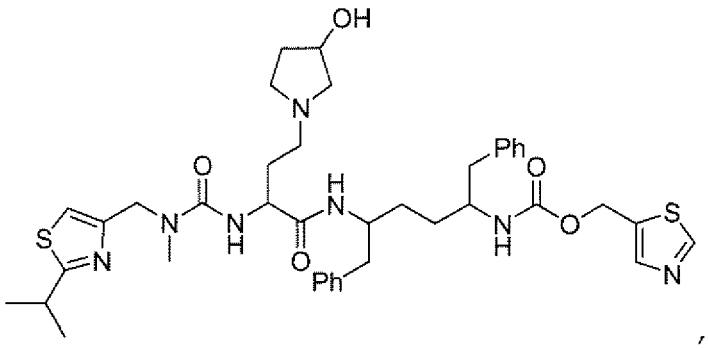

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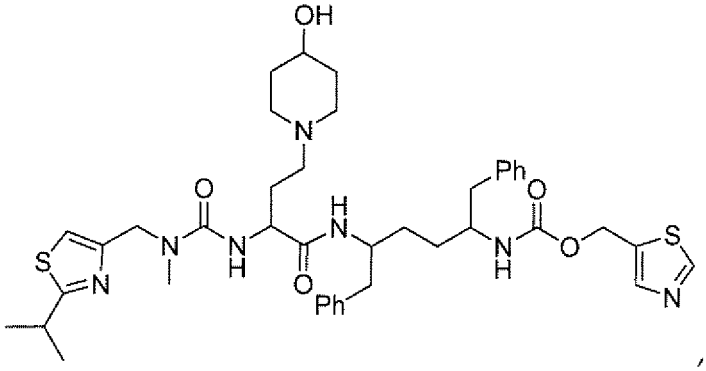

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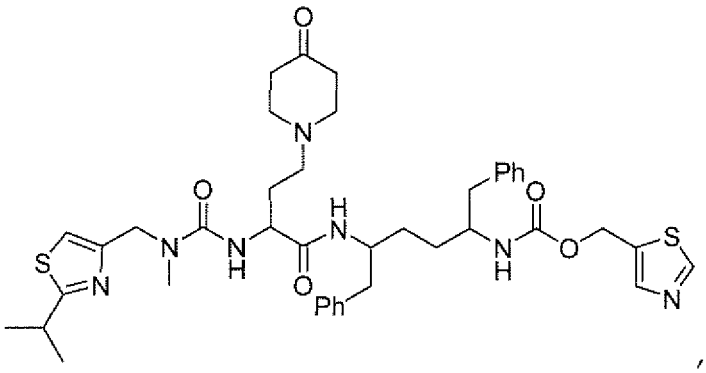

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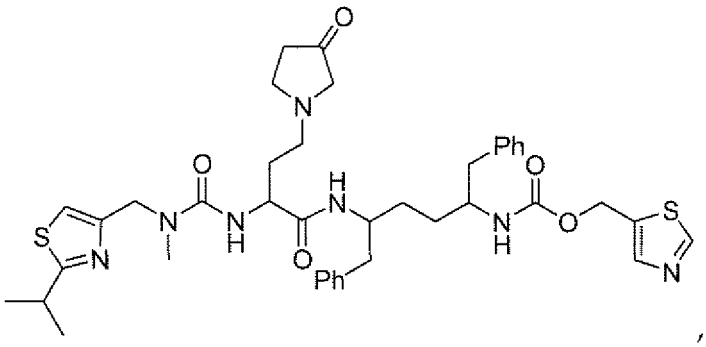

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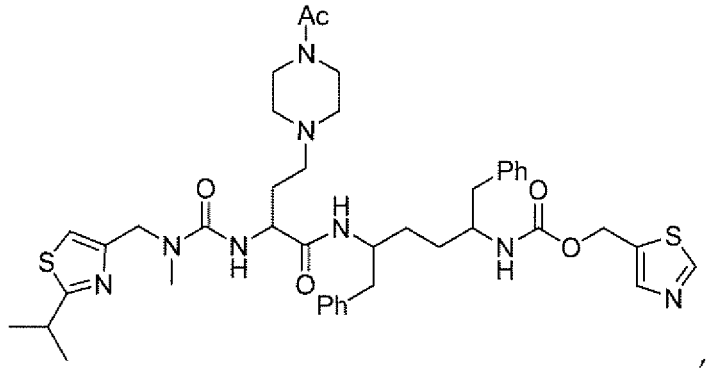

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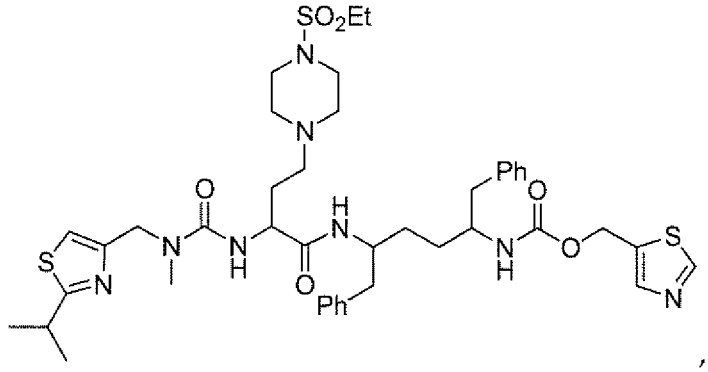

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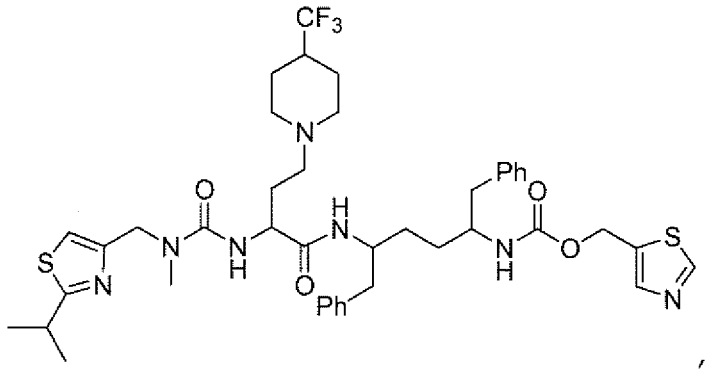

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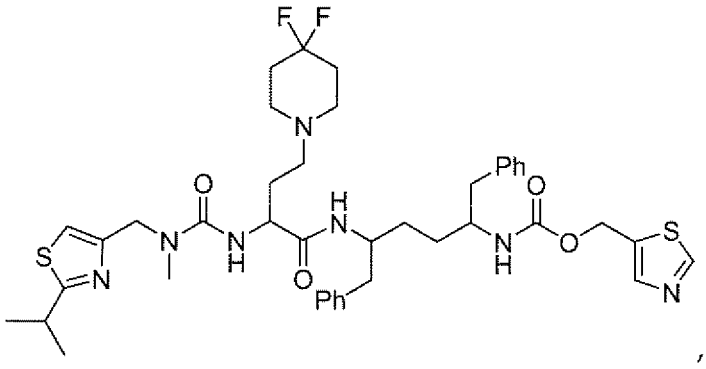

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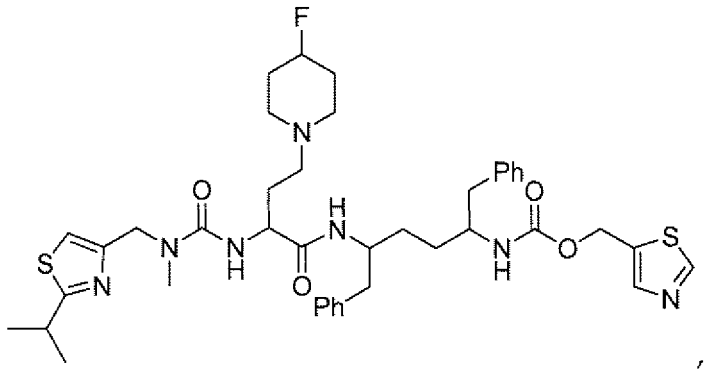

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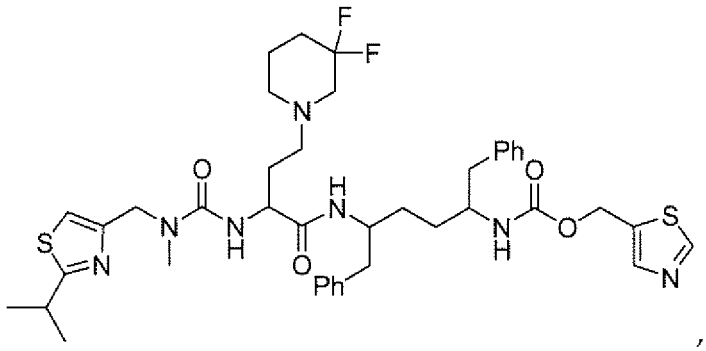

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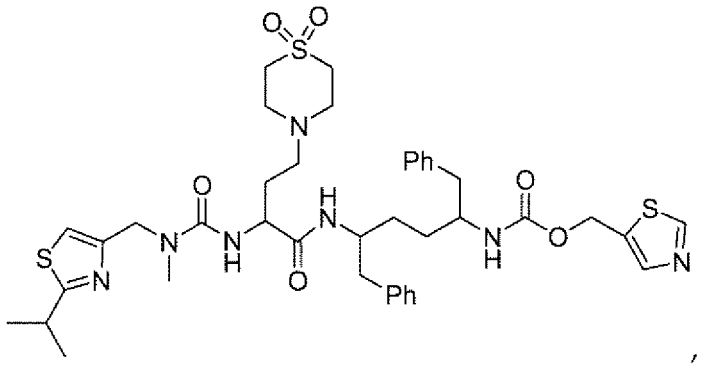

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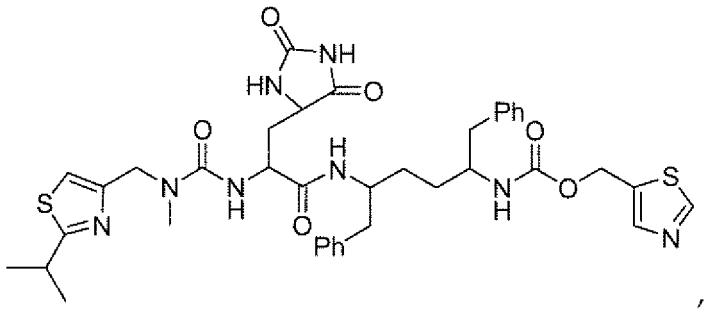

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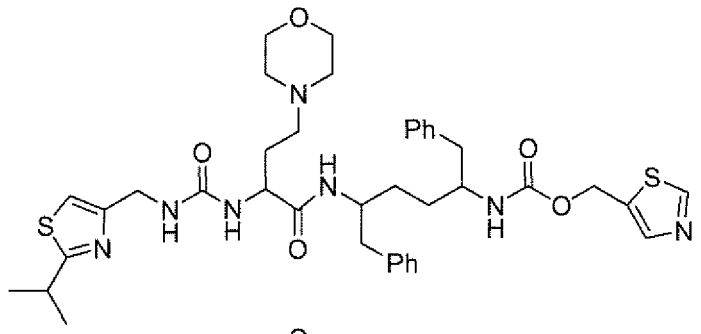

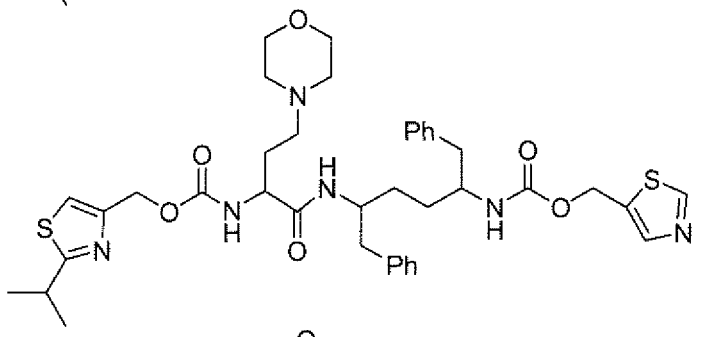

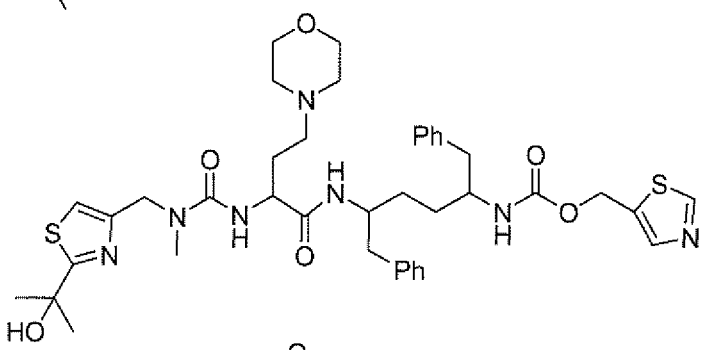

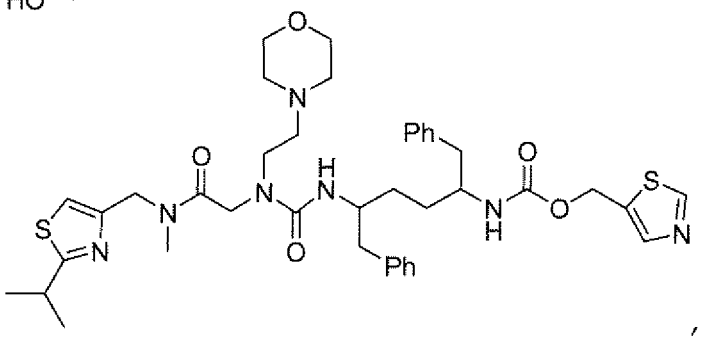

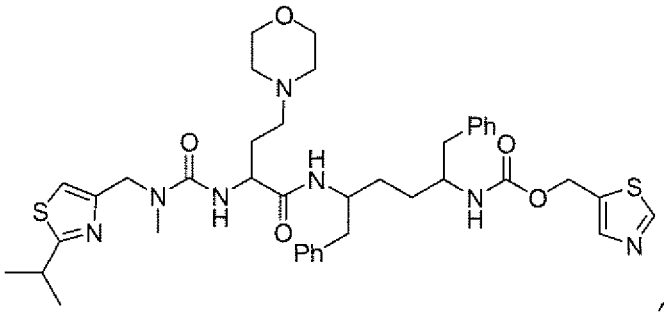

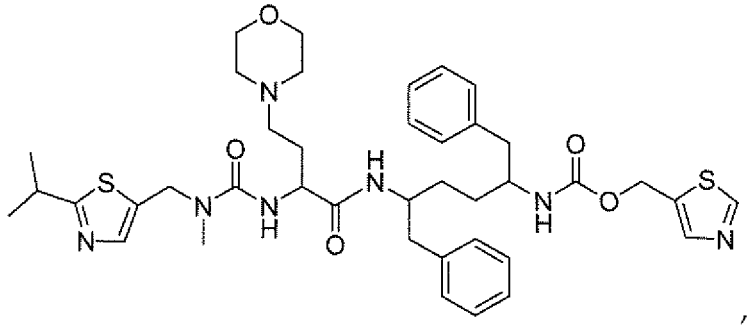

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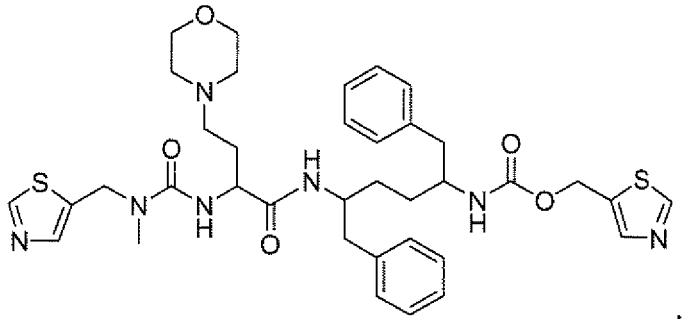
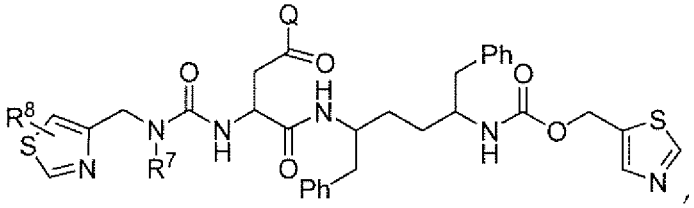


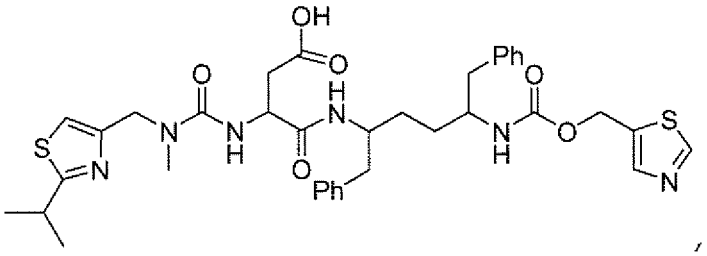
.

In other embodiments, the compounds of Formula IV have the following general formula:



,

wherein Q is –OH or -N(R^a)$_2$. In a particular embodiment, Q is –OH. In another particular embodiment, Q is -N(R^a)$_2$. In yet another particular embodiment, Q is –NH-pyridyl, -NH-pyrrolyl, or –NH-S(O_2)-alkyl. In other specific embodiments, the compounds of the above general formula have the following structures:



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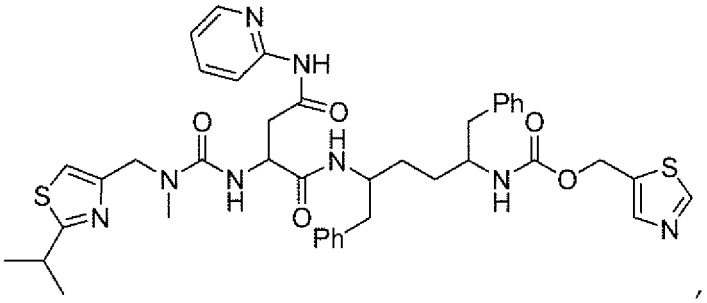

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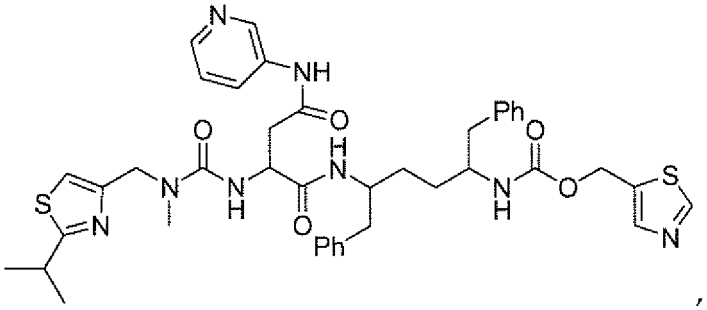

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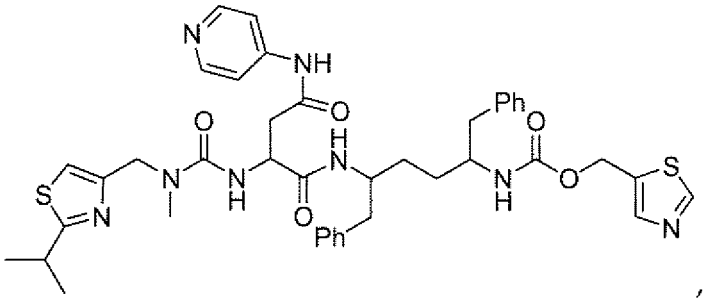

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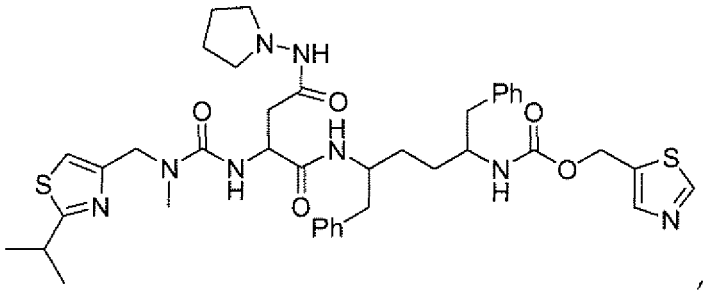

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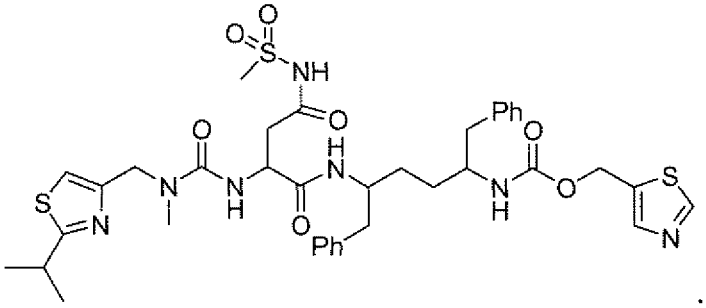
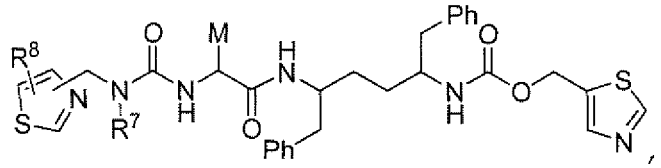


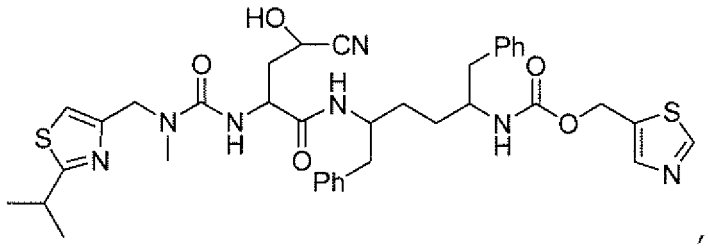
.

In other embodiments, the compounds of Formula IV have the following general formula:



,

wherein M is substituted or unsubstituted alkyl. In particular embodiments, M is a substituted alkyl, for example hydroxyalkyl, substituted hydroxyalkyl, cyanoalkyl, substituted cyanoalkyl, and trialkylsiloxyalkyl. In other particular embodiments, the compounds of the above general formula have the following structures:



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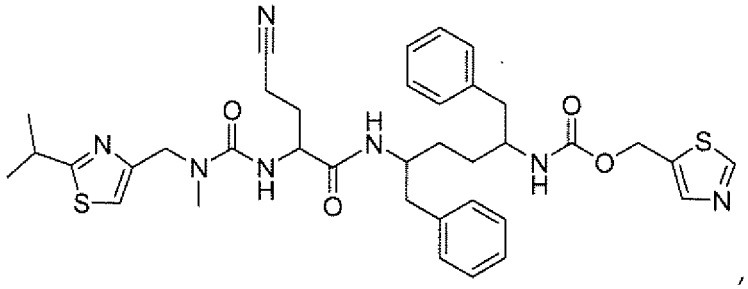

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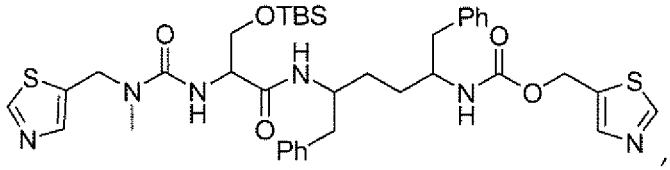

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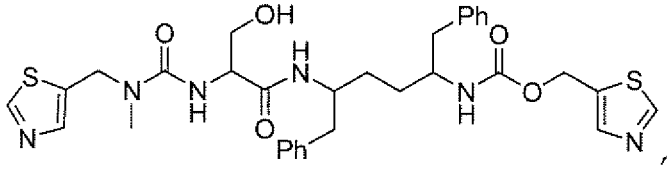

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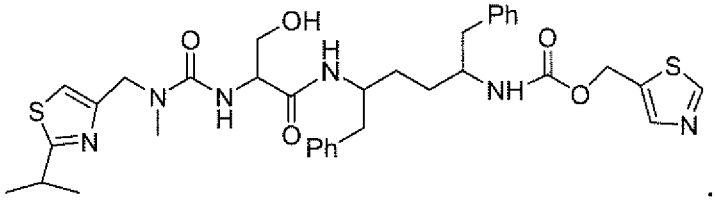
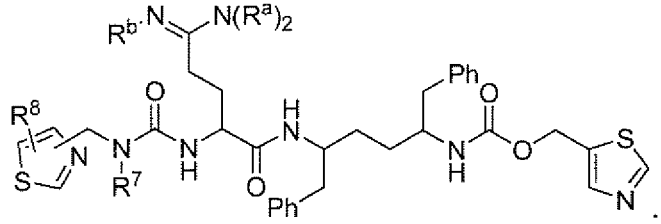
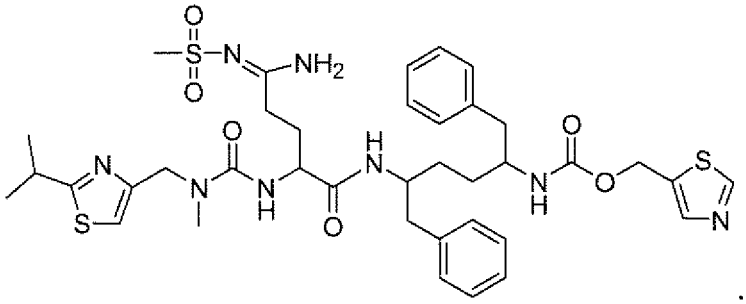


.

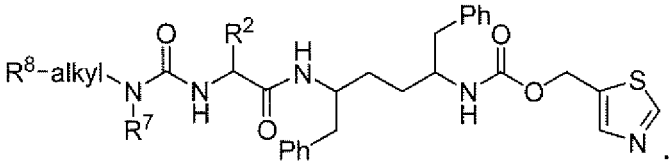
In still other embodiments, the compounds of Formula IV have the following general formula:



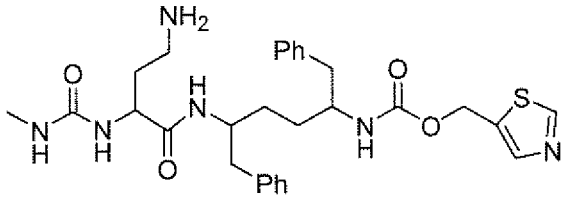
. In particular embodiments, a compound of the above general formula has the following structure:



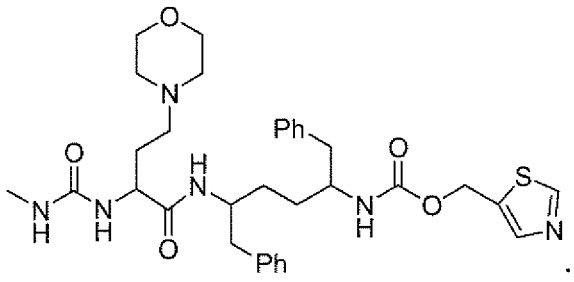
In still other embodiments of the compounds of Formula IV, Y is alkyl. In particular embodiments, such compounds have the following general formula:



. In specific embodiments, R^8-Y- is alkyl, for example any alkyl described herein. In a particular embodiment, R^8-Y- is methyl. Specific particular embodiments of the above general structure include the following structures:

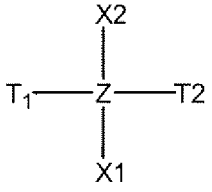


and



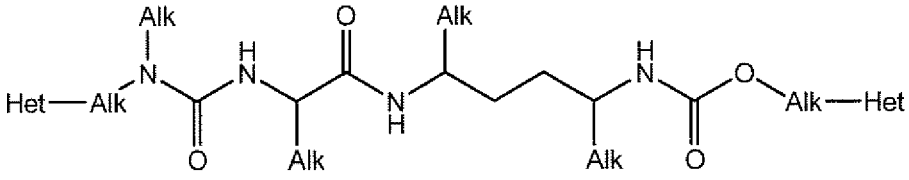
.

In still yet another embodiment, the compounds of Formula I are named below in tabular format (Table 6) as compounds of general Formula II:



Formula II.

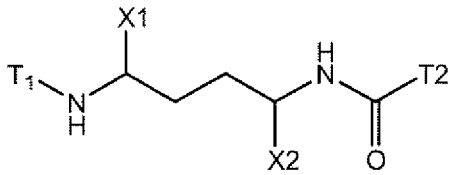
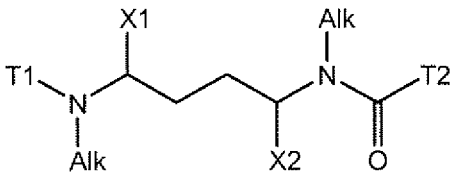
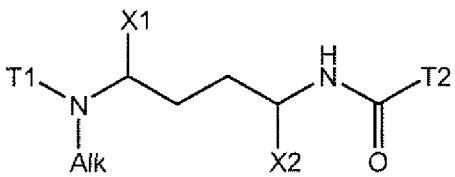
Compounds of general formula II are depicted as a "core" structure (Z) substituted with four moieties T1, T2, X1 and X2. The core structures Z are depicted in Table 1. The points of attachment of T1, T2, X1 and X2 are indicated on each of the core structures depicted in Table 1. Tables 2-5, respectively, show the structures of the T1, T2, X1 and X2 moieties. The point of attachment of the core structure Z is indicated in each of the structures of T1, T2, X1 and X2. Each core structure Z in Table 1, and each substituent T1, T2, X1 and X2 and Tables 2-5 is represented by a "code" comprising a letter and a number. Each structure of a compound of Formula II can be designated in tabular form by combining the "code" representing each structural moiety using the following syntax: Z.T1.T2.X1.X2. Thus, for example, Z1.T1A.T2B.X1A.X2A represents the following structure:



In the structures depicted in Tables 1-5, the term "Alk" means a substituted or unsubstituted alkyl, cycloalkyl, or alkylene group, wherein the terms "alkyl", "cycloalkyl", and "alkylene" are as defined herein. "Alk" means an alkyl or cycloalkyl group when depicted as monovalent, and an alkylene group when depicted as divalent. "Het" is a substituted or unsubstituted heterocyclyl or heterocyclylene group, wherein the term "heterocyclyl" is as defined herein, and the term "heterocyclylene" means a heterocyclyl group as defined herein, in which a hydrogen atom has been replaced by an open valence (in analogy to alkylene), thereby defining a divalent heterocyclyl. "Het" is a heterocyclyl when depicted as monovalent, and heterocyclylene when depicted as divalent. "Ar" is a substitute or unsubstituted aryl or arylene group, wherein the term "aryl" is as

defined herein, and the term "arylene" means an aryl group as defined herein, in which a hydrogen atom has been replaced by an open valence (in analogy to alkylene), thereby defining a divalent aryl. "Ar" is aryl when depicted as monovalent, and arylene when depicted as divalent. When substituted, "Alk", "Het", and "Ar" can be substituted with any of the substituents defined or exemplified herein. For example, substituents of "Alk" can include ether, halogen, -OH, amide, amine, etc., substituents of "Het" can include alkyl, aryl, carbonyl, -OH, halogen, and substituents of "Ar" can include alkyl, aryl, -OH, halogen, etc., with the proviso that the resulting structure is chemically reasonable, and would provide compounds which are sufficiently stable for formulation in a pharmaceutically acceptable composition. When a structure or substructure shown in the tables below contains more than one "Alk", "Het" or "Ar" group, these groups are independently selected and can be the same or different. So, for example, each of the "Alk" groups of substructure T1A are independently selected and may be the same or different.

Table 1: Core Structures

Code	Core Structure
Z1	
Z2	
Z3	

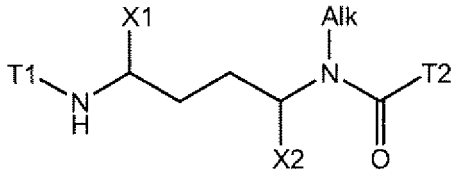
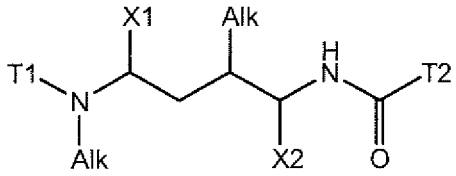
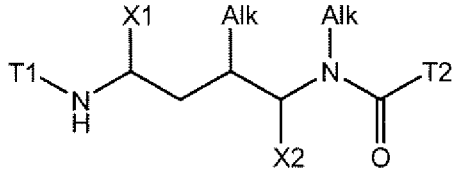
Code	Core Structure
Z4	
Z5	
Z6	

Table 2: T1 Structures

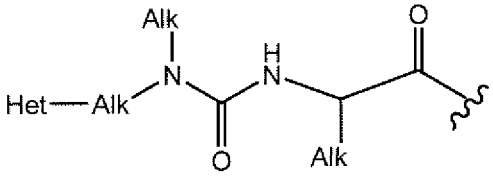
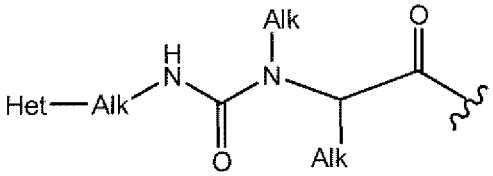
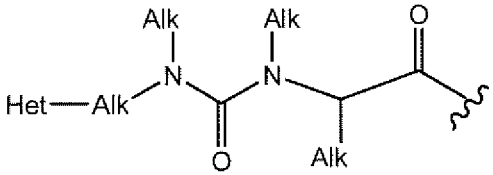
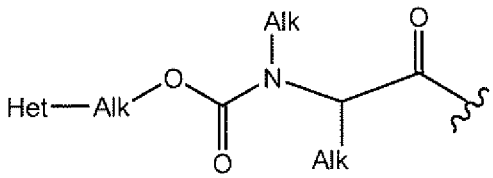
Code	T1 Structure
T1A	
T1B	
T1C	
T1D	

Table 3: T2 Structures

Code	T2 Structure
T2A	-O-Alk-Het
T2B	-NH-Alk-Het
T2C	-N(Alk)-Alk-Het
T2D	-N(Alk)-Het

Table 4: X1 Structures

Code	X1 Structure
X1A	-Alk
X1B	-Alk-Ar
X1C	-Alk-Het
X1D	-Alk-Ar-O-Alk-Ar
X1E	-Alk-Ar-O-Alk-Het

Table 5: X2 Structures

Code	X2 Structure
X2A	-Alk
X2B	-Alk-Ar
X2C	-Alk-Het
X2D	-Alk-Ar-O-Alk-Ar
X2E	-Alk-Ar-O-Alk-Het

Table 6: List of Compound Structures of Formula II

Z1.T1A.T2A.X1A.X2A, Z2.T1A.T2A.X1A.X2A, Z3.T1A.T2A.X1A.X2A,
Z4.T1A.T2A.X1A.X2A, Z5.T1A.T2A.X1A.X2A, Z6.T1A.T2A.X1A.X2A,
Z1.T1B.T2A.X1A.X2A, Z2.T1B.T2A.X1A.X2A, Z3.T1B.T2A.X1A.X2A,
Z4.T1B.T2A.X1A.X2A, Z5.T1B.T2A.X1A.X2A, Z6.T1B.T2A.X1A.X2A,
Z1.T1C.T2A.X1A.X2A, Z2.T1C.T2A.X1A.X2A, Z3.T1C.T2A.X1A.X2A,
Z4.T1C.T2A.X1A.X2A, Z5.T1C.T2A.X1A.X2A, Z6.T1C.T2A.X1A.X2A,
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Z1.T1B.T2D.X1C.X2E, Z2.T1B.T2D.X1C.X2E, Z3.T1B.T2D.X1C.X2E,
Z4.T1B.T2D.X1C.X2E, Z5.T1B.T2D.X1C.X2E, Z6.T1B.T2D.X1C.X2E,
Z1.T1C.T2D.X1C.X2E, Z2.T1C.T2D.X1C.X2E, Z3.T1C.T2D.X1C.X2E,
Z4.T1C.T2D.X1C.X2E, Z5.T1C.T2D.X1C.X2E, Z6.T1C.T2D.X1C.X2E,
Z1.T1D.T2D.X1C.X2E, Z2.T1D.T2D.X1C.X2E, Z3.T1D.T2D.X1C.X2E,
Z4.T1D.T2D.X1C.X2E, Z5.T1D.T2D.X1C.X2E, Z6.T1D.T2D.X1C.X2E,
Z1.T1A.T2A.X1D.X2E, Z2.T1A.T2A.X1D.X2E, Z3.T1A.T2A.X1D.X2E,
Z4.T1A.T2A.X1D.X2E, Z5.T1A.T2A.X1D.X2E, Z6.T1A.T2A.X1D.X2E,
Z1.T1B.T2A.X1D.X2E, Z2.T1B.T2A.X1D.X2E, Z3.T1B.T2A.X1D.X2E,
Z4.T1B.T2A.X1D.X2E, Z5.T1B.T2A.X1D.X2E, Z6.T1B.T2A.X1D.X2E,
Z1.T1C.T2A.X1D.X2E, Z2.T1C.T2A.X1D.X2E, Z3.T1C.T2A.X1D.X2E,
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Z4.T1D.T2A.X1D.X2E, Z5.T1D.T2A.X1D.X2E, Z6.T1D.T2A.X1D.X2E,
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Z4.T1A.T2B.X1D.X2E, Z5.T1A.T2B.X1D.X2E, Z6.T1A.T2B.X1D.X2E,
Z1.T1B.T2B.X1D.X2E, Z2.T1B.T2B.X1D.X2E, Z3.T1B.T2B.X1D.X2E,
Z4.T1B.T2B.X1D.X2E, Z5.T1B.T2B.X1D.X2E, Z6.T1B.T2B.X1D.X2E,
Z1.T1C.T2B.X1D.X2E, Z2.T1C.T2B.X1D.X2E, Z3.T1C.T2B.X1D.X2E,
Z4.T1C.T2B.X1D.X2E, Z5.T1C.T2B.X1D.X2E, Z6.T1C.T2B.X1D.X2E,
Z1.T1D.T2B.X1D.X2E, Z2.T1D.T2B.X1D.X2E, Z3.T1D.T2B.X1D.X2E,
Z4.T1D.T2B.X1D.X2E, Z5.T1D.T2B.X1D.X2E, Z6.T1D.T2B.X1D.X2E,
Z1.T1A.T2C.X1D.X2E, Z2.T1A.T2C.X1D.X2E, Z3.T1A.T2C.X1D.X2E,
Z4.T1A.T2C.X1D.X2E, Z5.T1A.T2C.X1D.X2E, Z6.T1A.T2C.X1D.X2E,

Z1.T1B.T2C.X1D.X2E, Z2.T1B.T2C.X1D.X2E, Z3.T1B.T2C.X1D.X2E,

Z4.T1B.T2C.X1D.X2E, Z5.T1B.T2C.X1D.X2E, Z6.T1B.T2C.X1D.X2E,

Z1.T1C.T2C.X1D.X2E, Z2.T1C.T2C.X1D.X2E, Z3.T1C.T2C.X1D.X2E,

Z4.T1C.T2C.X1D.X2E, Z5.T1C.T2C.X1D.X2E, Z6.T1C.T2C.X1D.X2E,

Z1.T1D.T2C.X1D.X2E, Z2.T1D.T2C.X1D.X2E, Z3.T1D.T2C.X1D.X2E,

Z4.T1D.T2C.X1D.X2E, Z5.T1D.T2C.X1D.X2E, Z6.T1D.T2C.X1D.X2E,

Z1.T1A.T2D.X1D.X2E, Z2.T1A.T2D.X1D.X2E, Z3.T1A.T2D.X1D.X2E,

Z4.T1A.T2D.X1D.X2E, Z5.T1A.T2D.X1D.X2E, Z6.T1A.T2D.X1D.X2E,

Z1.T1B.T2D.X1D.X2E, Z2.T1B.T2D.X1D.X2E, Z3.T1B.T2D.X1D.X2E,

Z4.T1B.T2D.X1D.X2E, Z5.T1B.T2D.X1D.X2E, Z6.T1B.T2D.X1D.X2E,

Z1.T1C.T2D.X1D.X2E, Z2.T1C.T2D.X1D.X2E, Z3.T1C.T2D.X1D.X2E,

Z4.T1C.T2D.X1D.X2E, Z5.T1C.T2D.X1D.X2E, Z6.T1C.T2D.X1D.X2E,

Z1.T1D.T2D.X1D.X2E, Z2.T1D.T2D.X1D.X2E, Z3.T1D.T2D.X1D.X2E,

Z4.T1D.T2D.X1D.X2E, Z5.T1D.T2D.X1D.X2E, Z6.T1D.T2D.X1D.X2E,

Z1.T1A.T2A.X1E.X2E, Z2.T1A.T2A.X1E.X2E, Z3.T1A.T2A.X1E.X2E,

Z4.T1A.T2A.X1E.X2E, Z5.T1A.T2A.X1E.X2E, Z6.T1A.T2A.X1E.X2E,

Z1.T1B.T2A.X1E.X2E, Z2.T1B.T2A.X1E.X2E, Z3.T1B.T2A.X1E.X2E,

Z4.T1B.T2A.X1E.X2E, Z5.T1B.T2A.X1E.X2E, Z6.T1B.T2A.X1E.X2E,

Z1.T1C.T2A.X1E.X2E, Z2.T1C.T2A.X1E.X2E, Z3.T1C.T2A.X1E.X2E,

Z4.T1C.T2A.X1E.X2E, Z5.T1C.T2A.X1E.X2E, Z6.T1C.T2A.X1E.X2E,

Z1.T1D.T2A.X1E.X2E, Z2.T1D.T2A.X1E.X2E, Z3.T1D.T2A.X1E.X2E,

Z4.T1D.T2A.X1E.X2E, Z5.T1D.T2A.X1E.X2E, Z6.T1D.T2A.X1E.X2E,

Z1.T1A.T2B.X1E.X2E, Z2.T1A.T2B.X1E.X2E, Z3.T1A.T2B.X1E.X2E,

Z4.T1A.T2B.X1E.X2E, Z5.T1A.T2B.X1E.X2E, Z6.T1A.T2B.X1E.X2E,

Z1.T1B.T2B.X1E.X2E, Z2.T1B.T2B.X1E.X2E, Z3.T1B.T2B.X1E.X2E,

Z4.T1B.T2B.X1E.X2E, Z5.T1B.T2B.X1E.X2E, Z6.T1B.T2B.X1E.X2E,

Z1.T1C.T2B.X1E.X2E, Z2.T1C.T2B.X1E.X2E, Z3.T1C.T2B.X1E.X2E,

Z4.T1C.T2B.X1E.X2E, Z5.T1C.T2B.X1E.X2E, Z6.T1C.T2B.X1E.X2E,

Z1.T1D.T2B.X1E.X2E, Z2.T1D.T2B.X1E.X2E, Z3.T1D.T2B.X1E.X2E,

Z4.T1D.T2B.X1E.X2E, Z5.T1D.T2B.X1E.X2E, Z6.T1D.T2B.X1E.X2E,

Z1.T1A.T2C.X1E.X2E, Z2.T1A.T2C.X1E.X2E, Z3.T1A.T2C.X1E.X2E,

Z4.T1A.T2C.X1E.X2E, Z5.T1A.T2C.X1E.X2E, Z6.T1A.T2C.X1E.X2E,

Z1.T1B.T2C.X1E.X2E, Z2.T1B.T2C.X1E.X2E, Z3.T1B.T2C.X1E.X2E,

Z4.T1B.T2C.X1E.X2E, Z5.T1B.T2C.X1E.X2E, Z6.T1B.T2C.X1E.X2E,

Z1.T1C.T2C.X1E.X2E, Z2.T1C.T2C.X1E.X2E, Z3.T1C.T2C.X1E.X2E,

Z4.T1C.T2C.X1E.X2E, Z5.T1C.T2C.X1E.X2E, Z6.T1C.T2C.X1E.X2E,

Z1.T1D.T2C.X1E.X2E, Z2.T1D.T2C.X1E.X2E, Z3.T1D.T2C.X1E.X2E,

Z4.T1D.T2C.X1E.X2E, Z5.T1D.T2C.X1E.X2E, Z6.T1D.T2C.X1E.X2E,

Z1.T1A.T2D.X1E.X2E, Z2.T1A.T2D.X1E.X2E, Z3.T1A.T2D.X1E.X2E,

Z4.T1A.T2D.X1E.X2E, Z5.T1A.T2D.X1E.X2E, Z6.T1A.T2D.X1E.X2E,

Z1.T1B.T2D.X1E.X2E, Z2.T1B.T2D.X1E.X2E, Z3.T1B.T2D.X1E.X2E,

Z4.T1B.T2D.X1E.X2E, Z5.T1B.T2D.X1E.X2E, Z6.T1B.T2D.X1E.X2E,

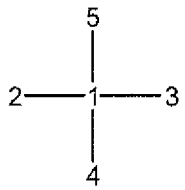
Z1.T1C.T2D.X1E.X2E, Z2.T1C.T2D.X1E.X2E, Z3.T1C.T2D.X1E.X2E,

Z4.T1C.T2D.X1E.X2E, Z5.T1C.T2D.X1E.X2E, Z6.T1C.T2D.X1E.X2E,

Z1.T1D.T2D.X1E.X2E, Z2.T1D.T2D.X1E.X2E, Z3.T1D.T2D.X1E.X2E,

Z4.T1D.T2D.X1E.X2E, Z5.T1D.T2D.X1E.X2E, and Z6.T1D.T2D.X1E.X2E.

In still another embodiment, selected compounds of Formula I are named below in tabular format (Table 12) as compounds of general Formula III (below):



Formula III

where 1, 2, 3, 4 and 5 are defined in Tables 7-11, below. Each compound is designated in tabular form by combining the "code" representing each structural moiety using the following syntax: 1.2.3.4.5. Thus, for example, 1a.2a.3a.4a.5a represents the following structure:

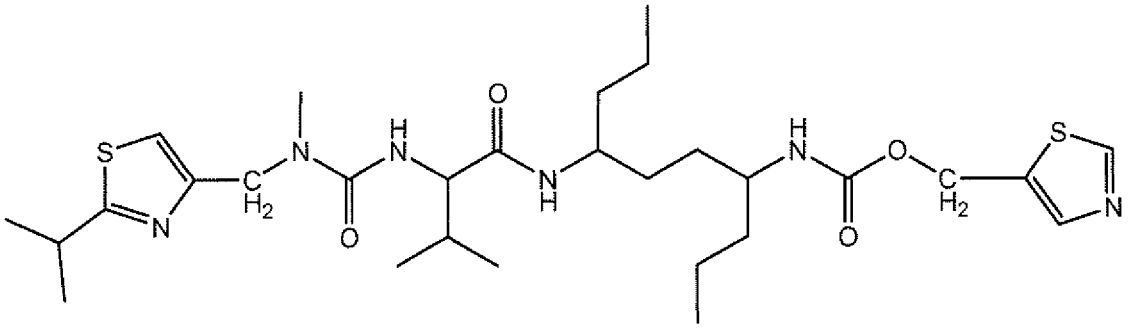
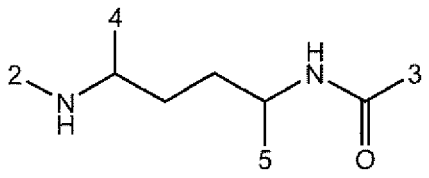
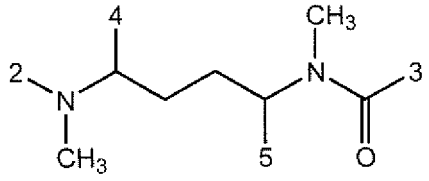
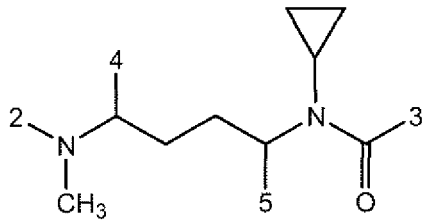
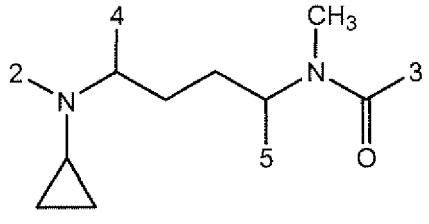
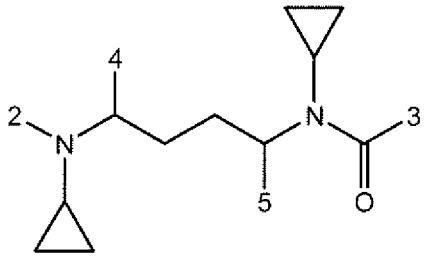
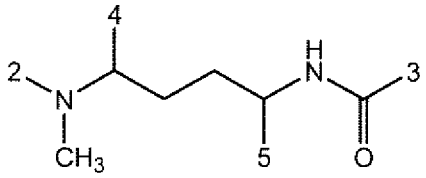
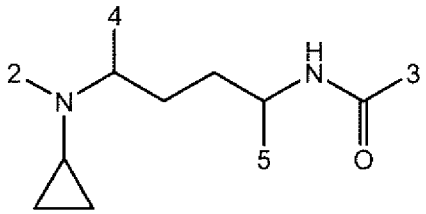
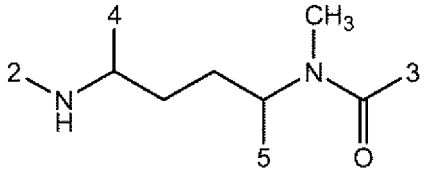
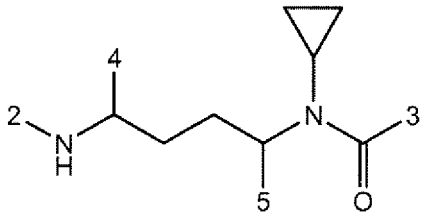
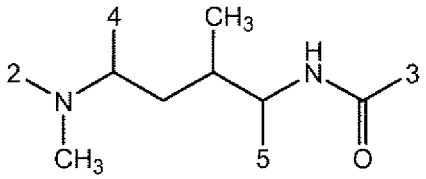
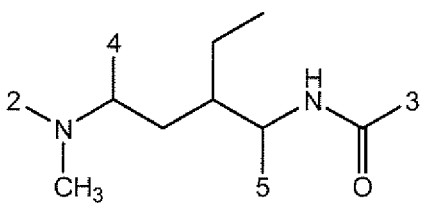
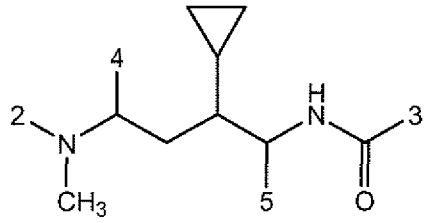
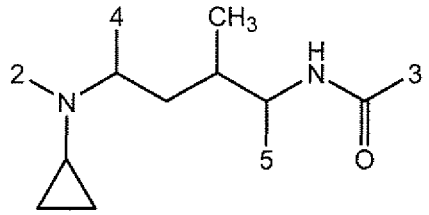
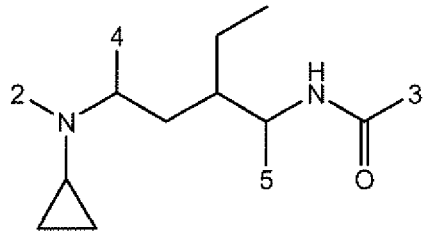
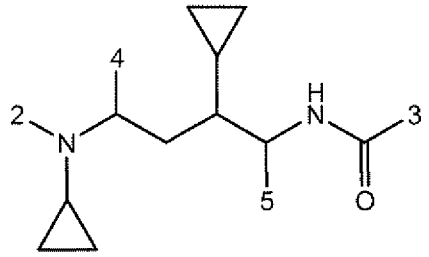
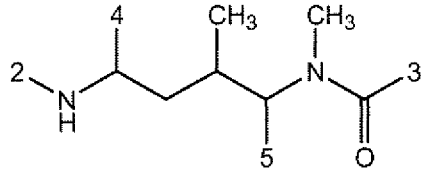
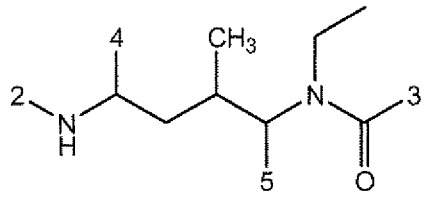


Table 7: "1" Structures

Code	"1" Structure
1a	
1b	
1c	
1d	

Code	"1" Structure
1e	
1f	
1g	
1h	
1i	
1j	
1k	

Code	"1" Structure
1l	
1m	
1n	
1o	
1p	
1q	

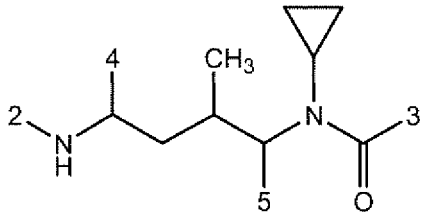
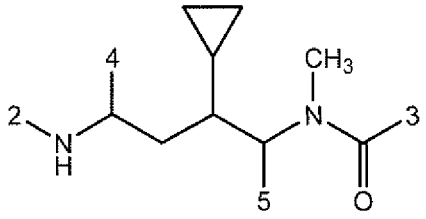
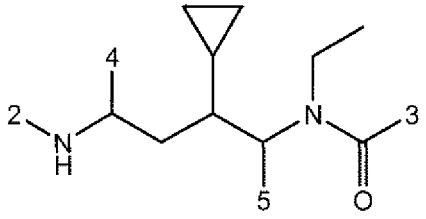
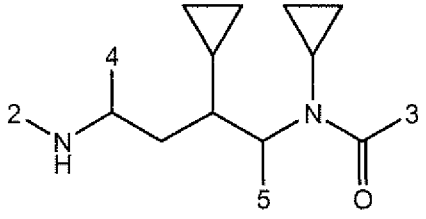
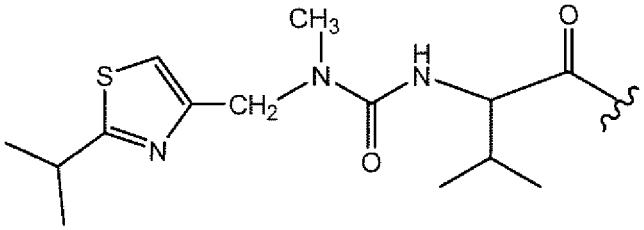
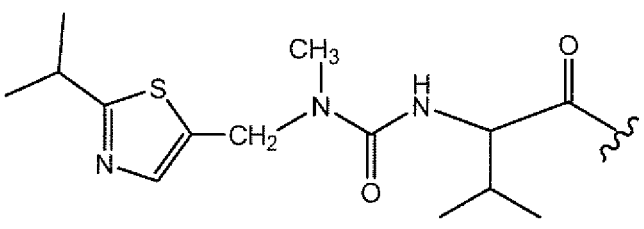
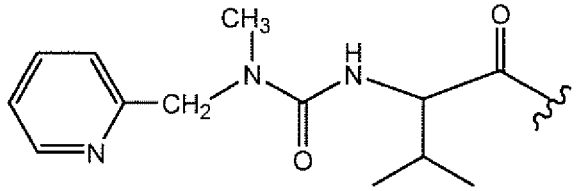
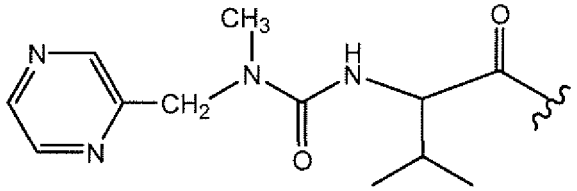
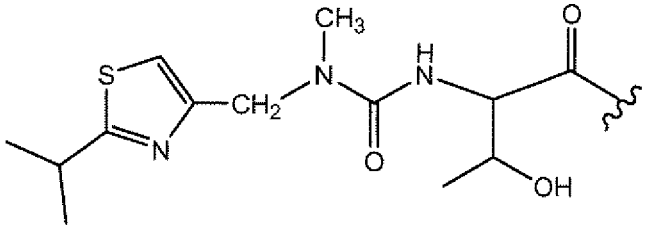
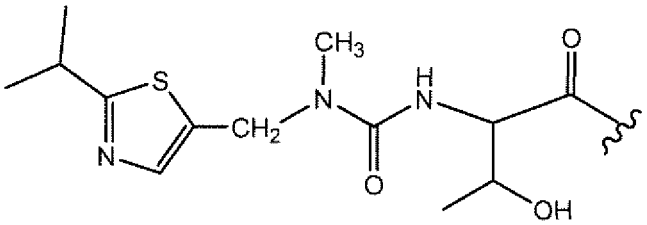
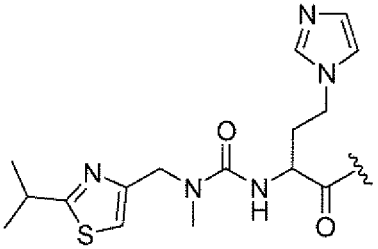
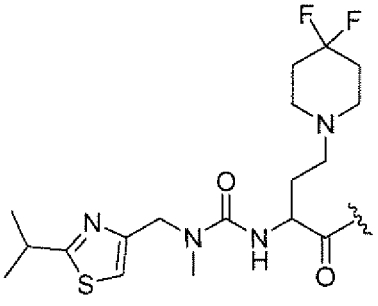
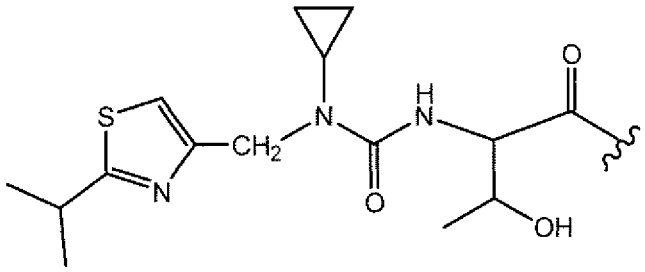
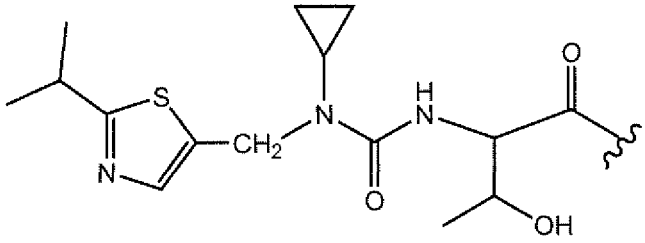
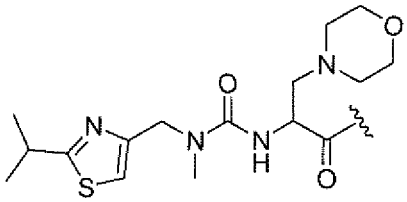
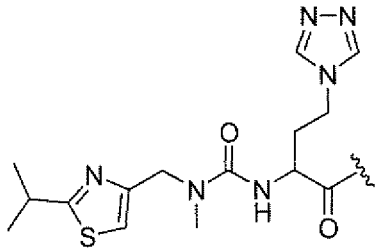
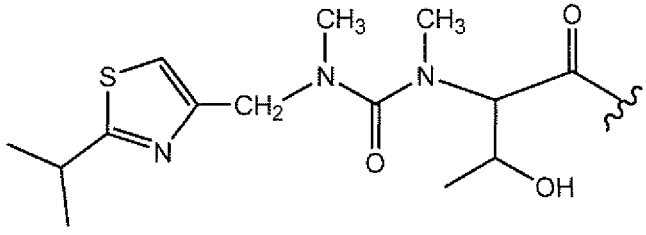
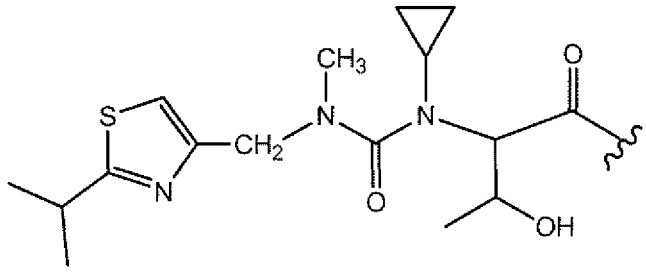
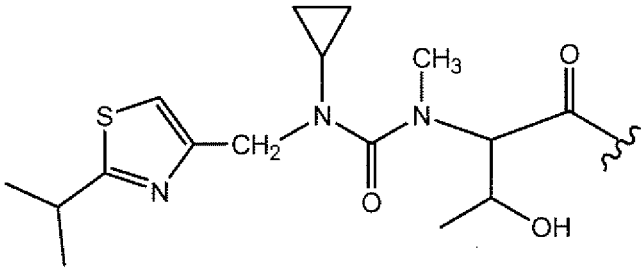
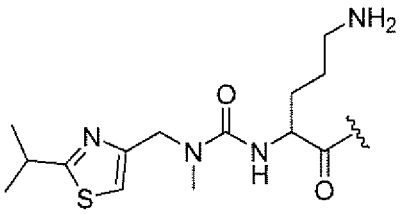
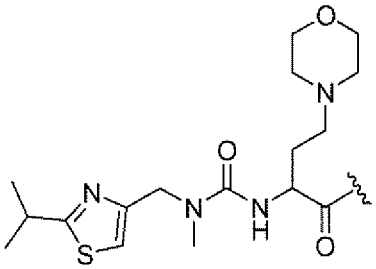
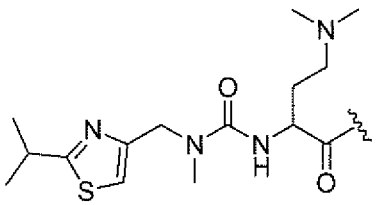
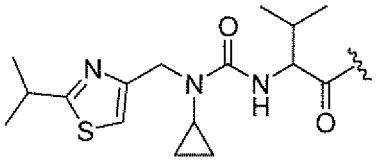
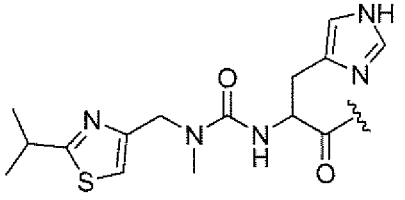
Code	"1" Structure
1r	
1s	
1t	
1u	

Table 8: "2" Structures

Code	"2" Structure
2a	
2b	

Code	"2" Structure
2c	
2d	
2e	
2f	
2g	
2h	

Code	"2" Structure
2i	
2j	
2k	
2l	
2m	
2n	

Code	"2" Structure
2o	
2p	
2q	
2r	
2s	
2t	

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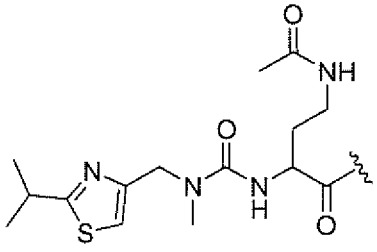
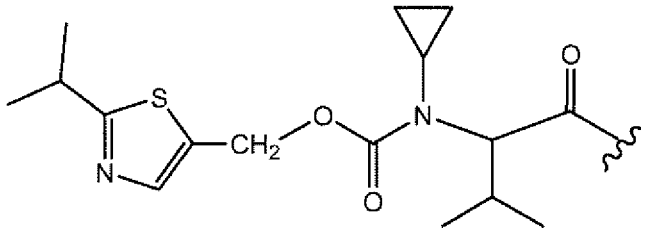
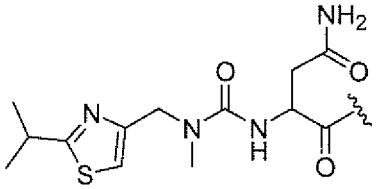
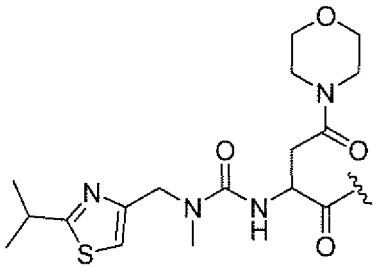
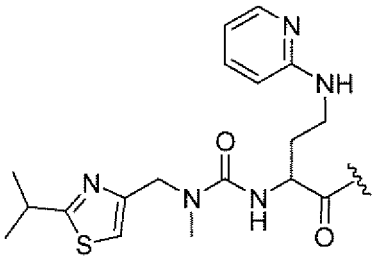
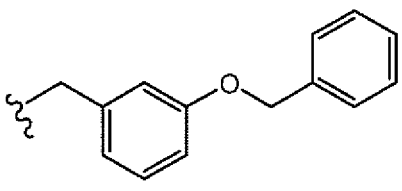
2u	
2v	
2w	
2x	
2y	

Table 9: "3" Structures

Code	"3" Structure
3a	-O-CH_2-(5-thiazolyl)
3b	-O-CH_2-(3-pyridyl)

Code	"3" Structure
3c	-NH-CH_2-(5-thiazolyl)
3d	-NH-CH_2-(3-pyridyl)
3e	-N(CH_3)-CH_2-(5-thiazolyl)
3f	-N(CH_3)-CH_2-(3-pyridyl)
3g	-N(CH_3)-(5-thiazolyl)
3h	-N(CH_3)-(3-pyridyl)

Table 10: "4" Structures

Code	"4" Structure
4a	n-propyl
4b	i-butyl
4c	-CH_2-cyclohexyl
4d	-CH_2-phenyl
4e	-CH_2-(4-methoxyphenyl)
4f	-CH_2-(3-fluorophenyl)
4g	-CH_2-(4-pyridyl)
4h	-CH_2-(3-pyridyl)
4i	-CH_2-(2-pyridyl)
4j	-CH_2CH_2-(4-morpholinyl)
4k	

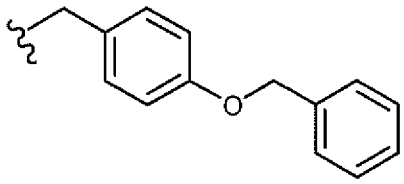
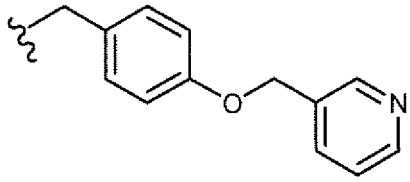
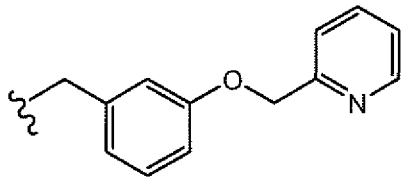
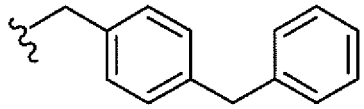
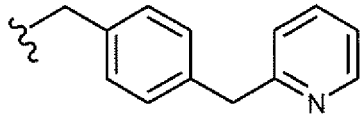
Code	"4" Structure
4l	
4m	
4n	
4o	
4p	

Table 11: "5" Structures

Code	"5" Structure
5a	n-propyl
5b	i-butyl
5c	-CH_2-cyclohexyl
5d	-CH_2-phenyl
5e	-CH_2-(4-methoxyphenyl)
5f	-CH_2-(3-fluorophenyl)
5g	-CH_2-(4-pyridyl)
5h	-CH_2-(3-pyridyl)

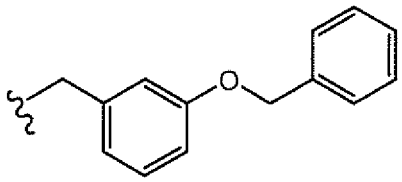
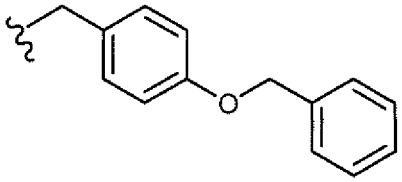
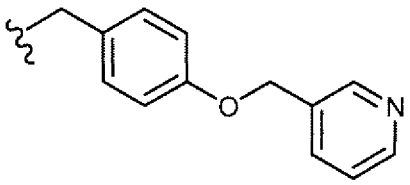
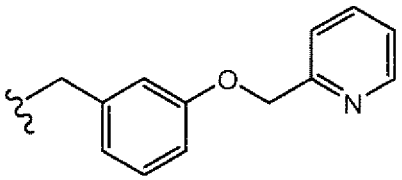
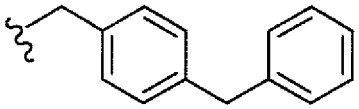
Code	"5" Structure
5i	-CH_2-(2-pyridyl)
5j	-CH_2CH_2-(4-morpholinyl)
5k	
5l	
5m	
5n	
5o	

Table 12: List of Compound Structures of Formula II

1a.2a.3a.4a.5a., 1b.2a.3a.4a.5a., 1f.2a.3a.4a.5a., 1h.2a.3a.4a.5a., 1j.2a.3a.4a.5a., 1p.2a.3a.4a.5a., 1a.2b.3a.4a.5a., 1b.2b.3a.4a.5a., 1f.2b.3a.4a.5a., 1h.2b.3a.4a.5a., 1j.2b.3a.4a.5a., 1p.2b.3a.4a.5a., 1a.2e.3a.4a.5a., 1b.2e.3a.4a.5a., 1f.2e.3a.4a.5a., 1h.2e.3a.4a.5a., 1j.2e.3a.4a.5a., 1p.2e.3a.4a.5a., 1a.2f.3a.4a.5a., 1b.2f.3a.4a.5a., 1f.2f.3a.4a.5a., 1h.2f.3a.4a.5a., 1j.2f.3a.4a.5a., 1p.2f.3a.4a.5a., 1a.2i.3a.4a.5a., 1b.2i.3a.4a.5a., 1f.2i.3a.4a.5a., 1h.2i.3a.4a.5a., 1j.2i.3a.4a.5a., 1p.2i.3a.4a.5a., 1a.2m.3a.4a.5a., 1b.2m.3a.4a.5a., 1f.2m.3a.4a.5a., 1h.2m.3a.4a.5a., 1j.2m.3a.4a.5a., 1p.2m.3a.4a.5a., 1a.2o.3a.4a.5a., 1b.2o.3a.4a.5a., 1f.2o.3a.4a.5a., 1h.2o.3a.4a.5a., 1j.2o.3a.4a.5a., 1p.2o.3a.4a.5a., 1a.2u.3a.4a.5a., 1b.2u.3a.4a.5a., 1f.2u.3a.4a.5a., 1h.2u.3a.4a.5a., 1j.2u.3a.4a.5a., 1p.2u.3a.4a.5a., 1a.2y.3a.4a.5a., 1b.2y.3a.4a.5a.,

1f.2y.3a.4a.5a., 1h.2y.3a.4a.5a., 1j.2y.3a.4a.5a., 1p.2y.3a.4a.5a., 1a.2a.3b.4a.5a., 1b.2a.3b.4a.5a., 1f.2a.3b.4a.5a., 1h.2a.3b.4a.5a., 1j.2a.3b.4a.5a., 1p.2a.3b.4a.5a., 1a.2b.3b.4a.5a., 1b.2b.3b.4a.5a., 1f.2b.3b.4a.5a., 1h.2b.3b.4a.5a., 1j.2b.3b.4a.5a., 1p.2b.3b.4a.5a., 1a.2e.3b.4a.5a., 1b.2e.3b.4a.5a., 1f.2e.3b.4a.5a., 1h.2e.3b.4a.5a., 1j.2e.3b.4a.5a., 1p.2e.3b.4a.5a., 1a.2f.3b.4a.5a., 1b.2f.3b.4a.5a., 1f.2f.3b.4a.5a., 1h.2f.3b.4a.5a., 1j.2f.3b.4a.5a., 1p.2f.3b.4a.5a., 1a.2i.3b.4a.5a., 1b.2i.3b.4a.5a., 1f.2i.3b.4a.5a., 1h.2i.3b.4a.5a., 1j.2i.3b.4a.5a., 1p.2i.3b.4a.5a., 1a.2m.3b.4a.5a., 1b.2m.3b.4a.5a., 1f.2m.3b.4a.5a., 1h.2m.3b.4a.5a., 1j.2m.3b.4a.5a., 1p.2m.3b.4a.5a., 1a.2o.3b.4a.5a., 1b.2o.3b.4a.5a., 1f.2o.3b.4a.5a., 1h.2o.3b.4a.5a., 1j.2o.3b.4a.5a., 1p.2o.3b.4a.5a., 1a.2u.3b.4a.5a., 1b.2u.3b.4a.5a., 1f.2u.3b.4a.5a., 1h.2u.3b.4a.5a., 1j.2u.3b.4a.5a., 1p.2u.3b.4a.5a., 1a.2y.3b.4a.5a., 1b.2y.3b.4a.5a., 1f.2y.3b.4a.5a., 1h.2y.3b.4a.5a., 1j.2y.3b.4a.5a., 1p.2y.3b.4a.5a., 1a.2a.3e.4a.5a., 1b.2a.3e.4a.5a., 1f.2a.3e.4a.5a., 1h.2a.3e.4a.5a., 1j.2a.3e.4a.5a., 1p.2a.3e.4a.5a., 1a.2b.3e.4a.5a., 1b.2b.3e.4a.5a., 1f.2b.3e.4a.5a., 1h.2b.3e.4a.5a., 1j.2b.3e.4a.5a., 1p.2b.3e.4a.5a., 1a.2e.3e.4a.5a., 1b.2e.3e.4a.5a., 1f.2e.3e.4a.5a., 1h.2e.3e.4a.5a., 1j.2e.3e.4a.5a., 1p.2e.3e.4a.5a., 1a.2f.3e.4a.5a., 1b.2f.3e.4a.5a., 1f.2f.3e.4a.5a., 1h.2f.3e.4a.5a., 1j.2f.3e.4a.5a., 1p.2f.3e.4a.5a., 1a.2i.3e.4a.5a., 1b.2i.3e.4a.5a., 1f.2i.3e.4a.5a., 1h.2i.3e.4a.5a., 1j.2i.3e.4a.5a., 1p.2i.3e.4a.5a., 1a.2m.3e.4a.5a., 1b.2m.3e.4a.5a., 1f.2m.3e.4a.5a., 1h.2m.3e.4a.5a., 1j.2m.3e.4a.5a., 1p.2m.3e.4a.5a., 1a.2o.3e.4a.5a., 1b.2o.3e.4a.5a., 1f.2o.3e.4a.5a., 1h.2o.3e.4a.5a., 1j.2o.3e.4a.5a., 1p.2o.3e.4a.5a., 1a.2u.3e.4a.5a., 1b.2u.3e.4a.5a., 1f.2u.3e.4a.5a., 1h.2u.3e.4a.5a., 1j.2u.3e.4a.5a., 1p.2u.3e.4a.5a., 1a.2y.3e.4a.5a., 1b.2y.3e.4a.5a., 1f.2y.3e.4a.5a., 1h.2y.3e.4a.5a., 1j.2y.3e.4a.5a., 1p.2y.3e.4a.5a., 1a.2a.3g.4a.5a., 1b.2a.3g.4a.5a., 1f.2a.3g.4a.5a., 1h.2a.3g.4a.5a., 1j.2a.3g.4a.5a., 1p.2a.3g.4a.5a., 1a.2b.3g.4a.5a., 1b.2b.3g.4a.5a., 1f.2b.3g.4a.5a., 1h.2b.3g.4a.5a., 1j.2b.3g.4a.5a., 1p.2b.3g.4a.5a., 1a.2e.3g.4a.5a., 1b.2e.3g.4a.5a., 1f.2e.3g.4a.5a., 1h.2e.3g.4a.5a., 1j.2e.3g.4a.5a., 1p.2e.3g.4a.5a., 1a.2f.3g.4a.5a., 1b.2f.3g.4a.5a., 1f.2f.3g.4a.5a., 1h.2f.3g.4a.5a., 1j.2f.3g.4a.5a., 1p.2f.3g.4a.5a., 1a.2i.3g.4a.5a., 1b.2i.3g.4a.5a., 1f.2i.3g.4a.5a., 1h.2i.3g.4a.5a., 1j.2i.3g.4a.5a., 1p.2i.3g.4a.5a., 1a.2m.3g.4a.5a., 1b.2m.3g.4a.5a., 1f.2m.3g.4a.5a., 1h.2m.3g.4a.5a., 1j.2m.3g.4a.5a., 1p.2m.3g.4a.5a., 1a.2o.3g.4a.5a., 1b.2o.3g.4a.5a., 1f.2o.3g.4a.5a., 1h.2o.3g.4a.5a., 1j.2o.3g.4a.5a., 1p.2o.3g.4a.5a., 1a.2u.3g.4a.5a., 1b.2u.3g.4a.5a., 1f.2u.3g.4a.5a., 1h.2u.3g.4a.5a., 1j.2u.3g.4a.5a., 1p.2u.3g.4a.5a., 1a.2y.3g.4a.5a., 1b.2y.3g.4a.5a., 1f.2y.3g.4a.5a., 1h.2y.3g.4a.5a., 1j.2y.3g.4a.5a., 1p.2y.3g.4a.5a., 1a.2a.3a.4d.5a., 1b.2a.3a.4d.5a., 1f.2a.3a.4d.5a., 1h.2a.3a.4d.5a., 1j.2a.3a.4d.5a., 1p.2a.3a.4d.5a., 1a.2b.3a.4d.5a., 1b.2b.3a.4d.5a., 1f.2b.3a.4d.5a., 1h.2b.3a.4d.5a., 1j.2b.3a.4d.5a., 1p.2b.3a.4d.5a., 1a.2e.3a.4d.5a., 1b.2e.3a.4d.5a., 1f.2e.3a.4d.5a., 1h.2e.3a.4d.5a., 1j.2e.3a.4d.5a., 1p.2e.3a.4d.5a., 1a.2f.3a.4d.5a., 1b.2f.3a.4d.5a., 1f.2f.3a.4d.5a., 1h.2f.3a.4d.5a., 1j.2f.3a.4d.5a., 1p.2f.3a.4d.5a., 1a.2i.3a.4d.5a., 1b.2i.3a.4d.5a., 1f.2i.3a.4d.5a., 1h.2i.3a.4d.5a., 1j.2i.3a.4d.5a., 1p.2i.3a.4d.5a., 1a.2m.3a.4d.5a., 1b.2m.3a.4d.5a., 1f.2m.3a.4d.5a., 1h.2m.3a.4d.5a., 1j.2m.3a.4d.5a., 1p.2m.3a.4d.5a., 1a.2o.3a.4d.5a., 1b.2o.3a.4d.5a., 1f.2o.3a.4d.5a.,

1h.2o.3a.4d.5a., 1j.2o.3a.4d.5a., 1p.2o.3a.4d.5a., 1a.2u.3a.4d.5a., 1b.2u.3a.4d.5a., 1f.2u.3a.4d.5a., 1h.2u.3a.4d.5a., 1j.2u.3a.4d.5a., 1p.2u.3a.4d.5a., 1a.2y.3a.4d.5a., 1b.2y.3a.4d.5a., 1f.2y.3a.4d.5a., 1h.2y.3a.4d.5a., 1j.2y.3a.4d.5a., 1p.2y.3a.4d.5a., 1a.2a.3b.4d.5a., 1b.2a.3b.4d.5a., 1f.2a.3b.4d.5a., 1h.2a.3b.4d.5a., 1j.2a.3b.4d.5a., 1p.2a.3b.4d.5a., 1a.2b.3b.4d.5a., 1b.2b.3b.4d.5a., 1f.2b.3b.4d.5a., 1h.2b.3b.4d.5a., 1j.2b.3b.4d.5a., 1p.2b.3b.4d.5a., 1a.2e.3b.4d.5a., 1b.2e.3b.4d.5a., 1f.2e.3b.4d.5a., 1h.2e.3b.4d.5a., 1j.2e.3b.4d.5a., 1p.2e.3b.4d.5a., 1a.2f.3b.4d.5a., 1b.2f.3b.4d.5a., 1f.2f.3b.4d.5a., 1h.2f.3b.4d.5a., 1j.2f.3b.4d.5a., 1p.2f.3b.4d.5a., 1a.2i.3b.4d.5a., 1b.2i.3b.4d.5a., 1f.2i.3b.4d.5a., 1h.2i.3b.4d.5a., 1j.2i.3b.4d.5a., 1p.2i.3b.4d.5a., 1a.2m.3b.4d.5a., 1b.2m.3b.4d.5a., 1f.2m.3b.4d.5a., 1h.2m.3b.4d.5a., 1j.2m.3b.4d.5a., 1p.2m.3b.4d.5a., 1a.2o.3b.4d.5a., 1b.2o.3b.4d.5a., 1f.2o.3b.4d.5a., 1h.2o.3b.4d.5a., 1j.2o.3b.4d.5a., 1p.2o.3b.4d.5a., 1a.2u.3b.4d.5a., 1b.2u.3b.4d.5a., 1f.2u.3b.4d.5a., 1h.2u.3b.4d.5a., 1j.2u.3b.4d.5a., 1p.2u.3b.4d.5a., 1a.2y.3b.4d.5a., 1b.2y.3b.4d.5a., 1f.2y.3b.4d.5a., 1h.2y.3b.4d.5a., 1j.2y.3b.4d.5a., 1p.2y.3b.4d.5a., 1a.2a.3e.4d.5a., 1b.2a.3e.4d.5a., 1f.2a.3e.4d.5a., 1h.2a.3e.4d.5a., 1j.2a.3e.4d.5a., 1p.2a.3e.4d.5a., 1a.2b.3e.4d.5a., 1b.2b.3e.4d.5a., 1f.2b.3e.4d.5a., 1h.2b.3e.4d.5a., 1j.2b.3e.4d.5a., 1p.2b.3e.4d.5a., 1a.2e.3e.4d.5a., 1b.2e.3e.4d.5a., 1f.2e.3e.4d.5a., 1h.2e.3e.4d.5a., 1j.2e.3e.4d.5a., 1p.2e.3e.4d.5a., 1a.2f.3e.4d.5a., 1b.2f.3e.4d.5a., 1f.2f.3e.4d.5a., 1h.2f.3e.4d.5a., 1j.2f.3e.4d.5a., 1p.2f.3e.4d.5a., 1a.2i.3e.4d.5a., 1b.2i.3e.4d.5a., 1f.2i.3e.4d.5a., 1h.2i.3e.4d.5a., 1j.2i.3e.4d.5a., 1p.2i.3e.4d.5a., 1a.2m.3e.4d.5a., 1b.2m.3e.4d.5a., 1f.2m.3e.4d.5a., 1h.2m.3e.4d.5a., 1j.2m.3e.4d.5a., 1p.2m.3e.4d.5a., 1a.2o.3e.4d.5a., 1b.2o.3e.4d.5a., 1f.2o.3e.4d.5a., 1h.2o.3e.4d.5a., 1j.2o.3e.4d.5a., 1p.2o.3e.4d.5a., 1a.2u.3e.4d.5a., 1b.2u.3e.4d.5a., 1f.2u.3e.4d.5a., 1h.2u.3e.4d.5a., 1j.2u.3e.4d.5a., 1p.2u.3e.4d.5a., 1a.2y.3e.4d.5a., 1b.2y.3e.4d.5a., 1f.2y.3e.4d.5a., 1h.2y.3e.4d.5a., 1j.2y.3e.4d.5a., 1p.2y.3e.4d.5a., 1a.2a.3g.4d.5a., 1b.2a.3g.4d.5a., 1f.2a.3g.4d.5a., 1h.2a.3g.4d.5a., 1j.2a.3g.4d.5a., 1p.2a.3g.4d.5a., 1a.2b.3g.4d.5a., 1b.2b.3g.4d.5a., 1f.2b.3g.4d.5a., 1h.2b.3g.4d.5a., 1j.2b.3g.4d.5a., 1p.2b.3g.4d.5a., 1a.2e.3g.4d.5a., 1b.2e.3g.4d.5a., 1f.2e.3g.4d.5a., 1h.2e.3g.4d.5a., 1j.2e.3g.4d.5a., 1p.2e.3g.4d.5a., 1a.2f.3g.4d.5a., 1b.2f.3g.4d.5a., 1f.2f.3g.4d.5a., 1h.2f.3g.4d.5a., 1j.2f.3g.4d.5a., 1p.2f.3g.4d.5a., 1a.2i.3g.4d.5a., 1b.2i.3g.4d.5a., 1f.2i.3g.4d.5a., 1h.2i.3g.4d.5a., 1j.2i.3g.4d.5a., 1p.2i.3g.4d.5a., 1a.2m.3g.4d.5a., 1b.2m.3g.4d.5a., 1f.2m.3g.4d.5a., 1h.2m.3g.4d.5a., 1j.2m.3g.4d.5a., 1p.2m.3g.4d.5a., 1a.2o.3g.4d.5a., 1b.2o.3g.4d.5a., 1f.2o.3g.4d.5a., 1h.2o.3g.4d.5a., 1j.2o.3g.4d.5a., 1p.2o.3g.4d.5a., 1a.2u.3g.4d.5a., 1b.2u.3g.4d.5a., 1f.2u.3g.4d.5a., 1h.2u.3g.4d.5a., 1j.2u.3g.4d.5a., 1p.2u.3g.4d.5a., 1a.2y.3g.4d.5a., 1b.2y.3g.4d.5a., 1f.2y.3g.4d.5a., 1h.2y.3g.4d.5a., 1j.2y.3g.4d.5a., 1p.2y.3g.4d.5a., 1a.2a.3a.4f.5a., 1b.2a.3a.4f.5a., 1f.2a.3a.4f.5a., 1h.2a.3a.4f.5a., 1j.2a.3a.4f.5a., 1p.2a.3a.4f.5a., 1a.2b.3a.4f.5a., 1b.2b.3a.4f.5a., 1f.2b.3a.4f.5a., 1h.2b.3a.4f.5a., 1j.2b.3a.4f.5a., 1p.2b.3a.4f.5a., 1a.2e.3a.4f.5a., 1b.2e.3a.4f.5a., 1f.2e.3a.4f.5a., 1h.2e.3a.4f.5a., 1j.2e.3a.4f.5a., 1p.2e.3a.4f.5a., 1a.2f.3a.4f.5a., 1b.2f.3a.4f.5a., 1f.2f.3a.4f.5a., 1h.2f.3a.4f.5a., 1j.2f.3a.4f.5a., 1p.2f.3a.4f.5a., 1a.2i.3a.4f.5a., 1b.2i.3a.4f.5a., 1f.2i.3a.4f.5a., 1h.2i.3a.4f.5a.,

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1j.2e.3g.4i.5f., 1p.2e.3g.4i.5f., 1a.2f.3g.4i.5f., 1b.2f.3g.4i.5f., 1f.2f.3g.4i.5f.,
1h.2f.3g.4i.5f., 1j.2f.3g.4i.5f., 1p.2f.3g.4i.5f., 1a.2i.3g.4i.5f., 1b.2i.3g.4i.5f.,
1f.2i.3g.4i.5f., 1h.2i.3g.4i.5f., 1j.2i.3g.4i.5f., 1p.2i.3g.4i.5f., 1a.2m.3g.4i.5f.,
1b.2m.3g.4i.5f., 1f.2m.3g.4i.5f., 1h.2m.3g.4i.5f., 1j.2m.3g.4i.5f., 1p.2m.3g.4i.5f.,
1a.2o.3g.4i.5f., 1b.2o.3g.4i.5f., 1f.2o.3g.4i.5f., 1h.2o.3g.4i.5f., 1j.2o.3g.4i.5f.,
1p.2o.3g.4i.5f., 1a.2u.3g.4i.5f., 1b.2u.3g.4i.5f., 1f.2u.3g.4i.5f., 1h.2u.3g.4i.5f.,
1j.2u.3g.4i.5f., 1p.2u.3g.4i.5f., 1a.2y.3g.4i.5f., 1b.2y.3g.4i.5f., 1f.2y.3g.4i.5f.,
1h.2y.3g.4i.5f., 1j.2y.3g.4i.5f., 1p.2y.3g.4i.5f., 1a.2a.3a.4a.5g., 1b.2a.3a.4a.5g.,
1f.2a.3a.4a.5g., 1h.2a.3a.4a.5g., 1j.2a.3a.4a.5g., 1p.2a.3a.4a.5g., 1a.2b.3a.4a.5g.,
1b.2b.3a.4a.5g., 1f.2b.3a.4a.5g., 1h.2b.3a.4a.5g., 1j.2b.3a.4a.5g., 1p.2b.3a.4a.5g.,
1a.2e.3a.4a.5g., 1b.2e.3a.4a.5g., 1f.2e.3a.4a.5g., 1h.2e.3a.4a.5g., 1j.2e.3a.4a.5g.,
1p.2e.3a.4a.5g., 1a.2f.3a.4a.5g., 1b.2f.3a.4a.5g., 1f.2f.3a.4a.5g., 1h.2f.3a.4a.5g.,
1j.2f.3a.4a.5g., 1p.2f.3a.4a.5g., 1a.2i.3a.4a.5g., 1b.2i.3a.4a.5g., 1f.2i.3a.4a.5g.,
1h.2i.3a.4a.5g., 1j.2i.3a.4a.5g., 1p.2i.3a.4a.5g., 1a.2m.3a.4a.5g., 1b.2m.3a.4a.5g.,
1f.2m.3a.4a.5g., 1h.2m.3a.4a.5g., 1j.2m.3a.4a.5g., 1p.2m.3a.4a.5g., 1a.2o.3a.4a.5g.,
1b.2o.3a.4a.5g., 1f.2o.3a.4a.5g., 1h.2o.3a.4a.5g., 1j.2o.3a.4a.5g., 1p.2o.3a.4a.5g.,
1a.2u.3a.4a.5g., 1b.2u.3a.4a.5g., 1f.2u.3a.4a.5g., 1h.2u.3a.4a.5g., 1j.2u.3a.4a.5g.,
1p.2u.3a.4a.5g., 1a.2y.3a.4a.5g., 1b.2y.3a.4a.5g., 1f.2y.3a.4a.5g., 1h.2y.3a.4a.5g.,
1j.2y.3a.4a.5g., 1p.2y.3a.4a.5g., 1a.2a.3b.4a.5g., 1b.2a.3b.4a.5g., 1f.2a.3b.4a.5g.,

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1f.2m.3b.4h.5i., 1h.2m.3b.4h.5i., 1j.2m.3b.4h.5i., 1p.2m.3b.4h.5i., 1a.2o.3b.4h.5i., 1b.2o.3b.4h.5i., 1f.2o.3b.4h.5i., 1h.2o.3b.4h.5i., 1j.2o.3b.4h.5i., 1p.2o.3b.4h.5i., 1a.2u.3b.4h.5i., 1b.2u.3b.4h.5i., 1f.2u.3b.4h.5i., 1h.2u.3b.4h.5i., 1j.2u.3b.4h.5i., 1p.2u.3b.4h.5i., 1a.2y.3b.4h.5i., 1b.2y.3b.4h.5i., 1f.2y.3b.4h.5i., 1h.2y.3b.4h.5i., 1j.2y.3b.4h.5i., 1p.2y.3b.4h.5i., 1a.2a.3e.4h.5i., 1b.2a.3e.4h.5i., 1f.2a.3e.4h.5i., 1h.2a.3e.4h.5i., 1j.2a.3e.4h.5i., 1p.2a.3e.4h.5i., 1a.2b.3e.4h.5i., 1b.2b.3e.4h.5i., 1f.2b.3e.4h.5i., 1h.2b.3e.4h.5i., 1j.2b.3e.4h.5i., 1p.2b.3e.4h.5i., 1a.2e.3e.4h.5i., 1b.2e.3e.4h.5i., 1f.2e.3e.4h.5i., 1h.2e.3e.4h.5i., 1j.2e.3e.4h.5i., 1p.2e.3e.4h.5i., 1a.2f.3e.4h.5i., 1b.2f.3e.4h.5i., 1f.2f.3e.4h.5i., 1h.2f.3e.4h.5i., 1j.2f.3e.4h.5i., 1p.2f.3e.4h.5i., 1a.2i.3e.4h.5i., 1b.2i.3e.4h.5i., 1f.2i.3e.4h.5i., 1h.2i.3e.4h.5i., 1j.2i.3e.4h.5i., 1p.2i.3e.4h.5i., 1a.2m.3e.4h.5i., 1b.2m.3e.4h.5i., 1f.2m.3e.4h.5i., 1h.2m.3e.4h.5i., 1j.2m.3e.4h.5i., 1p.2m.3e.4h.5i., 1a.2o.3e.4h.5i., 1b.2o.3e.4h.5i., 1f.2o.3e.4h.5i., 1h.2o.3e.4h.5i., 1j.2o.3e.4h.5i., 1p.2o.3e.4h.5i., 1a.2u.3e.4h.5i., 1b.2u.3e.4h.5i., 1f.2u.3e.4h.5i., 1h.2u.3e.4h.5i., 1j.2u.3e.4h.5i., 1p.2u.3e.4h.5i., 1a.2y.3e.4h.5i., 1b.2y.3e.4h.5i., 1f.2y.3e.4h.5i., 1h.2y.3e.4h.5i., 1j.2y.3e.4h.5i., 1p.2y.3e.4h.5i., 1a.2a.3g.4h.5i., 1b.2a.3g.4h.5i., 1f.2a.3g.4h.5i., 1h.2a.3g.4h.5i., 1j.2a.3g.4h.5i., 1p.2a.3g.4h.5i., 1a.2b.3g.4h.5i., 1b.2b.3g.4h.5i., 1f.2b.3g.4h.5i., 1h.2b.3g.4h.5i., 1j.2b.3g.4h.5i., 1p.2b.3g.4h.5i., 1a.2e.3g.4h.5i., 1b.2e.3g.4h.5i., 1f.2e.3g.4h.5i., 1h.2e.3g.4h.5i., 1j.2e.3g.4h.5i., 1p.2e.3g.4h.5i., 1a.2f.3g.4h.5i., 1b.2f.3g.4h.5i., 1f.2f.3g.4h.5i., 1h.2f.3g.4h.5i., 1j.2f.3g.4h.5i., 1p.2f.3g.4h.5i., 1a.2i.3g.4h.5i., 1b.2i.3g.4h.5i., 1f.2i.3g.4h.5i., 1h.2i.3g.4h.5i., 1j.2i.3g.4h.5i., 1p.2i.3g.4h.5i., 1a.2m.3g.4h.5i., 1b.2m.3g.4h.5i., 1f.2m.3g.4h.5i., 1h.2m.3g.4h.5i., 1j.2m.3g.4h.5i., 1p.2m.3g.4h.5i., 1a.2o.3g.4h.5i., 1b.2o.3g.4h.5i., 1f.2o.3g.4h.5i., 1h.2o.3g.4h.5i., 1j.2o.3g.4h.5i., 1p.2o.3g.4h.5i., 1a.2u.3g.4h.5i., 1b.2u.3g.4h.5i., 1f.2u.3g.4h.5i., 1h.2u.3g.4h.5i., 1j.2u.3g.4h.5i., 1p.2u.3g.4h.5i., 1a.2y.3g.4h.5i., 1b.2y.3g.4h.5i., 1f.2y.3g.4h.5i., 1h.2y.3g.4h.5i., 1j.2y.3g.4h.5i., 1p.2y.3g.4h.5i., 1a.2a.3a.4i.5i., 1b.2a.3a.4i.5i., 1f.2a.3a.4i.5i., 1h.2a.3a.4i.5i., 1j.2a.3a.4i.5i., 1p.2a.3a.4i.5i., 1a.2b.3a.4i.5i., 1b.2b.3a.4i.5i., 1f.2b.3a.4i.5i., 1h.2b.3a.4i.5i., 1j.2b.3a.4i.5i., 1p.2b.3a.4i.5i., 1a.2e.3a.4i.5i., 1b.2e.3a.4i.5i., 1f.2e.3a.4i.5i., 1h.2e.3a.4i.5i., 1j.2e.3a.4i.5i., 1p.2e.3a.4i.5i., 1a.2f.3a.4i.5i., 1b.2f.3a.4i.5i., 1f.2f.3a.4i.5i., 1h.2f.3a.4i.5i., 1j.2f.3a.4i.5i., 1p.2f.3a.4i.5i., 1a.2i.3a.4i.5i., 1b.2i.3a.4i.5i., 1f.2i.3a.4i.5i., 1h.2i.3a.4i.5i., 1j.2i.3a.4i.5i., 1p.2i.3a.4i.5i., 1a.2m.3a.4i.5i., 1b.2m.3a.4i.5i., 1f.2m.3a.4i.5i., 1h.2m.3a.4i.5i., 1j.2m.3a.4i.5i., 1p.2m.3a.4i.5i., 1a.2o.3a.4i.5i., 1b.2o.3a.4i.5i., 1f.2o.3a.4i.5i., 1h.2o.3a.4i.5i., 1j.2o.3a.4i.5i., 1p.2o.3a.4i.5i., 1a.2u.3a.4i.5i., 1b.2u.3a.4i.5i., 1f.2u.3a.4i.5i., 1h.2u.3a.4i.5i., 1j.2u.3a.4i.5i., 1p.2u.3a.4i.5i., 1a.2y.3a.4i.5i., 1b.2y.3a.4i.5i., 1f.2y.3a.4i.5i., 1h.2y.3a.4i.5i., 1j.2y.3a.4i.5i., 1p.2y.3a.4i.5i., 1a.2a.3b.4i.5i., 1b.2a.3b.4i.5i., 1f.2a.3b.4i.5i., 1h.2a.3b.4i.5i., 1j.2a.3b.4i.5i., 1p.2a.3b.4i.5i., 1a.2b.3b.4i.5i., 1b.2b.3b.4i.5i., 1f.2b.3b.4i.5i., 1h.2b.3b.4i.5i., 1j.2b.3b.4i.5i., 1p.2b.3b.4i.5i., 1a.2e.3b.4i.5i., 1b.2e.3b.4i.5i., 1f.2e.3b.4i.5i., 1h.2e.3b.4i.5i., 1j.2e.3b.4i.5i., 1p.2e.3b.4i.5i., 1a.2f.3b.4i.5i., 1b.2f.3b.4i.5i., 1f.2f.3b.4i.5i.,

1h.2f.3b.4i.5i., 1j.2f.3b.4i.5i., 1p.2f.3b.4i.5i., 1a.2i.3b.4i.5i., 1b.2i.3b.4i.5i., 1f.2i.3b.4i.5i., 1h.2i.3b.4i.5i., 1j.2i.3b.4i.5i., 1p.2i.3b.4i.5i., 1a.2m.3b.4i.5i., 1b.2m.3b.4i.5i., 1f.2m.3b.4i.5i., 1h.2m.3b.4i.5i., 1j.2m.3b.4i.5i., 1p.2m.3b.4i.5i., 1a.2o.3b.4i.5i., 1b.2o.3b.4i.5i., 1f.2o.3b.4i.5i., 1h.2o.3b.4i.5i., 1j.2o.3b.4i.5i., 1p.2o.3b.4i.5i., 1a.2u.3b.4i.5i., 1b.2u.3b.4i.5i., 1f.2u.3b.4i.5i., 1h.2u.3b.4i.5i., 1j.2u.3b.4i.5i., 1p.2u.3b.4i.5i., 1a.2y.3b.4i.5i., 1b.2y.3b.4i.5i., 1f.2y.3b.4i.5i., 1h.2y.3b.4i.5i., 1j.2y.3b.4i.5i., 1p.2y.3b.4i.5i., 1a.2a.3e.4i.5i., 1b.2a.3e.4i.5i., 1f.2a.3e.4i.5i., 1h.2a.3e.4i.5i., 1j.2a.3e.4i.5i., 1p.2a.3e.4i.5i., 1a.2b.3e.4i.5i., 1b.2b.3e.4i.5i., 1f.2b.3e.4i.5i., 1h.2b.3e.4i.5i., 1j.2b.3e.4i.5i., 1p.2b.3e.4i.5i., 1a.2e.3e.4i.5i., 1b.2e.3e.4i.5i., 1f.2e.3e.4i.5i., 1h.2e.3e.4i.5i., 1j.2e.3e.4i.5i., 1p.2e.3e.4i.5i., 1a.2f.3e.4i.5i., 1b.2f.3e.4i.5i., 1f.2f.3e.4i.5i., 1h.2f.3e.4i.5i., 1j.2f.3e.4i.5i., 1p.2f.3e.4i.5i., 1a.2i.3e.4i.5i., 1b.2i.3e.4i.5i., 1f.2i.3e.4i.5i., 1h.2i.3e.4i.5i., 1j.2i.3e.4i.5i., 1p.2i.3e.4i.5i., 1a.2m.3e.4i.5i., 1b.2m.3e.4i.5i., 1f.2m.3e.4i.5i., 1h.2m.3e.4i.5i., 1j.2m.3e.4i.5i., 1p.2m.3e.4i.5i., 1a.2o.3e.4i.5i., 1b.2o.3e.4i.5i., 1f.2o.3e.4i.5i., 1h.2o.3e.4i.5i., 1j.2o.3e.4i.5i., 1p.2o.3e.4i.5i., 1a.2u.3e.4i.5i., 1b.2u.3e.4i.5i., 1f.2u.3e.4i.5i., 1h.2u.3e.4i.5i., 1j.2u.3e.4i.5i., 1p.2u.3e.4i.5i., 1a.2y.3e.4i.5i., 1b.2y.3e.4i.5i., 1f.2y.3e.4i.5i., 1h.2y.3e.4i.5i., 1j.2y.3e.4i.5i., 1p.2y.3e.4i.5i., 1a.2a.3g.4i.5i., 1b.2a.3g.4i.5i., 1f.2a.3g.4i.5i., 1h.2a.3g.4i.5i., 1j.2a.3g.4i.5i., 1p.2a.3g.4i.5i., 1a.2b.3g.4i.5i., 1b.2b.3g.4i.5i., 1f.2b.3g.4i.5i., 1h.2b.3g.4i.5i., 1j.2b.3g.4i.5i., 1p.2b.3g.4i.5i., 1a.2e.3g.4i.5i., 1b.2e.3g.4i.5i., 1f.2e.3g.4i.5i., 1h.2e.3g.4i.5i., 1j.2e.3g.4i.5i., 1p.2e.3g.4i.5i., 1a.2f.3g.4i.5i., 1b.2f.3g.4i.5i., 1f.2f.3g.4i.5i., 1h.2f.3g.4i.5i., 1j.2f.3g.4i.5i., 1p.2f.3g.4i.5i., 1a.2i.3g.4i.5i., 1b.2i.3g.4i.5i., 1f.2i.3g.4i.5i., 1h.2i.3g.4i.5i., 1j.2i.3g.4i.5i., 1p.2i.3g.4i.5i., 1a.2m.3g.4i.5i., 1b.2m.3g.4i.5i., 1f.2m.3g.4i.5i., 1h.2m.3g.4i.5i., 1j.2m.3g.4i.5i., 1p.2m.3g.4i.5i., 1a.2o.3g.4i.5i., 1b.2o.3g.4i.5i., 1f.2o.3g.4i.5i., 1h.2o.3g.4i.5i., 1j.2o.3g.4i.5i., 1p.2o.3g.4i.5i., 1a.2u.3g.4i.5i., 1b.2u.3g.4i.5i., 1f.2u.3g.4i.5i., 1h.2u.3g.4i.5i., 1j.2u.3g.4i.5i., 1p.2u.3g.4i.5i., 1a.2y.3g.4i.5i., 1b.2y.3g.4i.5i., 1f.2y.3g.4i.5i., 1h.2y.3g.4i.5i., 1j.2y.3g.4i.5i., and 1p.2y.3g.4i.5i..

In still yet another embodiment, the compound of the present invention has an inhibition activity against P450 at a level equal to or better than the inhibition activity of a compound as represented by an IC_{50} of less than about 2000 nM, less than about 1500 nM, less than about 1000 nM, less than about 900 nM, less than about 800 nM, less than about 700 nM, less than about 650 nM, less than about 600 nM, less than about 550 nM, less than about 500 nM, less than about 400 nM, less than about 350 nM, less than about 300 nM, less than about 250 nM, less than about 200 nM, less than about 100 nM, or less than about 50 nM.

In still yet another embodiment, the compound of the present invention has an inhibition activity against an isozyme of P450, *e.g.*, 3A in a range represented by IC_{50} from about 2000 nM to about 100 nM, from about 1000 nM to about 100 nM, from about 900 nM to about 200 nM, from about 800 nM to about 300 nM, from about 700 nM to about 200 nM, from about 600 nM to about 200 nM, from about 500 nM to about 200 nM, from about 700 nM to about 300 nM, from about 600 nM to about 300 nM, from about 700 nM to about 400 nM, from about 600 nM to about 400 nM, from about 400 nM to about 100 nM, from about 300 nM to about 100 nM, or from about 600 nM to about 150 nM.

In still yet another embodiment, the compound of the present invention has an inhibition activity against P450 at a level equal to or better than the inhibition activity of a compound as represented by an IC_{50} of less than about 2000 nM, less than about 1500 nM, less than about 1000 nM, less than about 900 nM, less than about 800 nM, less than about 700 nM, less than about 650 nM, less than about 600 nM, less than about 550 nM, less than about 500 nM, less than about 400 nM, less than about 350 nM, less than about 300 nM, less than about 250 nM, less than about 200 nM, less than about 100 nM, or less than about 50 nM, provided that such compound also does not substantially exhibit biological activities other than its inhibition activity against P450. For example, the compound of the present invention can have a reduced or not significant activity of protease inhibition, including without any limitation a level of protease inhibition as represented by HIV EC_{50} of greater than about 1000 nM, greater than about 900 nM, greater than about 800 nM, greater than about 700 nM, greater than about 600 nM, greater than about 500 nM, greater than about 400 nM, greater than about 300 nM, greater than about 200 nM, greater than about 100 nM, greater than about 50 nM, greater than about 40 nM, greater than about 30 nM, greater than about 20

nM, greater than about 10 nM, greater than about 5 nM, or greater than about 1 nM.

In yet another embodiment, the compound of the present invention has an inhibition activity specifically against one or more isozymes of P450 including without limitation 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, and 3A4, 5, 7, etc.

In yet another embodiment, the compound of the present invention has an inhibition activity specifically against an isozyme of P450 that is involved in metabolizing anti-viral drugs, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir etc.

In still yet another embodiment, the compound of the present invention has an inhibition activity specifically against one or more isozymes of P450, but not the other(s). For example, the compound of the present invention can have an inhibition activity specifically against P450 3A, but a reduced, insubstantial, or minimum inhibition activity against another isozyme of P450, *e.g.*, P450 2C9.

Pharmaceutical Formulations

The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986), herein incorporated by reference in its entirety. Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient, e.g. a compound of the present invention, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.), herein incorporated by reference in its entirety. Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or

granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient.

For administration to the eye or other external tissues e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably,

a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be

prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a

condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as

sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For

example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 μm (including particle sizes in a range between 0.1 and 500 μm in increments such as 0.5 μm, 1 μm, 30 μm, 35 μm, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of infections as described herein.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing

in addition to the active ingredient such carriers as are known in the art to be appropriate.

Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients provided by the present invention the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

The invention further provides veterinary compositions comprising at least one active ingredient, *e.g.*, a compound of the present invention together with a veterinary carrier.

Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about 0.01 to about 5 mg/kg body weight per day. More typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, or between 5 mg and 500 mg, and may take the form of single or multiple doses.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable carrier or exipient.

In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or exipient.

According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be any agent that is accessible to oxidative metabolism by cytochrome P450 enzymes, especially cytochrome P450 monooxygenase, *e.g.*, 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, 3A4,5,7, etc.

In another example, the therapeutic agent used in combination with the compound of the present invention can be any anti-viral agent, *e.g.*, anti-HIV, anti-HCV, etc., anti-bacterial agent, anti-fungal agent, immuno-modulator, *e.g.*, immunosuppressant, anti-neoplastic agent, chemotherapeutic agent, agents useful for treating cardiovascular conditions, neurological conditions, etc.

In yet another example, the therapeutic agent used in combination with the compound of the present invention can be any proton pump inhibitor, anti-epileptics, NSAID, oral hypoglycemic agent, angiotensin II, sulfonylureas, beta blocker, antidepressant, antipsychotics, or anesthetics, or a combination thereof.

In yet another example, the therapeutic agent used in combination with the compound of the present invention can be any 1) macrolide antibiotics, *e.g.*, clarithromycin, erythromycin, telithromycin, 2) anti-arrhythmics, *e.g.*, quinidine=>3-OH, 3) benzodiazepines, *e.g.*, alprazolam, diazepam=>3OH, midazolam, triazolam, 4) immune modulators, *e.g.*, cyclosporine, tacrolimus (FK506), 5) HIV antivirals, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir, 6) prokinetic, *e.g.*, cisapride, 7) antihistamines, *e.g.*, astemizole, chlorpheniramine, terfenidine, 8) calcium channel blockers, *e.g.*, amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil, 9) HMG CoA reductase inhibitors, *e.g.*, atorvastatin, cerivastatin, lovastatin, simvastatin, or 10) steroid 6beta-OH, *e.g.*, estradiol, hydrocortisone, progesterone, testosterone.

In still yet another example, the therapeutic agent used in combination with the compound of the present invention can be any alfentanyl, aprepitant, aripiprazole, buspirone, cafergot, caffeine, TMU, cilostazol, cocaine, codeine- N-demethylation, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, or zolpidem or a combination thereof.

In one embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, non-nucleoside inhibitors of HCV, CCR5 inhibitors, and combinations thereof, and a pharmaceutically acceptable carrier or exipient.

In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, AG 1859, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, TMC-278 (rilpivirene),

BILR 355 BS, VRX 840773, UK-453061, RDEA806, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, Racivir (±-FTC), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine AVX754, amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), tenofovir disoproxil fumarate, adefovir dipivoxil, GS-9131, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, BA 011, enfuvirtide, sifuvirtide, FB006M, TRI-1144, AMD-070, SP01A, BMS-488043, BlockAide/ CR, immunitin, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, aplaviroc, vicriviroc, and maraviroc, cyclosporine, FK-506, rapamycin, taxol, taxotere, clarithromycin, A-77003, A-80987, MK-639, saquinavir, VX-478, AG1343, DMP-323, XM-450, BILA 2011 BS, BILA 1096 BS, BILA 2185 BS, BMS 186,318, LB71262, SC-52151, SC-629 (N,N-dimethylglycyl-N-(2-hydroxy-3-(((4-methoxyphenyl)sulphonyl)(2-methylpropyl)amino)-1 -(phenylmethyl)propyl)-3-methyl-L-valinamide), KNI-272, CGP 53437, CGP 57813 and U-103017 and a pharmaceutically acceptable carrier or exipient.

In still another embodiment, the present invention provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with two or three additional therapeutic agents. For example, a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, is combined with two or three additional therapeutic agents selected from

the classes of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and HIV integrase inhibitors. The two or three additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents. The compounds of the present invention in such ternary or quaternary combinations can include any of the compounds of Formula I disclosed herein, for example a compounds of Formula IIA-D or Formula IV. In a particular embodiment, the pharmaceutical compositions of the present invention comprises a compound of Formula IV, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, combined with two or three additional therapeutic agents selected from the classes of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and HIV integrase inhibitors. In a still more particular embodiment, the pharmaceutical composition of the present invention comprises Example P, S, or X, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with two or three additional therapeutic agents selected from the classes of HIV protease inhibitors, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, and HIV integrase inhibitors. For example, such combinations can comprise Example P, S, or X, or a pharmaceutically acceptable salt, solvate, and/or ester thereof in combination with two or three additional therapeutic agents selected from the group consisting of tenofovir disoproxil fumarate, GS-9131, emtricitabine, elvitegravir, efavrenz, atazanavir, darunavir, raltegravir, and rilpivirine (or pharmaceutically acceptable salts, solvates, and/or esters thereof).

Specific embodiments of ternary combinations comprise, for example, Example **P**/tenofovir disoproxil fumarate/GS-9131, Example **P**/tenofovir disoproxil fumarate/emtricitabine, Example **P**/tenofovir disoproxil fumarate/elvitegravir, Example **P**/tenofovir disoproxil fumarate/efavrenz, Example **P**/tenofovir disoproxil fumarate/atazanavir, Example **P**/tenofovir disoproxil fumarate/darunavir, Example **P**/tenofovir disoproxil fumarate/raltegravir, Example **P**/tenofovir disoproxil fumarate/rilpivirine, Example **P**/GS-9131/emtricitabine, Example **P**/GS-9131/elvitegravir, Example **P**/GS-9131/efavrenz, Example **P**/GS-9131/atazanavir, Example **P**/GS-9131/darunavir, Example **P**/GS-9131/raltegravir, Example **P**/GS-9131/rilpivirine, Example **P**/emtricitabine/elvitegravir, Example **P**/emtricitabine/efavrenz, Example **P**/emtricitabine/atazanavir, Example **P**/emtricitabine/darunavir, Example **P**/emtricitabine/raltegravir, Example **P**/emtricitabine/rilpivirine, Example **P**/elvitegravir/efavrenz, Example **P**/elvitegravir/atazanavir, Example **P**/elvitegravir/darunavir, Example **P**/elvitegravir/raltegravir, Example **P**/elvitegravir/rilpivirine, Example **P**/efavrenz/atazanavir, Example **P**/efavrenz/darunavir, Example **P**/efavrenz/raltegravir, Example **P**/efavrenz/rilpivirine, Example **P**/atazanavir/darunavir, Example **P**/atazanavir/raltegravir, Example **P**/atazanavir/rilpivirine, Example **P**/darunavir/raltegravir, Example **P**/darunavir/rilpivirine, Example **P**/raltegravir/rilpivirine, Example **S**/tenofovir disoproxil fumarate/GS-9131, Example **S**/tenofovir disoproxil fumarate/emtricitabine, Example **S**/tenofovir disoproxil fumarate/elvitegravir, Example **S**/tenofovir disoproxil fumarate/efavrenz, Example **S**/tenofovir disoproxil fumarate/atazanavir, Example **S**/tenofovir disoproxil fumarate/darunavir, Example **S**/tenofovir disoproxil fumarate/raltegravir, Example **S**/tenofovir disoproxil fumarate/rilpivirine, Example **S**/GS-9131/emtricitabine, Example **S**/GS-9131/elvitegravir, Example

S/GS-9131/efavrenz, Example S/GS-9131/atazanavir, Example S/GS-9131/darunavir, Example S/GS-9131/raltegravir, Example S/GS-9131/rilpivirine, Example S/emtricitabine/elvitegravir, Example S/emtricitabine/efavrenz, Example S/emtricitabine/atazanavir, Example S/emtricitabine/darunavir, Example S/emtricitabine/raltegravir, Example S/emtricitabine/rilpivirine, Example S/elvitegravir/efavrenz, Example S/elvitegravir/atazanavir, Example S/elvitegravir/darunavir, Example S/elvitegravir/raltegravir, Example S/elvitegravir/rilpivirine, Example S/efavrenz/atazanavir, Example S/efavrenz/darunavir, Example S/efavrenz/raltegravir, Example S/efavrenz/rilpivirine, Example S/atazanavir/darunavir, Example S/atazanavir/raltegravir, Example S/atazanavir/rilpivirine, Example S/darunavir/raltegravir, Example S/darunavir/rilpivirine, Example S/raltegravir/rilpivirine, Example X/tenofovir disoproxil fumarate/GS-9131, Example X/tenofovir disoproxil fumarate/emtricitabine, Example X/tenofovir disoproxil fumarate/elvitegravir, Example X/tenofovir disoproxil fumarate/efavrenz, Example X/tenofovir disoproxil fumarate/atazanavir, Example X/tenofovir disoproxil fumarate/darunavir, Example X/tenofovir disoproxil fumarate/raltegravir, Example X/tenofovir disoproxil fumarate/rilpivirine, Example X/GS-9131/emtricitabine, Example X/GS-9131/elvitegravir, Example X/GS-9131/efavrenz, Example X/GS-9131/atazanavir, Example X/GS-9131/darunavir, Example X/GS-9131/raltegravir, Example X/GS-9131/rilpivirine, Example X/emtricitabine/elvitegravir, Example X/emtricitabine/efavrenz, Example X/emtricitabine/atazanavir, Example X/emtricitabine/darunavir, Example X/emtricitabine/raltegravir, Example X/emtricitabine/rilpivirine, Example X/elvitegravir/efavrenz, Example X/elvitegravir/atazanavir, Example X/elvitegravir/darunavir, Example X/elvitegravir/raltegravir, Example X/elvitegravir/rilpivirine, Example X/efavrenz/atazanavir, Example

X/efavrenz/darunavir, Example **X**/efavrenz/raltegravir, Example **X**/efavrenz/rilpivirine, Example **X**/atazanavir/darunavir, Example **X**/atazanavir/raltegravir, Example **X**/atazanavir/rilpivirine, Example **X**/darunavir/raltegravir, Example **X**/darunavir/rilpivirine, and Example **X**/raltegravir/rilpivirine (including pharmaceutically acceptable salts, solvates, and/or esters of any of the above).

Specific embodiments of quaternary combinations comprise, for example, Example **P**/tenofovir disoproxil fumarate/GS-9131/emtricitabine, Example **P**/tenofovir disoproxil fumarate/GS-9131/elvitegravir, Example **P**/tenofovir disoproxil fumarate/GS-9131/efavrenz, Example **P**/tenofovir disoproxil fumarate/GS-9131/atazanavir, Example **P**/tenofovir disoproxil fumarate/GS-9131/darunavir, Example **P**/tenofovir disoproxil fumarate/GS-9131/raltegravir, Example **P**/tenofovir disoproxil fumarate/GS-9131/rilpivirine, Example **P**/tenofovir disoproxil fumarate/emtricitabine/elvitegravir, Example **P**/tenofovir disoproxil fumarate/emtricitabine/efavrenz, Example **P**/tenofovir disoproxil fumarate/emtricitabine/atazanavir, Example **P**/tenofovir disoproxil fumarate/emtricitabine/darunavir, Example **P**/tenofovir disoproxil fumarate/emtricitabine/raltegravir, Example **P**/tenofovir disoproxil fumarate/emtricitabine/rilpivirine, Example **P**/tenofovir disoproxil fumarate/elvitegravir/efavrenz, Example **P**/tenofovir disoproxil fumarate/elvitegravir/atazanavir, Example **P**/tenofovir disoproxil fumarate/elvitegravir/darunavir, Example **P**/tenofovir disoproxil fumarate/elvitegravir/raltegravir, Example **P**/tenofovir disoproxil fumarate/elvitegravir/rilpivirine, Example **P**/tenofovir disoproxil fumarate/efavrenz/atazanavir, Example **P**/tenofovir disoproxil fumarate/efavrenz/darunavir, Example **P**/tenofovir disoproxil fumarate/efavrenz/raltegravir, Example **P**/tenofovir disoproxil

fumarate/efavrenz/rilpivirine, Example **P**/tenofovir disoproxil fumarate/atazanavir/darunavir, Example **P**/tenofovir disoproxil fumarate/atazanavir/raltegravir, Example **P**/tenofovir disoproxil fumarate/atazanavir/rilpivirine, Example **P**/tenofovir disoproxil fumarate/darunavir/raltegravir, Example **P**/tenofovir disoproxil fumarate/darunavir/rilpivirine, Example **P**/tenofovir disoproxil fumarate/raltegravir/rilpivirine, Example **P**/GS-9131/emtricitabine/elvitegravir, Example **P**/GS-9131/emtricitabine/efavrenz, Example **P**/GS-9131/emtricitabine/atazanavir, Example **P**/GS-9131/emtricitabine/darunavir, Example **P**/GS-9131/emtricitabine/raltegravir, Example **P**/GS-9131/emtricitabine/rilpivirine, Example **P**/GS-9131/elvitegravir/efavrenz, Example **P**/GS-9131/elvitegravir/atazanavir, Example **P**/GS-9131/elvitegravir/darunavir, Example **P**/GS-9131/elvitegravir/raltegravir, Example **P**/GS-9131/elvitegravir/rilpivirine, Example **P**/GS-9131/efavrenz/atazanavir, Example **P**/GS-9131/efavrenz/darunavir, Example **P**/GS-9131/efavrenz/raltegravir, Example **P**/GS-9131/efavrenz/rilpivirine, Example **P**/GS-9131/atazanavir/darunavir, Example **P**/GS-9131/atazanavir/raltegravir, Example **P**/GS-9131/atazanavir/rilpivirine, Example **P**/GS-9131/darunavir/raltegravir, Example **P**/GS-9131/darunavir/rilpivirine, Example **P**/GS-9131/raltegravir/rilpivirine, Example **P**/emtricitabine/elvitegravir/efavrenz, Example **P**/emtricitabine/elvitegravir/atazanavir, Example **P**/emtricitabine/elvitegravir/darunavir, Example **P**/emtricitabine/elvitegravir/raltegravir, Example **P**/emtricitabine/elvitegravir/rilpivirine, Example **P**/emtricitabine/efavrenz/atazanavir, Example **P**/emtricitabine/efavrenz/darunavir, Example **P**/emtricitabine/efavrenz/raltegravir, Example

P/emtricitabine/efavrenz/rilpivirine, Example

P/emtricitabine/atazanavir/darunavir, Example

P/emtricitabine/atazanavir/raltegravir, Example

P/emtricitabine/atazanavir/rilpivirine, Example

P/emtricitabine/darunavir/raltegravir, Example

P/emtricitabine/darunavir/rilpivirine, Example

P/emtricitabine/raltegravir/rilpivirine, Example

P/elvitegravir/efavrenz/atazanavir, Example **P**/elvitegravir/efavrenz/darunavir, Example **P**/elvitegravir/efavrenz/raltegravir, Example

P/elvitegravir/efavrenz/rilpivirine, Example **P**/elvitegravir/atazanavir/darunavir, Example **P**/elvitegravir/atazanavir/raltegravir, Example

P/elvitegravir/atazanavir/rilpivirine, Example

P/elvitegravir/darunavir/raltegravir, Example **P**/elvitegravir/darunavir/rilpivirine, Example **P**/elvitegravir/raltegravir/rilpivirine, Example

P/efavrenz/atazanavir/darunavir, Example **P**/efavrenz/atazanavir/raltegravir, Example **P**/efavrenz/atazanavir/rilpivirine, Example

P/efavrenz/darunavir/raltegravir, Example **P**/efavrenz/darunavir/rilpivirine, Example **P**/efavrenz/raltegravir/rilpivirine, Example

P/atazanavir/darunavir/raltegravir, Example **P**/atazanavir/darunavir/rilpivirine, Example **P**/darunavir/raltegravir/rilpivirine, Example **S**/tenofovir disoproxil fumarate/GS-9131/emtricitabine, Example **S**/tenofovir disoproxil fumarate/GS-9131/elvitegravir, Example **S**/tenofovir disoproxil fumarate/GS-9131/efavrenz, Example **S**/tenofovir disoproxil fumarate/GS-9131/atazanavir, Example **S**/tenofovir disoproxil fumarate/GS-9131/darunavir, Example **S**/tenofovir disoproxil fumarate/GS-9131/raltegravir, Example **S**/tenofovir disoproxil fumarate/GS-9131/rilpivirine, Example **S**/tenofovir disoproxil fumarate/emtricitabine/elvitegravir, Example **S**/tenofovir disoproxil

fumarate/emtricitabine/efavrenz, Example S/tenofovir disoproxil fumarate/emtricitabine/atazanavir, Example S/tenofovir disoproxil fumarate/emtricitabine/darunavir, Example S/tenofovir disoproxil fumarate/emtricitabine/raltegravir, Example S/tenofovir disoproxil fumarate/emtricitabine/rilpivirine, Example S/tenofovir disoproxil fumarate/elvitegravir/efavrenz, Example S/tenofovir disoproxil fumarate/elvitegravir/atazanavir, Example S/tenofovir disoproxil fumarate/elvitegravir/darunavir, Example S/tenofovir disoproxil fumarate/elvitegravir/raltegravir, Example S/tenofovir disoproxil fumarate/elvitegravir/rilpivirine, Example S/tenofovir disoproxil fumarate/efavrenz/atazanavir, Example S/tenofovir disoproxil fumarate/efavrenz/darunavir, Example S/tenofovir disoproxil fumarate/efavrenz/raltegravir, Example S/tenofovir disoproxil fumarate/efavrenz/rilpivirine, Example S/tenofovir disoproxil fumarate/atazanavir/darunavir, Example S/tenofovir disoproxil fumarate/atazanavir/raltegravir, Example S/tenofovir disoproxil fumarate/atazanavir/rilpivirine, Example S/tenofovir disoproxil fumarate/darunavir/raltegravir, Example S/tenofovir disoproxil fumarate/darunavir/rilpivirine, Example S/tenofovir disoproxil fumarate/raltegravir/rilpivirine, Example S/GS-9131/emtricitabine/elvitegravir, Example S/GS-9131/emtricitabine/efavrenz, Example S/GS-9131/emtricitabine/atazanavir, Example S/GS-9131/emtricitabine/darunavir, Example S/GS-9131/emtricitabine/raltegravir, Example S/GS-9131/emtricitabine/rilpivirine, Example S/GS-9131/elvitegravir/efavrenz, Example S/GS-9131/elvitegravir/atazanavir, Example S/GS-9131/elvitegravir/darunavir, Example S/GS-9131/elvitegravir/raltegravir, Example S/GS-9131/elvitegravir/rilpivirine, Example S/GS-9131/efavrenz/atazanavir, Example

S/GS-9131/efavrenz/darunavir, Example S/GS-9131/efavrenz/raltegravir, Example S/GS-9131/efavrenz/rilpivirine, Example S/GS-9131/atazanavir/darunavir, Example S/GS-9131/atazanavir/raltegravir, Example S/GS-9131/atazanavir/rilpivirine, Example S/GS-9131/darunavir/raltegravir, Example S/GS-9131/darunavir/rilpivirine, Example S/GS-9131/raltegravir/rilpivirine, Example S/emtricitabine/elvitegravir/efavrenz, Example S/emtricitabine/elvitegravir/atazanavir, Example S/emtricitabine/elvitegravir/darunavir, Example S/emtricitabine/elvitegravir/raltegravir, Example S/emtricitabine/elvitegravir/rilpivirine, Example S/emtricitabine/efavrenz/atazanavir, Example S/emtricitabine/efavrenz/darunavir, Example S/emtricitabine/efavrenz/raltegravir, Example S/emtricitabine/efavrenz/rilpivirine, Example S/emtricitabine/atazanavir/darunavir, Example S/emtricitabine/atazanavir/raltegravir, Example S/emtricitabine/atazanavir/rilpivirine, Example S/emtricitabine/darunavir/raltegravir, Example S/emtricitabine/darunavir/rilpivirine, Example S/emtricitabine/raltegravir/rilpivirine, Example S/elvitegravir/efavrenz/atazanavir, Example S/elvitegravir/efavrenz/darunavir, Example S/elvitegravir/efavrenz/raltegravir, Example S/elvitegravir/efavrenz/rilpivirine, Example S/elvitegravir/atazanavir/darunavir, Example S/elvitegravir/atazanavir/raltegravir, Example S/elvitegravir/atazanavir/rilpivirine, Example S/elvitegravir/darunavir/raltegravir, Example S/elvitegravir/darunavir/rilpivirine, Example S/elvitegravir/raltegravir/rilpivirine, Example

S/efavrenz/atazanavir/darunavir, Example **S**/efavrenz/atazanavir/raltegravir, Example **S**/efavrenz/atazanavir/rilpivirine, Example **S**/efavrenz/darunavir/raltegravir, Example **S**/efavrenz/darunavir/rilpivirine, Example **S**/efavrenz/raltegravir/rilpivirine, Example **S**/atazanavir/darunavir/raltegravir, Example **S**/atazanavir/darunavir/rilpivirine, Example **S**/darunavir/raltegravir/rilpivirine, Example **X**/tenofovir disoproxil fumarate/GS-9131/emtricitabine, Example **X**/tenofovir disoproxil fumarate/GS-9131/elvitegravir, Example **X**/tenofovir disoproxil fumarate/GS-9131/efavrenz, Example **X**/tenofovir disoproxil fumarate/GS-9131/atazanavir, Example **X**/tenofovir disoproxil fumarate/GS-9131/darunavir, Example **X**/tenofovir disoproxil fumarate/GS-9131/raltegravir, Example **X**/tenofovir disoproxil fumarate/GS-9131/rilpivirine, Example **X**/tenofovir disoproxil fumarate/emtricitabine/elvitegravir, Example **X**/tenofovir disoproxil fumarate/emtricitabine/efavrenz, Example **X**/tenofovir disoproxil fumarate/emtricitabine/atazanavir, Example **X**/tenofovir disoproxil fumarate/emtricitabine/darunavir, Example **X**/tenofovir disoproxil fumarate/emtricitabine/raltegravir, Example **X**/tenofovir disoproxil fumarate/emtricitabine/rilpivirine, Example **X**/tenofovir disoproxil fumarate/elvitegravir/efavrenz, Example **X**/tenofovir disoproxil fumarate/elvitegravir/atazanavir, Example **X**/tenofovir disoproxil fumarate/elvitegravir/darunavir, Example **X**/tenofovir disoproxil fumarate/elvitegravir/raltegravir, Example **X**/tenofovir disoproxil fumarate/elvitegravir/rilpivirine, Example **X**/tenofovir disoproxil fumarate/efavrenz/atazanavir, Example **X**/tenofovir disoproxil fumarate/efavrenz/darunavir, Example **X**/tenofovir disoproxil fumarate/efavrenz/raltegravir, Example **X**/tenofovir disoproxil fumarate/efavrenz/rilpivirine, Example **X**/tenofovir disoproxil

fumarate/atazanavir/darunavir, Example **X**/tenofovir disoproxil fumarate/atazanavir/raltegravir, Example **X**/tenofovir disoproxil fumarate/atazanavir/rilpivirine, Example **X**/tenofovir disoproxil fumarate/darunavir/raltegravir, Example **X**/tenofovir disoproxil fumarate/darunavir/rilpivirine, Example **X**/tenofovir disoproxil fumarate/raltegravir/rilpivirine, Example **X**/GS-9131/emtricitabine/elvitegravir, Example **X**/GS-9131/emtricitabine/efavrenz, Example **X**/GS-9131/emtricitabine/atazanavir, Example **X**/GS-9131/emtricitabine/darunavir, Example **X**/GS-9131/emtricitabine/raltegravir, Example **X**/GS-9131/emtricitabine/rilpivirine, Example **X**/GS-9131/elvitegravir/efavrenz, Example **X**/GS-9131/elvitegravir/atazanavir, Example **X**/GS-9131/elvitegravir/darunavir, Example **X**/GS-9131/elvitegravir/raltegravir, Example **X**/GS-9131/elvitegravir/rilpivirine, Example **X**/GS-9131/efavrenz/atazanavir, Example **X**/GS-9131/efavrenz/darunavir, Example **X**/GS-9131/efavrenz/raltegravir, Example **X**/GS-9131/efavrenz/rilpivirine, Example **X**/GS-9131/atazanavir/darunavir, Example **X**/GS-9131/atazanavir/raltegravir, Example **X**/GS-9131/atazanavir/rilpivirine, Example **X**/GS-9131/darunavir/raltegravir, Example **X**/GS-9131/darunavir/rilpivirine, Example **X**/GS-9131/raltegravir/rilpivirine, Example **X**/emtricitabine/elvitegravir/efavrenz, Example **X**/emtricitabine/elvitegravir/atazanavir, Example **X**/emtricitabine/elvitegravir/darunavir, Example **X**/emtricitabine/elvitegravir/raltegravir, Example **X**/emtricitabine/elvitegravir/rilpivirine, Example **X**/emtricitabine/efavrenz/atazanavir, Example **X**/emtricitabine/efavrenz/darunavir, Example **X**/emtricitabine/efavrenz/raltegravir, Example **X**/emtricitabine/efavrenz/rilpivirine, Example

X/emtricitabine/atazanavir/darunavir, Example **X**/emtricitabine/atazanavir/raltegravir, Example **X**/emtricitabine/atazanavir/rilpivirine, Example **X**/emtricitabine/darunavir/raltegravir, Example **X**/emtricitabine/darunavir/rilpivirine, Example **X**/emtricitabine/raltegravir/rilpivirine, Example **X**/elvitegravir/efavrenz/atazanavir, Example **X**/elvitegravir/efavrenz/darunavir, Example **X**/elvitegravir/efavrenz/raltegravir, Example **X**/elvitegravir/efavrenz/rilpivirine, Example **X**/elvitegravir/atazanavir/darunavir, Example **X**/elvitegravir/atazanavir/raltegravir, Example **X**/elvitegravir/atazanavir/rilpivirine, Example **X**/elvitegravir/darunavir/raltegravir, Example **X**/elvitegravir/darunavir/rilpivirine, Example **X**/elvitegravir/raltegravir/rilpivirine, Example **X**/efavrenz/atazanavir/darunavir, Example **X**/efavrenz/atazanavir/raltegravir, Example **X**/efavrenz/atazanavir/rilpivirine, Example **X**/efavrenz/darunavir/raltegravir, Example **X**/efavrenz/darunavir/rilpivirine, Example **X**/efavrenz/raltegravir/rilpivirine, Example **X**/atazanavir/darunavir/raltegravir, Example **X**/atazanavir/darunavir/rilpivirine, and Example **X**/darunavir/raltegravir/rilpivirine (including pharmaceutically acceptable salts, solvates, and/or esters of any of the above).

In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Routes of Administration

One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

In one embodiment, the compounds of the present invention can be used alone, e.g., for inhibiting cytochrome P450 monooxygenase. In another embodiment, the compounds of the present invention are used in combination with other active therapeutic ingredients or agents. Preferably, the other active therapeutic ingredients or agents are metabolized or accessible to the oxidative metabolism by cytochrome P450 enzymes, *e.g.*, monooxygenase enzymes such as 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, 3A4,5,7, etc.

Combinations of the compounds of the present invention are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HIV or HCV), the compositions of the invention are combined with anti-infective agents (such as those described herein).

In one embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more anti-viral agents, *e.g.*, anti-HIV, anti-HCV, etc., anti-bacterial agents, anti-fungal agents, immuno-modulators, *e.g.*, immunosuppressant, anti-neoplastic agents, chemotherapeutic agents, agents useful for treating cardiovascular conditions, neurological conditions, etc.

In another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more proton pump inhibitors, anti-epileptics, NSAIDs, oral hypoglycemic agents, angiotensin II, sulfonylureas, beta blockers, antidepressants, antipsychotics, or anesthetics, or a combination thereof.

In yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more 1) macrolide antibiotics, *e.g.*, clarithromycin, erythromycin, telithromycin, 2) anti-arrhythmics, *e.g.*, quinidine=>3-OH, 3) benzodiazepines, *e.g.*, alprazolam, diazepam=>3OH, midazolam, triazolam, 4) immune modulators, *e.g.*, cyclosporine, tacrolimus (FK506), 5) HIV antivirals, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir, 6) prokinetic, *e.g.*, cisapride, 7) antihistamines, *e.g.*, astemizole, chlorpheniramine, terfenidine, 8) calcium channel blockers, *e.g.*, amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil, 9) HMG CoA reductase inhibitors, *e.g.*,

atorvastatin, cerivastatin, lovastatin, simvastatin, or 10) steroid 6beta-OH, *e.g.*, estradiol, hydrocortisone, progesterone, testosterone.

In still yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more compounds selected from the group consisting of alfentanyl, aprepitant, aripiprazole, buspirone, cafergot, caffeine=>TMU, cilostazol, cocaine, codeine- N-demethylation, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, odanestron, pimozide, propranolol, quetiapine, quinine, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, and zolpidem or a combination thereof.

In still yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, and other drugs for treating HIV, interferons, ribavirin analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684,

GW640385X, DG17, GS-8374, PPL-100, DG35, and AG 1859, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.*, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, UK-453061, and RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.*, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), GS-7340, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.*, tenofovir disoproxil fumarate and adefovir dipivoxil, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, and TRI-1144, 7) a CXCR4 inhibitor, *e.g.*, AMD-070, 8) an entry inhibitor, *e.g.*, SP01A, 9) a gp120 inhibitor, *e.g.*, BMS-488043 or BlockAide/ CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.*, immunitin, 11) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004, 12) other drugs for treating HIV, *e.g.*, BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040), 13) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha

2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta, 14) a ribavirin analog, *e.g.*, rebetol, copegus, viramidine (taribavirin), 15) a NS5b polymerase inhibitor, *e.g.*, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433, 16) A NS3 protease inhibitor, *e.g.*, SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191, 17) an alpha-glucosidase 1 inhibitor, *e.g.*, MX-3253 (celgosivir), UT-231B, 18) hepatoprotectants, *e.g.*, IDN-6556, ME 3738, LB-84451, and MitoQ, 19) a non-nucleoside inhibitor of HCV, *e.g.*, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, GS-9190, and A-689; and 20) other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

It is also contemplated that the compounds of the present invention can be used with any other active therapeutic agent or ingredient which is appreciably metabolized by cytochrome P450 monooxygenase enzymes, e.g. cytochrome P450 monooxygenase 3A, thereby reducing the amount or rate at which the other active therapeutic agent or ingredient is metabolized, whereby the pharmacokinetics of the other active therapeutic agent or ingredient is improved. Such improvements can include elevating the blood plasma levels of the other therapeutic agent or ingredient or maintaining a more therapeutically effective blood plasma level of the other therapeutic active agent or ingredient -- compared to blood plasma

levels of the other therapeutic agent or ingredient administered without the compound of the present invention.

It is also possible to combine any compound of the invention with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to

administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

In yet another embodiment, the present application provides a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a combination comprising said drug and a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase 3A, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a combination comprising said drug and a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase 3A, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

In yet another embodiment, the present application provides a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and wherein

the amount of the compound of the present invention administered is effective to inhibit cytochrome P450 monooxygenase.

In yet another embodiment, the present application provides a method for inhibiting cytochrome P450 monooxygenase in a patient comprising administering to a patient in need thereof an amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase.

In yet another embodiment, the present application provides a method for inhibiting cytochrome P450 monooxygenase 3A in a patient comprising administering to a patient in need thereof an amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase 3A.

In yet another embodiment, the present application provides a method for inhibiting cytochrome P450 monooxygenase comprising contacting cytochrome P450 monooxygenase with an amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase.

In yet another embodiment, the present application provides a method for inhibiting cytochrome P450 monooxygenase 3A comprising contacting cytochrome P450 monooxygenase 3A with an amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase 3A.

In yet another embodiment, the present application provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic

agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

In yet another embodiment, the present application provides a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, DG35, AG 1859, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, , UK-453061, RDEA806, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, fosalvudine tidoxil (formerly HDP 99.0003), tenofovir disoproxil fumarate, adefovir dipivoxil, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011,

enfuvirtide, sifuvirtide, FB006M, and TRI-1144, AMD-070, an entry inhibitor, SP01A, BMS-488043, BlockAide/ CR, a G6PD and NADH-oxidase inhibitor, immunitin, aplaviroc, vicriviroc, maraviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), CCR5mAb004, BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

In yet another embodiment, the present application provides a method for treating an HCV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, locteron, albuferon, rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and pegylated IFN-beta, rebetol, copegus, viramidine (taribavirin), NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, GSK625433, SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, ITMN-191, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, LB-84451, MitoQ, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, A-689, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for inhibiting cytochrome P450 monooxygenase in a patient.

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for treating an HIV infection.

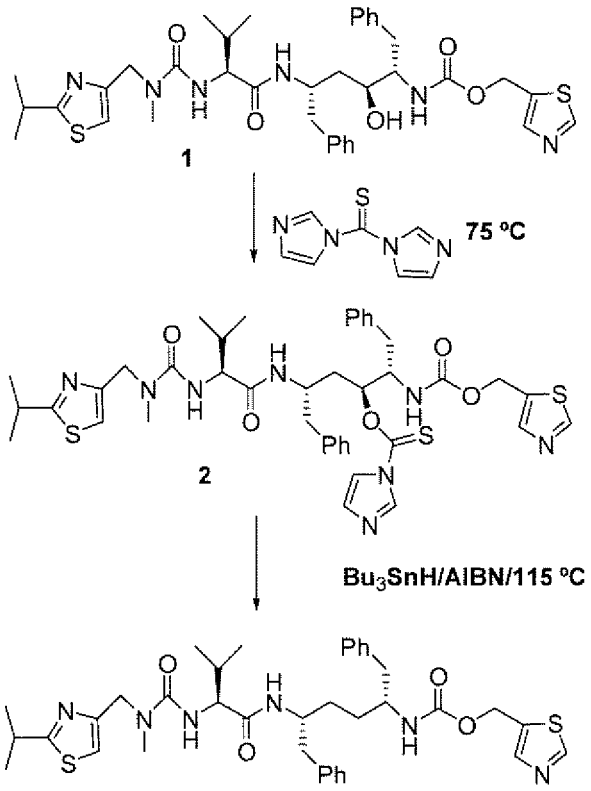
In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for increasing blood plasma levels of the drug which is metabolized by cytochrome P450 monooxygenase.

In still yet another embodiment, the present application provides for the use of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for the preparation of a medicament for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase.

Examples

Preparation of Example A

Scheme 1



Example A

Compound 2

To a solution of Compound **1** (ritonavir) (1.8 g, 2.5 mmol) in 1,2-dichloroethane (15 mL) was added 1,1′-thiocarbonyldiimidazole (890 mg, 5.0 mmol). The mixture was heated at 75°C for 6 hours and cooled to 25°C. Evaporation under reduced pressure gave a white solid. Purification by flash column chromatography (stationary phase: silica gel; eluent: EtOAc) gave Compound **2** (1.6 g). m/z: 831.1 $(M+H)^+$.

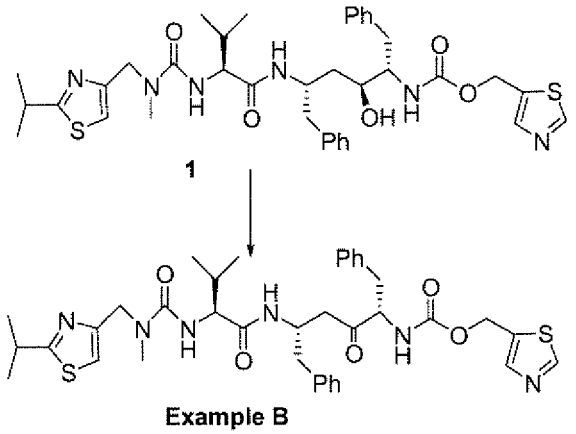
Example A

To the refluxing solution of tributyltin hydride (0.78 mL, 2.9 mmol) in toluene (130 mL) was added a solution of Compound **2** (1.6 g, 1.9 mmol) and 2,2′-azobisisobutyronitrile (31 mg, 0.19 mmol) in toluene (30 mL) over 30 minutes.

The mixture was heated at 115°C for 6 hours and cooled to 25°C. Toluene was removed under reduced pressure. Purification by flash column chromatography (stationary phase: silica gel; eluent: hexane/EtOAc = 1/10) gave Example **A** (560 mg). m/z: 705.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.79 (1 H, s), 7.82 (1 H, s), 7.26-7.05 (10 H, m), 6.98 (1 H, s), 6.28 (1 H, m), 6.03 (1 H, m), 5.27 (1 H, m), 5.23 (2 H, s), 4.45-4.22 (2 H, m), 4.17 (1 H, m), 3.98 (1 H, m), 3.75 (1 H, m), 3.25 (1 H, m), 2.91 (3 H, s), 2.67 (4 H, m), 2.36 (1 H, m), 1.6-1.2 (10 H, m), 0.85 (6 H, m).

Preparation of Example B

Scheme 2

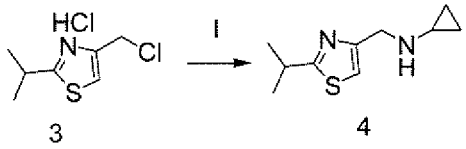


Example B

To a solution of Compound **1** (ritonavir) (98 mg, 0.136 mmol) in dichloromethane (4 mL) was added Dess-Martin periodinane (61 mg, 0.143 mmol). The mixture was stirred at room temperature for 6 hours. The mixture was then partitioned between dichloromethane and brine, the dichloromethane layer was separated, dried and evaporated to dryness. Purification with CombiFlash® (stationary phase: silica gel; eluent: 40-80% EtOAc/Hexane gradient) gave Example **B** as a white solid. Example **B** was further purified by trituration with MeOH/hexane to give 83 mg of a white solid. m/z: 719 $(M+H)^+$.

Preparation of Example C

Scheme 3



3 4

I. cyclopropylamine, MeCN, rt

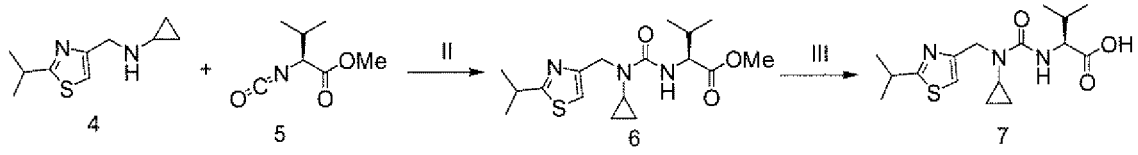
Compound 3

Compound **3** was prepared according to the procedures of J. Med. Chem. 1998, 41, 602, herein incorporated by reference in its entirety for all purposes.

Compound 4

A flask was charged with cyclopropylamine (8.2 mL, 117.8 mmol) at room temperature. A solution of Compound **3** (1 g, 4.71 mmol) in MeCN (8.5 mL) was added dropwise over 5 min. to produce a clear yellow solution that was allowed to stand at room temperature overnight. Volatiles were removed *in vacuo*, and the resulting residue was purified via silica gel chromatography (gradient elution, 0 to 50% EtOAc/hexane) to afford 0.65 g (70%) of **4** as a yellow liquid (LC/MS *m/z* 197 $(M+H)^+$; 218 $(M+Na)^+$).

Scheme 4



4 5 6 7

II. rt, DCM; III. 1M LiOH, THF/H_2O

Compound 5

Compound **5** was purchased from Aldrich or alternatively prepared according to the procedures of J. Org. Chem. 1994, 59, 1937, herein incorporated by reference in its entirety for all purposes.

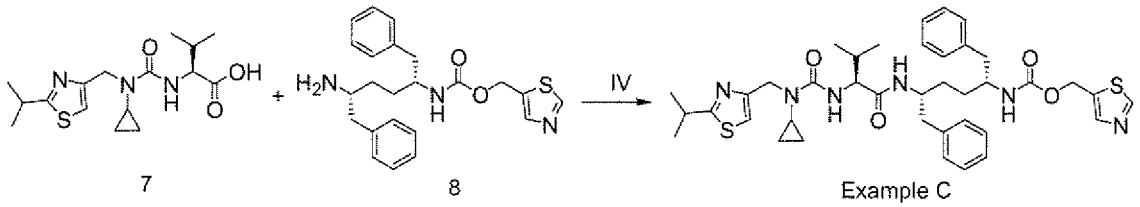
Compound 6

To a solution of Compound **4** in DCM (3 mL) at room temperature was added **5** (0.1 mL, 0.695 mmol). The resulting clear solution was allowed to stand at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was chromatographed directly using silica gel chromatography (gradient elution, 0 to 50% EtOAc/hexane) to produce 0.218 g (89%) of **6** (LC/MS *m/z* 354 $(M+H)^+$; 729 $(2M + Na)^+$) as a colorless glass.

Compound 7

Compound **6** was taken up in THF (5 mL) at room temperature, and LiOH (1 M in H_2O) was added. The resulting reaction mixture was then stirred vigorously for 1.5 h. The reaction mixture was acidified with 1 M HCl to a pH of 3 (monitored using pH test strips). The acidified reaction mixture was then extracted several times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to produce 0.20 g (quantitative yield) of **7** (LC/MS *m/z* 340 $(M+H)^+$) as a colorless film. This material was used without further purification.

Scheme 5



IV. EDC, HOBt, DIPEA, THF

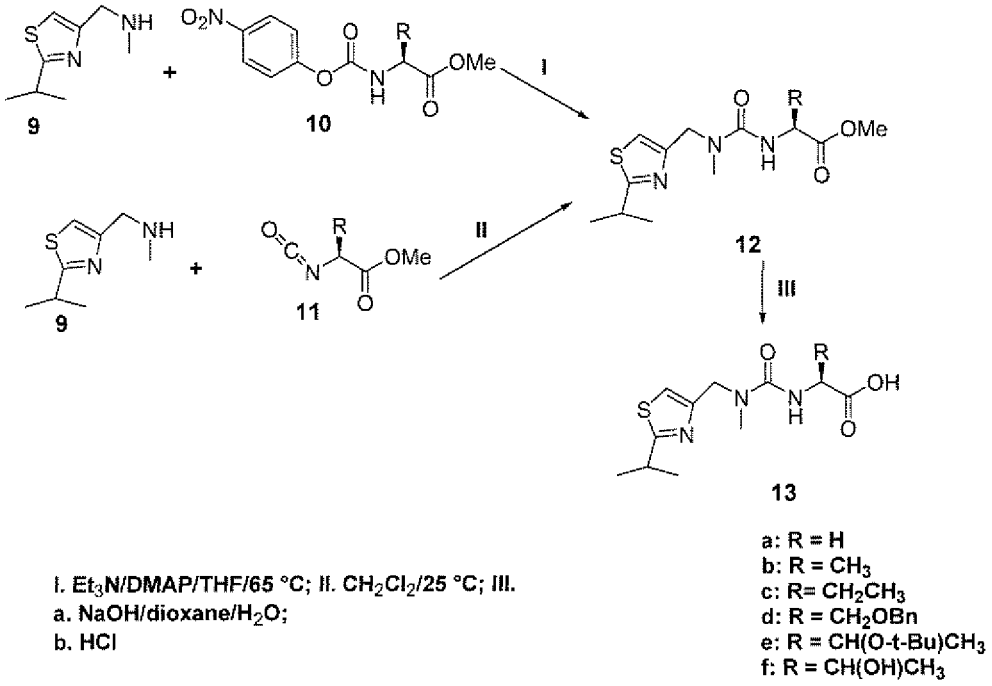
Example C

Compounds **7** (0.034 g, 0.100 mmol) and **8**, (0.034 g, 0.083 mmol) were diluted in THF (2 mL) at room temperature. To the resulting solution were added *N,N*-diisopropylethylamine (0.022 mL, 0.125 mmol), EDC (0.018 mL, 0.099 mmol) and HOBt (0.013 g, 0.099 mmol). The solution was then allowed to stand overnight at room temperature. The solvent was removed *in vacuo* and the residue was taken up in MeCN (0.5 mL) and passed through an Acrodisc LC13

PVDF filter (0.45 μM) prior to purification by preparatory HPLC to afford 0.043 g (71%) of Example **C** as a fluffy white solid. (^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H); 7.82 (s, 1H); 7.27-7.02 (m, 10 H); 6.81 (s, 1H); 5.97 (br d, *J* = 8.7 Hz, 1H); 5.76 (br d, *J* = 7.2 Hz, 1H); 5.21 (dt, *J* = 7.5, 12.6 Hz, 2H); 5.02, br d, *J* = 8.4 Hz, 1H); 4.58 (s, 2H); 4.16 (m, 1H); 3.99 (br t, *J* = 6.6 Hz, 1H); 3.79 (m, 1H); 3.27 (pent, *J* = 6.6 Hz, 1H); 2.85-2.50 (m, 3H); 2.23 (m, 1H); 1.82 (br s, 2H); 1.60-1.22 (m, 4H); 1.36 (d, *J* = 6.6 Hz, 6H); 0.91 (d, *J* = 6.6 Hz, 3H); 0.90-0.7 (m, 4H); 0.80 (d, *J* = 6.6 Hz, 3H); LC/MS *m/z* 731 (M^+)).

Preparation of Examples D-I

Scheme 6



Compound 9

Compound **9** was prepared according to the procedures of J. Med. Chem. 1998, 41, 602.

Compound 10

The structures of Compound **10** were prepared according to the procedures of J. Med. Chem. 1998, 41, 602.

Compound 11

The structures of Compound **11** were purchased from Aldrich or prepared according to the procedures of J. Org. Chem. 1994, 59, 1937.

Compound 12

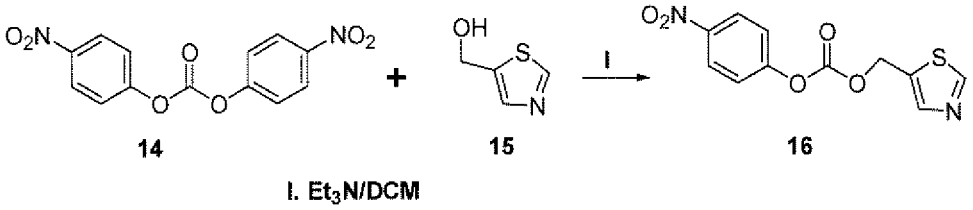
Method 1: To a solution of Compound **9** (0.8 mmol) in THF (2 mL) was added a carbamate of Compound **10** (0.6 mmol), followed by DMAP (16 mg) and triethylamine (0.25 mL). The resulting mixture was heated at 70°C for two hours and diluted with EtOAc. The organic phase was separated, and washed sequentially with saturated aqueous Na_2CO_3, water, and brine, then concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1/1 – 1/3 hexanes/EtOAc gradient) gave compounds of Structure **12**.

Method 2: To a solution of Compound **9** (2.4 mmol) in CH_2Cl_2 (2 mL) was added an isocyanate of Compound **11** (2 mmol). The resulting mixture was stirred for 4 hours and concentrated. Purification of the residue by flash column chromatography (silica gel, hexane/EtOAc 1/1 – 1/3) gave structures of Compound **12**.

Compound 13

To a solution of structures of Compound **12** (1.8 mmol) in dioxane (8 mL) and water (8 mL) was added sodium hydroxide (3.6 mmol). The resulting reaction mixture was stirred for 1 hour and acidified with HCl in dioxane (3.6 mmol). The reaction mixture was extracted with EtOAc and the organic phase was dried with anhydrous $MgSO_4$. Concentration of the dried organic phase gave structures of Compound **13**.

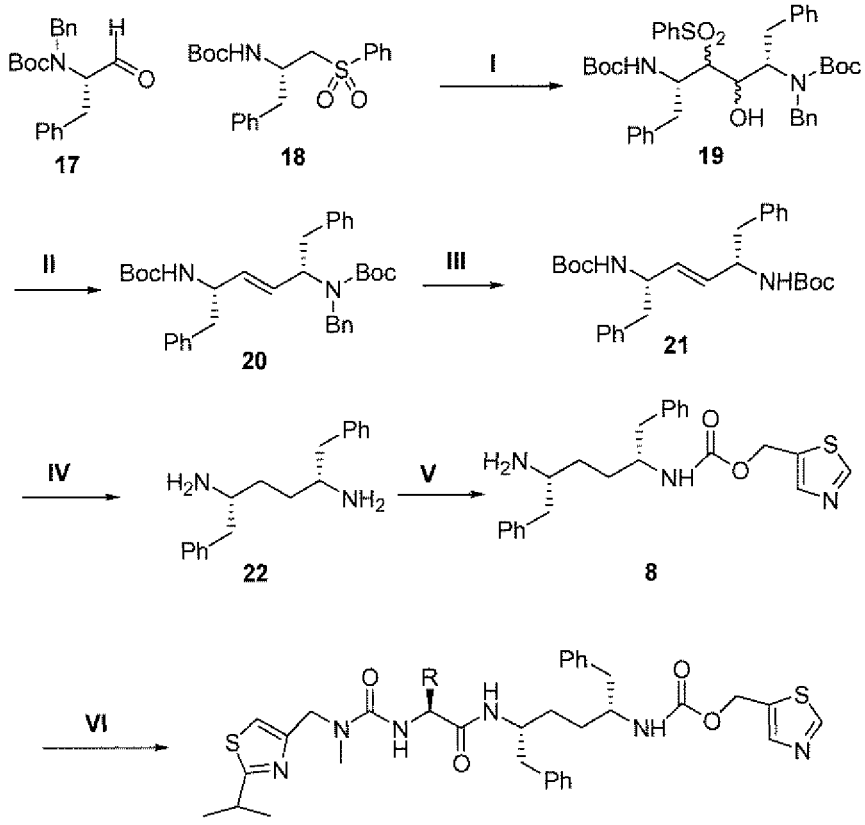
Scheme 7



Compound 16

To a solution of Compound **15** (obtained commercially from Molekula) (17 mmol) in DCM (40 mL) was added Compound **14** (19 mmol), followed by triethylamine (26 mmol). The resulting reaction mixture was stirred for 12 hour and concentrated under reduced pressure. The reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 1/1) gave Compound **16** (4.7 g).

Scheme 8



Examples:
D: R = H
E: R = CH_3
F: R = CH_2CH_3
G: R = CH_2OBn
H: R = $CH(O\text{-}t\text{-}Bu)CH_3$
I: R = $CH(OH)CH_3$

I. a. n-BuLI/-78 C; b.i-$Bu_2Al(OMe)$; II. a. Ac_2O/pyridine; b. Na-Hg/MeOH/THF; III. Na/NH_3/-33 C; IV. a. H_2/10%Pd/C; b. TFA/DCM; V. 16/Et_3N; VI. acid of structure 13/EDC/HOBt

Compound 17

Compound **17** was prepared according to the procedures of Tetrahedron 1997, 53, 4769, herein incorporated by reference in its entirety for all purposes.

Compound 18

Compound **18** was prepared according to the procedures of J. Org. Chem. 1987, 52, 3759, herein incorporated by reference in its entirety for all purposes.

Compound 19

A suspension of Compound **18** (7.4 mmol) in THF (200 mL) was heated under reflux until a clear solution was obtained. The solution was cooled to -78°C and n-butyllithium (14.8 mmol) was added dropwise to provide a solution of the dianion of sulfone **18**.

To a DIBAL-H solution (7.8 mmol) at 0°C was added a solution of MeOH (7.8 mmol) in THF (5 mL). The mixture was stirred for 5 minutes and cooled to -78°C. A solution of Compound **17** (6.6 mmol) in THF (5 mL) was added to the above DIBAL-H/MeOH solution, and the resulting reaction mixture was stirred for another 5 minutes. The resulting solution of aldehyde complexes was transferred to solution of the dianion of sulfone **18**. The resulting mixture was stirred at -78°C for 30 minutes, quenched with an aqueous solution of NH_4Cl, and warmed to 25°C. The mixture was then extracted with EtOAc, and concentrated to give Compound **19** as a mixture of diastereomers. (m/z 737.3 $(M+Na)^+$.

Example 20

To a solution of Compound **19** in DCM (20 mL) was added Ac_2O (1.5 mL), followed by pyridine (3 mL). The resulting mixture was stirred for 12 hours and concentrated. The concentrate was dissolved in MeOH (30 mL) and cooled to 0°C. NaH_2PO_4 (4.9 g) was added to the solution, followed by freshly prepared Na-Hg (6%, 6 g). The resulting mixture was warmed to 25°C and stirred for 12 hours. Water (50 mL) was then added, and the mixture was filtered and concentrated. The concentrate was diluted with EtOAc and washed with brine. The organic phase was concentrated. Purification by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 10/1) gave Compound **20** (1.4 g).

Compound 21

To liquid ammonia (25 mL) at -33°C was added a solution of Compound **20** (1.4 g) in THF (2.5 mL). Sodium was slowly added until the blue color of the

solution persisted. The resulting mixture was stirred for 1 hour. Solid NH_4Cl (6 g) was then added slowly, the mixture was warmed to 25°C, and the ammonia was evaporated. The mixture was diluted with EtOAc, and washed sequentially with water and brine. The solvent was removed under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 5/1) gave Compound **21** (1.15 g).

Compound 22

A mixture of Compound **21** (1.15 g) and 10%Pd/C (160 mg) in MeOH (20 mL) was hydrogenated for 12 hours. CELITE was added and the resulting mixture was stirred for 5 minutes. The mixture was then filtered and concentrated to give an intermediate (1 g). The intermediate (700 mg) was dissolved in DCM (20 mL) and TFA (4 mL), and the resulting mixture was stirred for 4 hours, then concentrated under reduced pressure. The concentrated mixture was diluted with EtOAc, and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. Concentration of the washed EtOAc mixture gave Compound **22** (420 mg).

Compound 8

To a solution of Compound **22** (1.57 mmol) in CH_3CN (16 mL) was added Compound **16** (1.57 mmol), followed by diisopropylethylamine (3.14 mmol). The resulting mixture was stirred for 12 hours. The mixture was then diluted with EtOAc, and washed sequentially with saturated aqueous Na_2CO_3, water and brine. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Compound **8** (460 mg).

Example D

To the solution of Compound **13a** (R= H; 0.08 mmol) and Compound **8** (0.06 mmol) in THF (1 mL) were added HOBt (15 mg), EDC (26 mg), and disopropylethylamine (0.25 mL). The mixture was stirred for 12 hours and

concentrated. Purification by reverse phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Example **D** (27 mg). m/z 663.1 $(M+H)^+$. ^1H-NMR ($CDCl_3$) δ 8.79 (1 H, s), 7.83 (1 H, s), 7.25-7.04 (10 H, m), 6.98 (1 H, s), 6.25 (1 H, m), 5.25 (3 H, m), 4.40 (2 H, s), 4.12 (1 H, m), 3.8 (3 H, m), 3.22 (1 H, m), 2.95 (3 H, s), 2.70 (4 H, m), 1.60 (4 H, m), 1.26 (6 H, d, J = 7 Hz).

Example E

Example **E** was prepared following the procedure for Example **D** (30 mg), except that Compound **13b** was used instead of Compound **13a**. m/z 677.1 $(M+H)^+$.

Example F

Compound **F** was prepared following the procedure for Example **D** (40 mg), except that Compound **13c** was used instead of Compound **13a**. m/z 691.2 $(M+H)^+$. ^1H-NMR ($CDCl_3$) δ 8.80 (1 H, s), 7.83 (1 H, s), 7.25-7.06 (10 H, m), 6.98 (1 H, s), 6.35 (1 H, m), 6.23 (1 H, m), 5.24 (2 H, s), 5.12 (1 H, m), 4.34 (2 H, s), 4.10 (2 H, m), 3.78 (1 H, m), 3.23 (1 H, m), 2.90 (3 H, s), 2.68 (4 H, m), 1.90 (2 H, m), 1.7-1.4 (4 H, m), 1.36 (6 H, d, J = 7.0 Hz), 0.90 (3 H, t, J = 7.3 Hz)

Example G

Example **G** was prepared following the procedure for Example **D** (84 mg), except that Compound **13d** was used instead of Compound **13a**. m/z 783.2 $(M+H)^+$.

Example H

Example **H** was prepared following the procedure for Example **D** (90 mg), except that Compound **13e** was used instead of Compound **13a**. m/z 763.2 $(M+H)^+$.

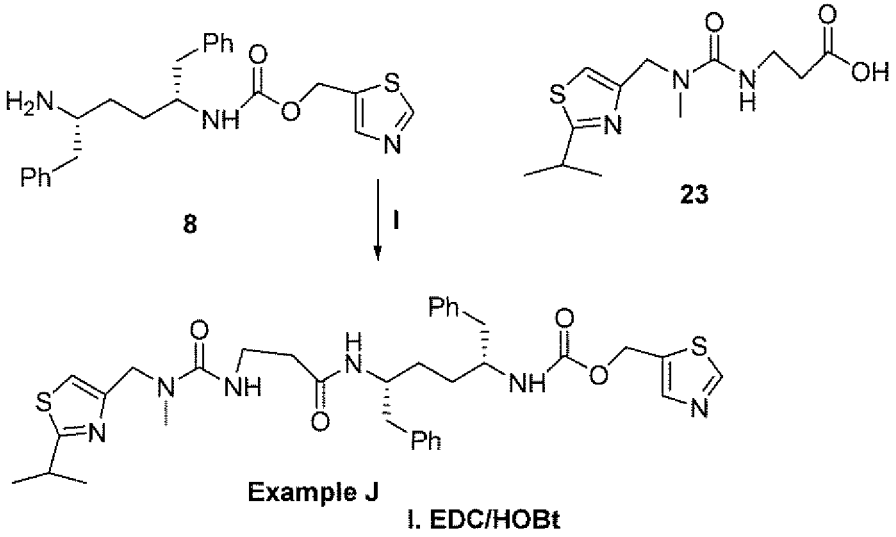
Example I

Example **H** (24 mg) was dissolved in TFA (2 mL) and the mixture was stirred for 12 hours, then concentrated. Purification by reverse phase HPLC

(Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Example I (14 mg). m/z 707.2 $(M+H)^+$. ^1H-NMR ($CDCl_3$) δ 8.82 (1 H, s), 7.85 (1 H, s), 7.26-7.04 (10 H, m), 7.0 (1 H, s), 5.25 (2 H, s), 4.86 (1 H, m), 4.56 (1 H, m), 4.37 (2 H, m), 4.13 (1 H, m), 4.06 (1 H, m), 3.86 (1 H, m), 3.32 (1 H, m), 2.99 (3 H, s), 2.8-2.6 (4 H, m), 1.6-1.4 (4 H, m), 1.37 (6 H, m), 1.15 (3 H, m).

Preparation of Example J

Scheme 9



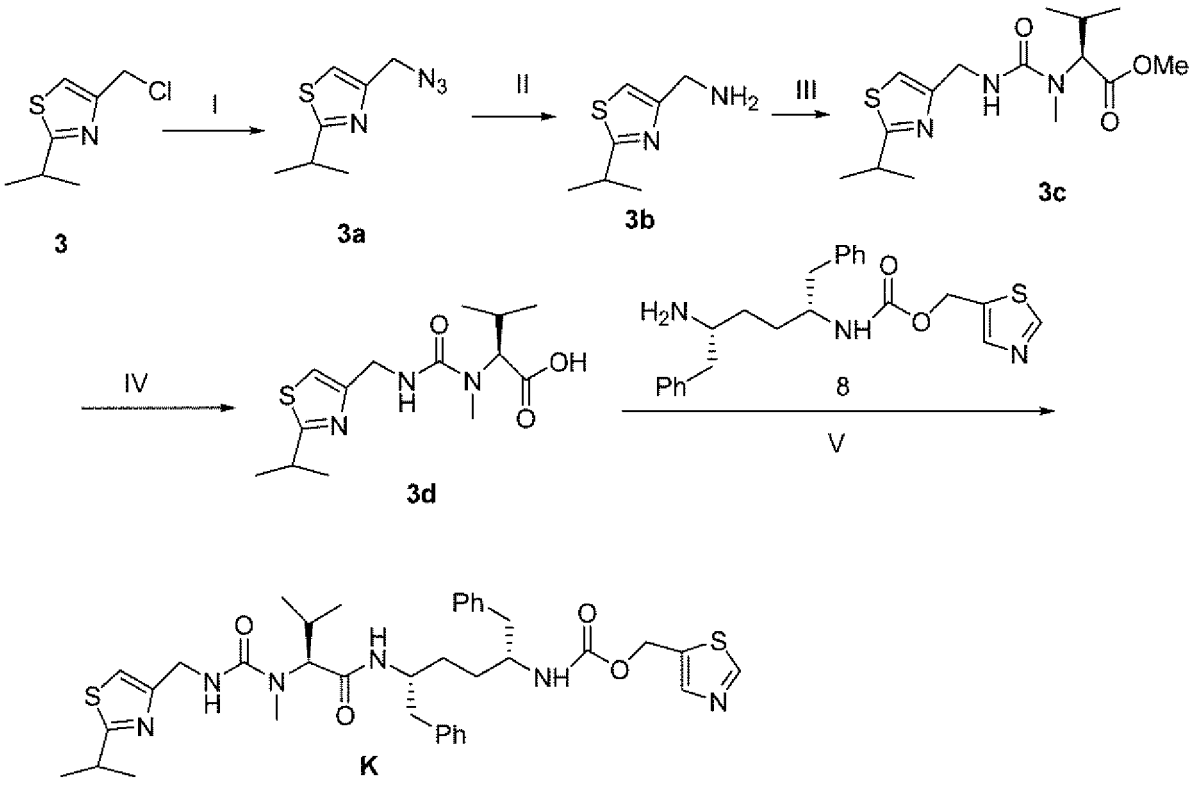
Example J

Compound **23** was prepared following the procedure for Compound **13**, with the exception that methyl 3-isocyanatopropionate was used instead of Compound **11**.

Example **J** was prepared following the procedure for Example **D** (37 mg), except that Compound **23** was used instead of Compound **13a**. m/z 677.2 $(M+H)^+$.

Preparation of Example K

Scheme 10



1. NaN_3/DMF; II. PPh_3/H_2O; III. a. $Cl_3COCOOCCl_3$; b. HCl-$NH_2CHiPrCO_2Et$; IV. a. NaOH; b. HCl; V. EDC/HOBt/compound 8

Example K

Compound 3a

Compound **5a** was prepared following the literature procedure of Synthesis 823, 1976, herein incorporated by reference in its entirety for all purposes.

Compound 3b

To the solution of Compound **3a** (700 mg, 3.9 mmol) in THF (10 mL) was added water (69 μL, 3.9 mmol), followed by triphenylphosphine (1.06 g, 4.0 mmol). The mixture was stirred for 12 hours. Solvents were removed and the mixture was dried to give Compound **3b**, which was used for next step without further purification.

Compound **3c**

To a solution of triphosgene (110 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at 0°C was added a solution of Compound **3b** (1 mmol) and iPrNEt$_2$ (0.38 mL, 2.2 mmol) in CH_2Cl_2 (3.5 mL) over 30 minutes period. The mixture was stirred for 30 minutes, and a solution of amino N-methyl leucine methyl ester HCl salt (182 mg, 1 mmol) and iPrNEt$_2$ (0.34 mL, 2.2 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred for 12 hours, and diluted with EtOAc. The solution was washed with sat. Na_2CO_3 (2x), water (2x), and brine, and dried over Na_2SO_4. Concentration and purification with silica gel flash column gave Compound **5c** (300 mg).

Compound 3d

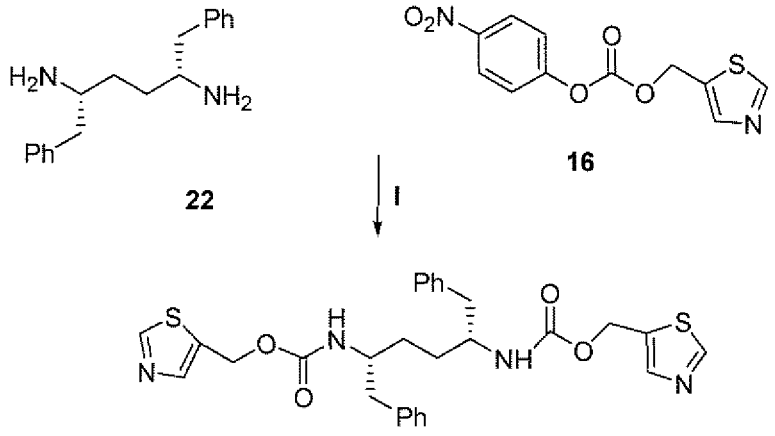
Compound **3d** was prepared following the procedure for Compound **13**, with the exception that Compound **3c** was used instead of Compound **12**.

Example K

Example **K** was prepared following the procedure for Example **D** (7 mg), except that Compound **3d** was used instead of Compound **13a**. m/z 705.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.8 (1 H, m), 7.86 (1 H, s), 7.26-6.8 (11 H, m), 6.10 (1 H, m), 5.5-5.10 (4 H, m), 4.46 (2 H, m), 4.2-3.75 (3 H, m), 3.25 (1 H, m), 2.82/2.4 (3 H), 2.8-2.5 (4 H, m), 2.17 (1 H, m), 1.7-1.2 (10 H, m), 0.8 (6 H, m).

Preparation of Example L

Scheme 11



Example L

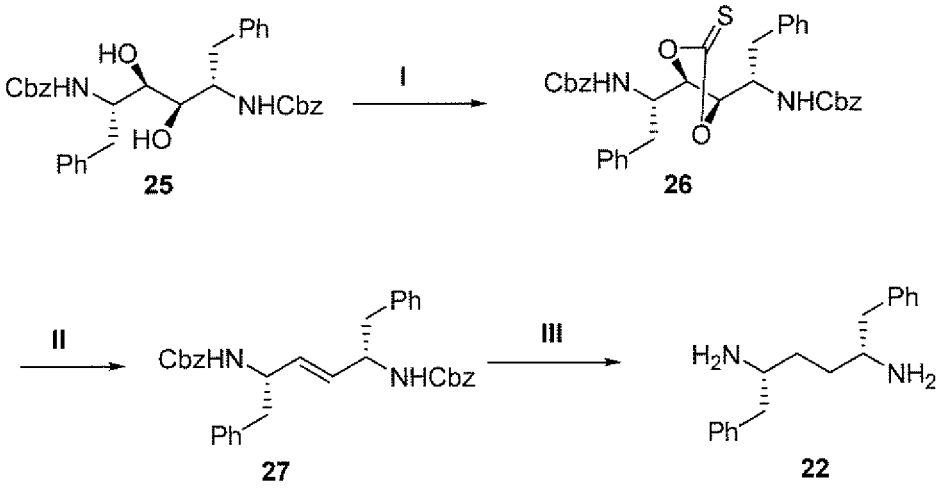
I. Et_3N

Example L

To a solution of Compound **22** (1.57 mmol) in CH_3CN (16 mL) was added Compound **16** (3.14 mmol), followed by triethylamine (4.71 mmol). The resulting mixture was stirred for 12 hours. The reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 1/1) gave Example **L** (460 mg). m/z 551.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.81 (2 H, s), 7.85 (2 H, s), 7.26-7.0 (10 H, m), 5.24 (4 H, s), 4.50 (2 H, m), 3.87 (2 H, m), 2.73 (4 H, m), 1.4-1.2 (4 H, m).

Alternate Preparation of Compound 22

Scheme 12



I. TCDI/THF/65 °C; II. $P(OEt)_3$/160 °C; III. 10%Pd/C/i-PrOH/EtOAc

Compound 25

Compound **25** was prepared following the literature procedure described in J. Org. Chem. 1996, 61, 444 (herein incorporated by reference in its entirety), except that the L-isomer was prepared instead of the D-isomer.

Compound 26

A mixture of Compound **25** (7.4 g) and 1,1'-thiocarbonyldiimidaxole (4.5 g) in THF (260 mL) was heated at 65°C for 54 hours. Solvent was removed from the mixture under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 1/1) gave Compound **26** (7.33 g).

Compound 27

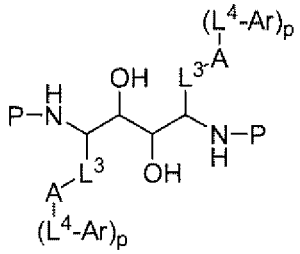
The mixture of Compound **26** (7.3 g) and triethylphosphite (100 mL) was heated at 160°C for 4 hours. Excess reagents were removed under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 3/1) gave Compound **27** (5 g).

Compound 22

A mixture of Compound **27** (250 mg) in i-PrOH/EtOAc (5mL/5mL) was hydrogenated for 14 hours in the presence of 10%Pd/C (75 mg). CELITE was

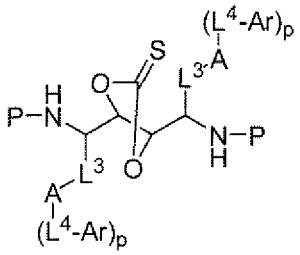
added to the mixture, and the mixture was stirred for 5 minutes. Filtration and evaporation of solvents gave Compound **22** (116 mg).

The skilled practitioner will recognize that the procedure outlined in Scheme 12 can be used to prepare a variety of 1,4-substituted 1,4-diamines analogous to Compound **22**. For example, an amine-protected 2,3-dihydroxy-1,4-diamine analogous to Compound **25** can be prepared:



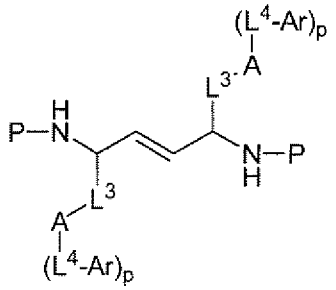
Analogs of Compound 25

wherein L^3, A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group described in described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9), which is herein incorporated by reference in its entirety for all purposes. The analogs of Compound **25** can then be transformed, according to the methods outlined in Scheme **12**, to form analogs of Compound **26**:



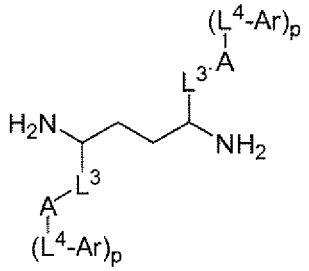
Analogs of Compound **26**;

analogs of Compound **27**:



Analogs of Compound **27**; and

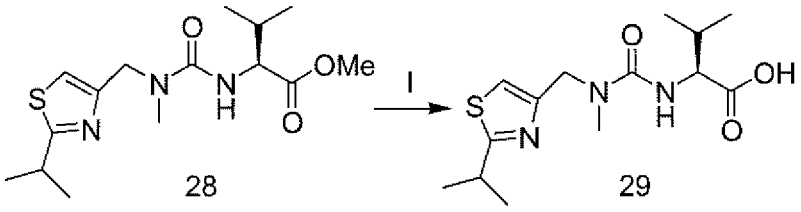
analogs of Compound **22**:



Analogs of Compound **22**.

Preparation of Examples M and N

Scheme 13



I. a. LiOH, THF/H_2O, 25 °C; b. HCl

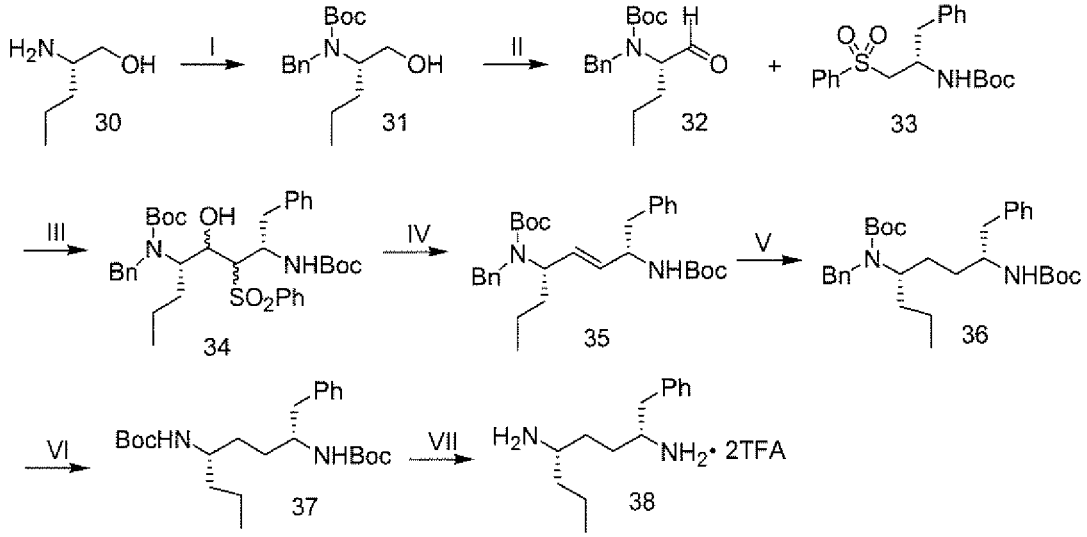
Compound 29

Compound **28** was prepared using a procedure similar to that used to prepare Compound **6** (described in Scheme 4) except that Compound **9** was used instead of Compound **4**.

To a solution of Compound **28** (0.757 g, 2.31 mmol) in THF (9 mL) at room temperature was added freshly prepared 1M LiOH (4.6 mL, 4.6 mmol). After 1.5 h, 1 M HCl (7 mL, 7 mmol) was added and the reaction mixture extracted thoroughly with EtOAc (5 X 15mL). The combined organic layers were dried over

anhydrous Na_2SO_4 and the volatiles removed *in vacuo* to afford 0.677 g (93%) of Compound **29** as a colorless glassy solid (LC/MS *m/z* 314.0 $(M+H)^+$) that was used in the following procedures without further purification.

Scheme 14



I. a. PhCHO, MeOH; b. $NaBH_4$; c. Boc_2O, THF/H_2O. II. $Pyr{\bullet}SO_3$, Et_3N, DMSO 0 °C. III. *n*-BuLi, $MeOAl(i\text{-}Bu)_2$, THF, -78 °C. IV. a. Ac_2O, pyr, CH_2Cl_2, b. 6% Na/Hg, Na_2HPO_4, MeOH. V. H_2, 10% Pd/C, MeOH. VI. Na/NH_3, THF, -35 °C. VII. 20% TFA/DCM.

Compound 30

Compound **30** was purchased from Aldrich Chemical Co., and used without further purification.

Compound 31

To a solution of Compound **30** (8.25 g, 80 mmol) in MeOH (50 mL), was added benzaldehyde (8.1 mL, 80 mmol) and the resulting solution was allowed to stir at room temperature. After 2 h, the reaction mixture was cooled to 0°C and $NaBH_4$ (3.33 g, 88 mmol) was added in portions. After allowing the reaction mixture to warm to room temperature over 2 h, glacial acetic acid (2 mL) was added. The resulting viscous solution was concentrated *in vacuo*. EtOAc and H_2O (50 mL each) were added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$, brine, and

concentrated *in vacuo*. The resulting material was taken up in THF (25 mL) and H_2O (25 mL) at room temperature and Boc_2O (15.1 g, 69.2 mmol) was added to produce an opaque suspension that was stirred vigorously for 2 h at room temperature. THF was removed *in vacuo*, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography on SiO_2 (3/1 Hex/EtOAC) afforded 18.5 g (79%) of Compound **31** as a colorless oil (LC/MS *m/z* 293.9 $(M+H)^+$.

Compound 32

Compound **31** (5.95 g, 20.3 mmol) and Et_3N (9.9 mL, 71 mmol) were diluted in DMSO (65 mL) and allowed to age at room temperature for 30 min before cooling to 0°C. Pyridine•SO_3 was added in one portion and the reaction mixture was maintained at 5°C to prevent freezing. After 45 min, the reaction mixture was poured into icewater and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, H_2O, and dried over anhydrous $MgSO_4$ prior to concentration *in vacuo* (bath temperature 25 °C) to produce 4.39 g (74%) of Compound **32** as a clear, yellow colored oil that was used without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (major rotamer) 9.36 (br s, 1H); 5.01 (d, J = 15 Hz, 1H); 4.12 (d, J = 15 Hz, 1H); 3.45 (m, 1H); 2.04-1.88 (m, 1H); 1.80-1.58 (m, 1H); 1.54-1.20 (m, 2H); 1.47 (s, 9H); 0.91 (t, J = 7.2 Hz, 3H). (minor rotamer) 9.46 (br s, 1H); 4.71 (d, J = 15 Hz, 1H); 4.20 (d, J = 15 Hz, 1H); 3.78 (m, 1H); 2.04-1.88 (m, 1H); 1.80-1.58 (m, 1H); 1.54-1.20 (m, 2H); 1.47 (s, 9H); 0.91 (t, J = 7.2 Hz, 3H)

Compound 34

A suspension of Compound **33** (6.23 g, 16.6 mmol) in THF (500 mL) was heated under reflux until a homogeneous solution was obtained. The solution was cooled to -78°C and 1.6M *n*-BuLi (19.7 mL, 31.5 mmol) was introduced to produce a clear yellow solution. Meanwhile, DIBAL-OMe was prepared by

dilution of DIBAL-H (1M in hexanes, 18.1 mL, 18.1 mmol) in THF (8 mL) and cooling to 0°C prior to addition of MeOH (0.73 mL, 18.1 mmol). This solution was allowed to age while Compound **32** (4.39 g, 15.1 mmol) was diluted in THF (15 mL) and cooled to -78°C. The DIBAL-OMe solution was cannulated to the solution of Compound **32** and allowed to age for 5 min prior to cannulation to the sulfur dianion solution. The resulting clear yellow solution was allowed to age at -78°C for 1h. The reaction was quenched by addition of saturated NH_4Cl (100 mL) at -78°C and allowed to warm to room temperature. Water was added until all precipitated solids were dissolved and the layers separated. The THF layer was concentrated *in vacuo* while the aqueous layer was extracted with EtOAc. The recombined organic layers were washed with brine, and the resulting emulsion was treated with solid NaOH until homogeneous bilayers resulted. The aqueous layer was extracted with EtOAc and the combined organics dried over anhydrous Na_2SO_4. Concentration *in vacuo* produced 9.57 g (95%) of Compound **34** as an amorphous white solid (LC/MS *m/z*: 689.3 $(M+Na)^+$) that was used in the following procedures without further purification.

Compound 35

Crude Compound **34** was suspended in CH_2Cl_2 (65 mL) followed by addition of pyridine (6.7 mL, 83 mmol) and acetic anhydride (3.5 mL, 36.5 mmol). The resulting solution was allowed to age at room temperature overnight. MeOH (6 mL) was added and after 10 min, the reaction was poured into brine. Addition of water produced a bilayer that was separated and the aqueous phase was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce 8.95 g (88%) of a white solid that was immediately taken up in MeOH (100 mL). Na_2HPO_4 (11.4 g, 80.3 mmol) was added and the resulting slurry was cooled to 0°C prior to addition of Na-Hg (6%, 14.5 g, 37.8 mmol) in portions. After aging at room temperature

overnight, H_2O (30 mL) was added and the reaction was filtered through a celite pad. MeOH was removed *in vacuo* and the aqueous residue was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a yellow oil that was purified by chromatography on SiO_2 (0-15% EtOAc/hexanes) to afford 2.14 g (34%) of Compound **35** as a colorless oil (LC/MS *m/z*: 531.2 $(M+Na)^+$).

Compound 36

Compound **35** (1.73 g, 3.4 mmol) was diluted in MeOH (7.5 mL) and 10% Pd/C (0.36 g, 0.34 mmol) was added. The atmosphere was replaced with a H_2 balloon and the reaction mixture allowed to age at room temperature. After 2 h, the reaction mixture was filtered through a pad of celite, the filtrate was washed several times with MeOH, and the combined organic layers were concentrated *in vacuo* to afford 1.45 g (83%) of Compound **36** as a colorless oil (LC/MS *m/z*: 533.2 $(M+Na)^+$) that was used in the following procedures without further purification.

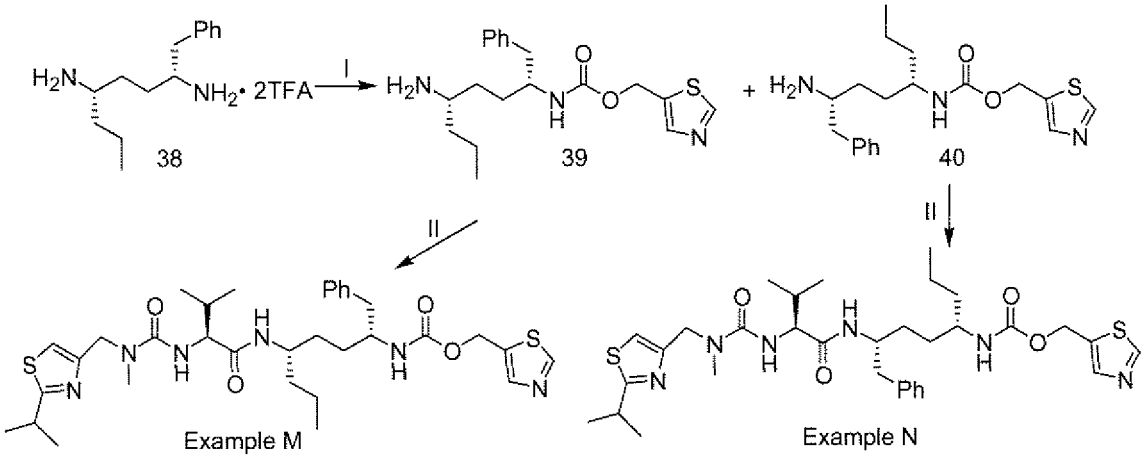
Compound 37

Compound **36** (0.528 g, 1.03 mmol) was diluted in THF (3 mL) and added to liquefied ammonia (approx. 20 mL) at -35°C. Small pieces of Na were added until a blue color persisted. After 1.5 h, solid NH_4Cl was added in portions until the remaining Na was destroyed and the ammonia was allowed to escape at ambient temperature. Water and EtOAc (20 mL each) were added, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford 0.395 g (91%) of Compound **37** as an amorphous white solid that was used without further purification in the following procedures (LC/MS *m/z*: 421.1 $(M+H)^+$; 443.2 $(M+Na)^+$).

Compound 38

Compound **37** (0.362 g, 0.861 mmol) was diluted in CH_2Cl_2 (3.2 mL). Trifluoroacetic acid (0.8 mL) was added and the clear solution was allowed to age overnight. Following concentration *in vacuo,* the residue was azeotroped with toluene several times to remove residual TFA. 0.382 g (99%) of the bis-trifluoroacetate salt of Compound **38** was collected as a colorless oil that was used without further purification (LC/MS *m/z*: 221.1$(M+H)^+$).

Scheme 15



I. carbonate 16, DIPEA, MeCN; II. acid 29, EDC, HOBt, DIPEA, THF

Compounds 39 and 40

Compound **38** (0.382 g, 0.852 mmol) was diluted in MeCN (10 mL) and *N,N*-diisopropylethylamine (0.60 mL, 3.41 mmol) was added, followed by a solution of Compound **16** in MeCN (1.5 mL). The clear, yellow solution was allowed to age at room temperature for 4h and the volatiles were removed *in vacuo.* The residue was taken up in a 3/1 $CHCl_3$/IPA (v/v, 13 mL) and treated with saturated Na_2CO_3 (3 mL). The resulting suspension was diluted with H_2O (3 mL), and the aqueous phase thoroughly extracted with 3/1 $CHCl_3$/IPA. The combined organic layers were dried over a 3/2 (w/w) mixture of anhydrous Na_2SO_4/anhydrous Na_2CO_3 and concentrated *in vacuo.* Chromatography on SiO_2 (0-20% MeOH/CH_2Cl_2) afforded 0.043 g (14%) of Compound **39** as a colorless film

(LC/MS *m/z*: 362.1 $(M+H)^+$) and 0.105 g (34%) of Compound **40** as a colorless film (LC/MS *m/z*: 362.1 $(M+H)^+$).

Example M

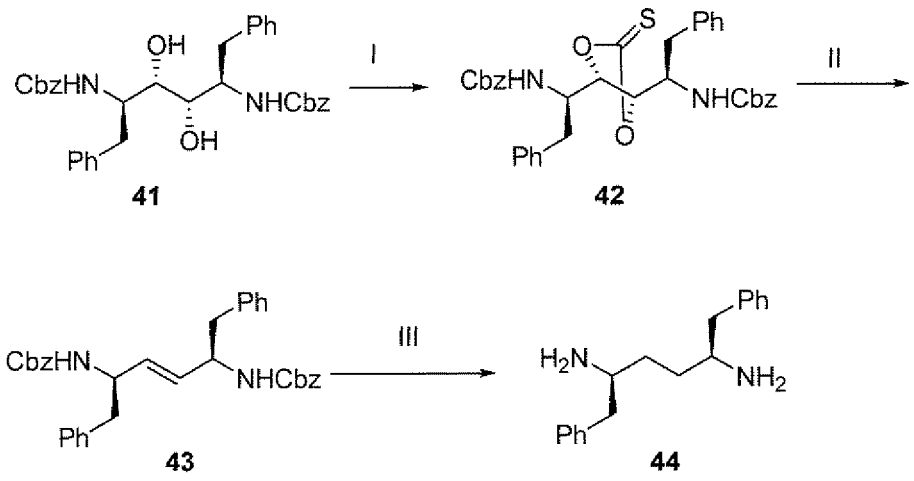
A flask was charged with Compound **39** (0.048 g, 0.133 mmol) and Compound **29** was added as a 0.2 M solution in THF (0.8 mL, 0.160 mmol). THF (1 mL) was added, followed by DIPEA (0.026 mL, 0.145 mmol), HOBt (0.022 g, 0.160 mmol) and finally EDC (0.028 mL, 0.160 mmol). The clear, colorless solution was allowed to age overnight. Volatiles were removed *in vacuo* and the residue chromatographed on SiO_2 (0-20% $MeOH/CH_2Cl_2$). Fractions containing the desired compound were concentrated *in vacuo* and submitted to preparatory LC/MS purification to afford 0.018 g (20%) of Example **M** as a colorless film LC/MS *m/z*: 657.2 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 8.95 (s, 1H); 7.88 (br s, 1H); 7.27-7.04 (m, 5H); 7.04 (s, 1H); 6.60-6.20 (m, 2H); 5.22 (m, 2H); 5.12 (d, *J* = 9.3 Hz, 1H); 4.50 (m, 2H); 4.01 (br s, 1H); 3.83 (m, 2H); 3.38 (m, 1H); 3.10-2.94 (m, 3H); 2.74 (m, 2H); 2.23 (m, 1H); 1.64-1.15 (m, 8H); 1.40 (d, *J* = 6.9Hz, 6H); 0.96 (m, 6H); 0.83 (t, *J* = 6.9 Hz, 3H).

Example N

Example **N** was prepared using procedures similar to those used to prepare Example **M**, using the following reagents: Compound **40** (0.055 g, 0.152 mmol); Compound **29** (0.92 mL of 0.2 M THF solution, 0.183 mmol); THF (1 mL); DIPEA (0.040 mL, 0.228 mmol); HOBt (0.025 g, 0.182 mmol); EDC (0.032 mL, 0.182 mmol). 0.087 g (87%) of Example **N** was isolated as a colorless film (LC/MS *m/z*: 657.2 $(M+H)^+$; ^{1}H-NMR CDCl3, 300 MHz) δ 8.84 (s, 1H); 7.86 (s, 1H); 7.27-7.04 (m, 5H); 7.04 (s, 1H); 6.28 (br s, 1H); 6.12 (br s, 1H); 5.25 (m, 2H); 5.11 (d, *J* = 9.0 Hz, 1H); 4.62-4.32 (m, 2H); 4.19 (m, 1H); 4.01 (br s, 1H); 3.53 (m, 1H); 3.10-2.90 (m, 3H); 2.72 (d, *J* = 6.0 Hz, 2H); 2.29 (m, 1H); 1.65-1.18 (m, 8H); 1.39 (d, *J* = 6.9 Hz, 6H); 1.00-0.78 (m, 9H).

Preparation of Examples O and P

Scheme 16



I. TCDI/THF/65 °C; II. $P(OEt)_3$/160 °C; III. H_2, 10% Pd/C.

Compound 41

Compound **41** was prepared following the procedure described in *J. Org. Chem.* 1996, *61*, 444-450.

Compound 42

A mixture of Compound **41** (1.73 g, 3 mmol) and 1,1'-thiocarbonyldiimidazole (1.14 g, 6.1 mmol) in THF (60 mL) was heated at 65°C for 72 hours. Solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and washed successively with 1N HCl, water, and brine, and dried over $MgSO_4$. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 1/1) gave Compound **42** (980 mg). m/z: 611.1 $(M+H)^+$.

Compound 43

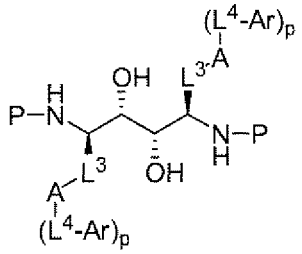
A mixture of Compound **42** (980 mg) and triethyl phosphite (10 mL) was

heated at 160°C for 14 hours. The excess reagents were removed under reduced pressure. Recrystallization from a mixture of hexanes (11 mL) and EtOAc (3.6 mL) gave Compound **57** (580 mg). m/z: 557.3 $(M+Na)^+$.

Compound 44

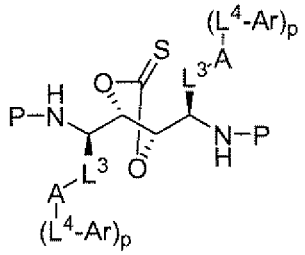
A mixture of Compound **43** (580 mg) in i-PrOH/EtOAc (12 mL/12 mL) was hydrogenated under high pressure (100 psi) for 24 hours in the presence of 10%Pd/C (200 mg). Celite was added and the mixture was stirred for 5 minutes. Filtration and evaporation gave Compound **44** (285 mg). m/z: 269.1 $(M+H)^+$.

The skilled practitioner will recognize that the procedure outlined in Scheme **16** can be used to prepare a variety of 1,4-substituted 1,4-diamines analogous to Compound **44**. For example, an amine-protected 2,3-dihydroxy-1,4-diamine analogous to Compound **41** can be prepared:



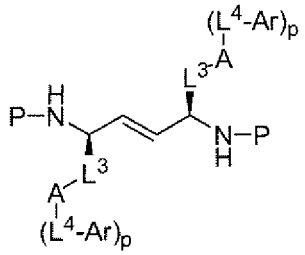
Analogs of Compound **41**

wherein L^3, A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group described in described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9). The analogs of Compound **41** can then be transformed, according to the methods outlined in Scheme **16**, to form analogs of Compound **42**:



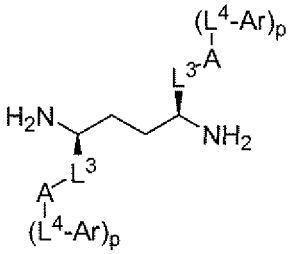
Analogs of Compound **42**;

analogs of Compound **43**:



Analogs of Compound **43**; and

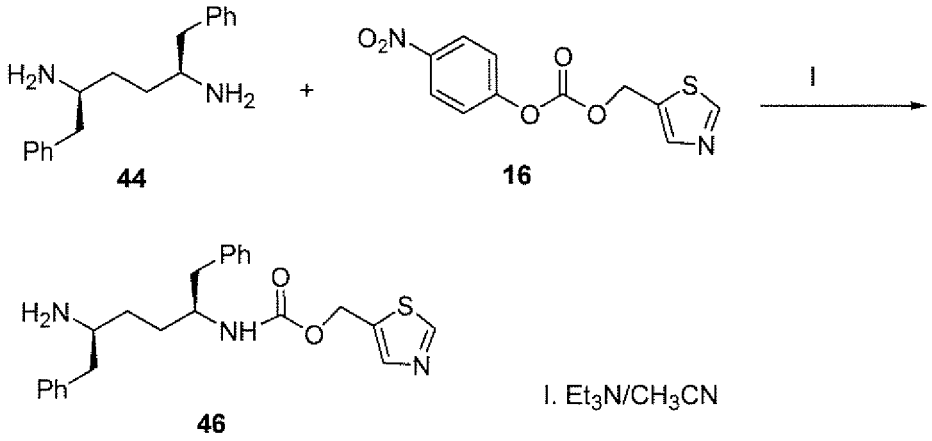
analogs of Compound **44**:



Analogs of Compound **44**.

It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **41** having the appropriate stereochemical configuration at the chiral centers.

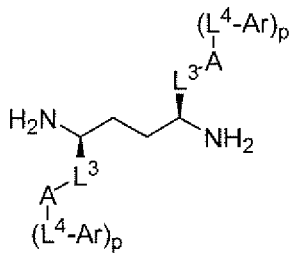
Scheme 17



Compound 46

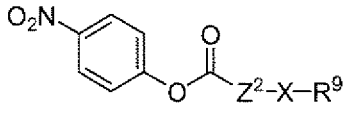
To the solution of Compound **45** (950 mg, 3.5 mmol) in CH_3CN (36 mL) at 0°C was added Compound **16** (892 mg, 3.2 mmol), followed by diisopropylethylamine (1.2 mL, 7 mmol). The mixture was stirred for 12 hours at 25°C. The mixture was diluted with EtOAc, and washed successively with saturated Na_2CO_3, water, and brine. Purification by flash column chromatography (silica gel, 100% EtOAc to CH_2Cl_2/MeOH = 4/1) gave Compound **46** (770 mg). m/z: 410.1 $(M+H)^+$.

The skilled practitioner will recognize that the procedure outlined in Scheme **17** can be used to prepare a variety of compounds analogous to Compound **46**. For example, 1,4-diamines analogous to Compound **44** can be prepared as discussed above:



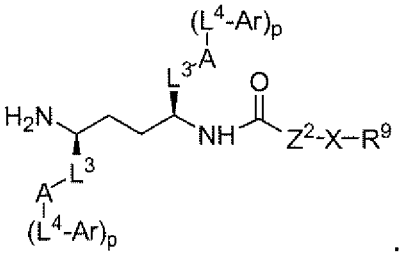
Analogs of Compound **44**.

The analogs of Compound **44** can then be reacted with analogs of Compound **16**:



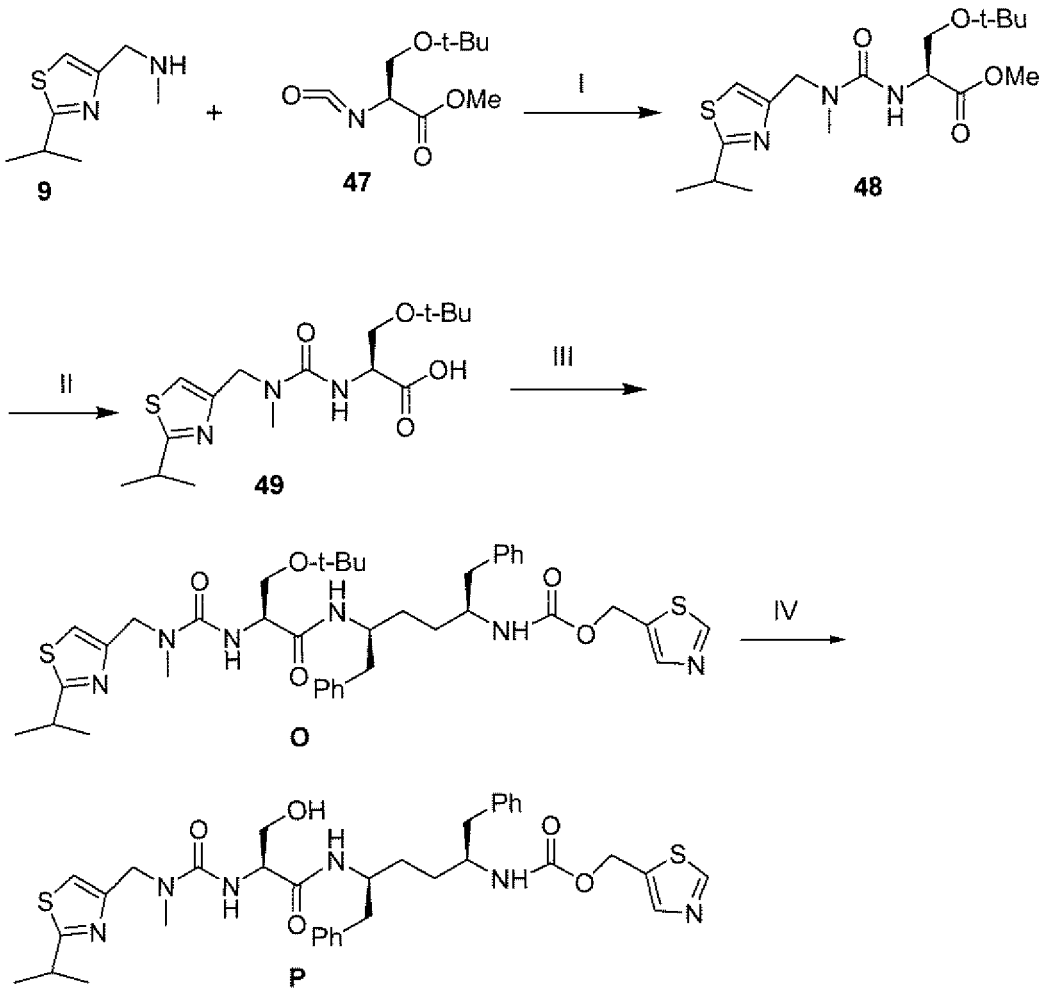
Analogs of Compound **16**,

(wherein Z^2, X, and R^9 are as defined herein) to form analogs of Compound **46**:



It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **44** having the appropriate stereochemical configuration at the chiral centers.

Scheme 18



I. CH_2Cl_2/25 °C; II. a. NaOH/*dioxane*/H_2O; b. HCl; III. amine 46/EDC/HOBt; IV. a. TFA; b. NaOH

Compound 47

Compound **47** is commercially available from TCI.

Compound 48

To a solution of Compound **9** (500 mg, 3 mmol) in CH_2Cl_2 (3 mL) was added Compound **47** (500 mg, 2.5 mmol). The mixture was stirred for 14 hours. Purification by flash column chromatography (hexanes/EtOAc = 1/1.5) gave Compound **48** (242 mg). m/z: 372.1 $(M+H)^+$.

Compound 49

To a solution of Compound **48** (240 mg, 0.65 mmol) in dioxane (4 mL) and water (4 mL) was added sodium hydroxide (40 mg, 1 mmol). The mixture was stirred for 1 hour and acidified with 4 N HCl in dioxane (0.25 mL, 1 mmol). The mixture was extracted with EtOAc and organic phase was dried with $MgSO_4$. Concentration gave Compound **49** (200 mg). m/z: 356.2 $(M-H)^+$.

Example O

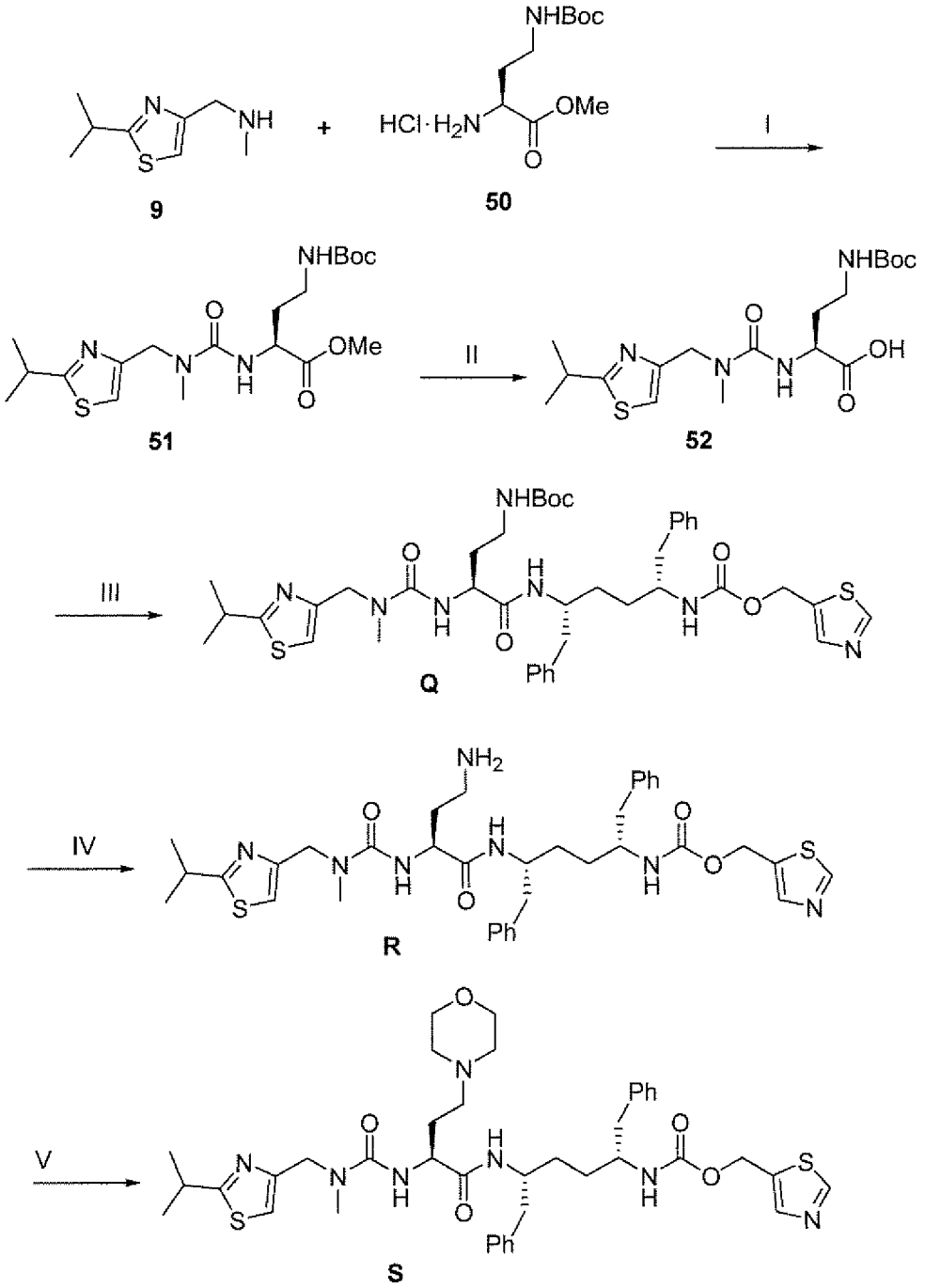
To a solution of corresponding acid **49** (30 mg, 0.08 mmol) and Compound **46** (22 mg, 0.05 mmol) in THF (1 mL) were added HOBt (15 mg, 0.11 mmol), EDC (20 μL, 0.11 mmol), and disopropylethylamine (0.2 mL). The mixture was stirred for 12 hours and concentrated. Purification by flash column chromatography (hexanes/EtOAc = 1/5 to 0/100) gave Example **O** (17 mg). m/z: 749.3 $(M+H)^+$.

Example P

To Example **O** (17 mg) was added TFA (2 mL). The mixture was stirred for 3 hours and concentrated. The mixture was diluted with THF (2 mL) and 1.0 N NaOH solution was added until pH 11. The mixture was stirred for 10 minutes, and extracted with EtOAc. The organic phase was washed with water and brine. Purification by flash column chromatography (EtOAc) gave Example **P** (12 mg). ^{1}H-NMR ($CDCl_3$) δ 8.76 (1 H, s), 7.79 (1 H, s), 7.25-6.9 (11 H, m), 6.51 (1 H, broad), 5.42 (1 H, m), 5.18 (2 H, m), 4.42 (2 H, m), 4.22 (1 H, m), 4.10 (1 H, m), 3.95 (1 H, m), 3.79 (1 H, m), 3.58 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.9-2.5 (4 H, m), 1.6-1.2 (10 H, m); m/z: 693.2 $(M+H)^+$.

Preparation of Examples Q, R, and S

Scheme 19



I. CDI, DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, DIPEA, EDC, HOBt, THF;
IV.a. HCl/dioxane; b. Na_2CO_3; V.
$(BrCH_2CH_2)_2O$, $NaHCO_3$, DMF

Compound 50

Compound **50** is commercially available from Chem Impex International, and used without further purification.

Compound 51

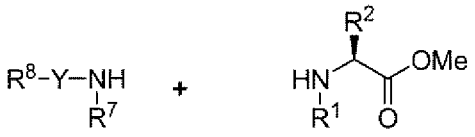
Compound **50** (7.0 g, 26.0 mmol) was dissolved in CH_2Cl_2 (330 mL) and 1,1-carbonyldiimidazole (4.22 g, 26.0 mmol) was added, followed by i-Pr_2NEt (19 mL, 104 mmol). The solution was stirred at 25°C for 12 hours. Compound **9** (4.44 g, 26.0 mmol) was dissolved in 20 mL of CH_2Cl_2 and added to the reaction mixture. The solution was stirred at 25°C for 7 hours. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate and washed with water and brine. The organic layers were dried (Na_2SO_4), filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 66-100% EtOAc/Hexane gradient) gave Compound **51** (7.34 g). m/z: 429.0 $(M+H)^+$.

Compound 52

Compound **51** (7.34 g, 17.13 mmol) was dissolved in THF (90 mL) and 1M aqueous LiOH (35 mL) was added. The mixture was stirred at 25°C for 0.5 hour. The reaction was quenched with 1M HCl (51 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to provide Compound **52** (7.00 g). The recovered Compound **52** was used in the next step without further purification. m/z: 415.0 $(M+H)^+$.

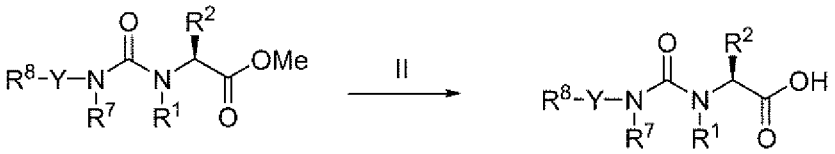
The skilled practitioner will recognize that the procedure outlined in Scheme **19** can be used to prepare a variety of compounds analogous to

Compounds **51** and **52**. For example, amines analogous to Compound **9** can be reacted with the appropriate amino ester analogous to Compound **50**:



Cmpd **9** Analog Cmpd **50** Analog,

to form compounds analogous to Compound **51**, which are further reacted to form compounds analogous to Compound **52**:



Cmpd **51** Analogs Cmpd **52** Analogs;

wherein R^1, R^2, R^7, R^8 and Y are as defined herein.

It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **50** having the appropriate stereochemical configuration at the chiral center.

Example Q

Compound **52** (2.57 g, 6.21 mmol) was dissolved in THF (67 mL). Compound **8** (2.10 g, 5.13 mmol) was added, followed by HOBt (1.04 g, 7.70 mmol), i-Pr_2NEt (3.67 mL, 20.52 mmol), and EDC (1.82 mL, 10.26 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5% iPrOH/CH_2Cl_2) gave Example **Q** (3.02 g). m/z: 806.2 $(M+H)^+$.

Example R

Example **Q** (3.02 g, 3.74 mmol) was suspended in 4.0 N HCl/dioxane solution (30 mL) and stirred at 25°C for 3 hours. Solvent was removed under reduced pressure and Et_2O was poured into the reaction mixture. The resulting suspension was stirred vigorously for 1.5 hours. The solid was allowed to settle and the ether layer was decanted. Washing of the precipitate with Et_2O was repeated two more times. The product was dried *in vacuo* to afford a white solid (3.18 g, quantitative yield). Saturated aqueous Na_2CO_3 solution was added to above solid (3.18 g) with stirring until solid disappeared. The aqueous solution was extracted with ethyl acetate. The organic phases were dried over Na_2SO_4, filtered, and evaporated to afford Example **R** as a yellow foam (2.44g, 81%). The recovered Example **R** was used without further purification in the next step. m/z: 706.1 $(M+H)^+$.

Example S

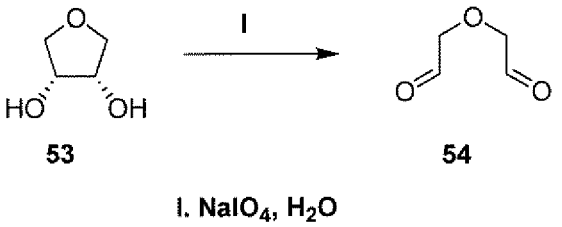
Method I:

Example **R** (1.00g, 1.42 mmol) was dissolved in DMF (20 mL) and bromoethyl ether (196 μL, 1.56 mmol) was added dropwise, followed by $NaHCO_3$ (0.239 g, 2.84 mmol). The reaction mixture was stirred at 25°C for 2 hours. The solution was heated to 65°C and stirred for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 filtered, and evaporated. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/water) gave Compound **70** (580 mg, 53%). ^1H NMR ($CDCl_3$) δ 8.98 (s, 1H); 7.90 (s, 1H); 7.75 (m, 1H); 7.40-7.00 (m, 11H), 6.55 (br s, 1H); 5.58 (m, 1H); 5.28, 5.19 (d_{AB}, J=14 Hz, 2H); 4.70-4.37 (m,

3H); 3.99 (m, 5H); 3.76 (br s, 1H); 3.65-3.30 (m, 3H); 2.97 (m, 5H); 2.90-2.60 (m, 6H); 2.28 (br s, 1H); 1.91 (br s, 1H); 1.60-1.30 (m, 10H). m/z: 776.2 $(M+H)^+$

Method II:

Scheme 20



53 **54**

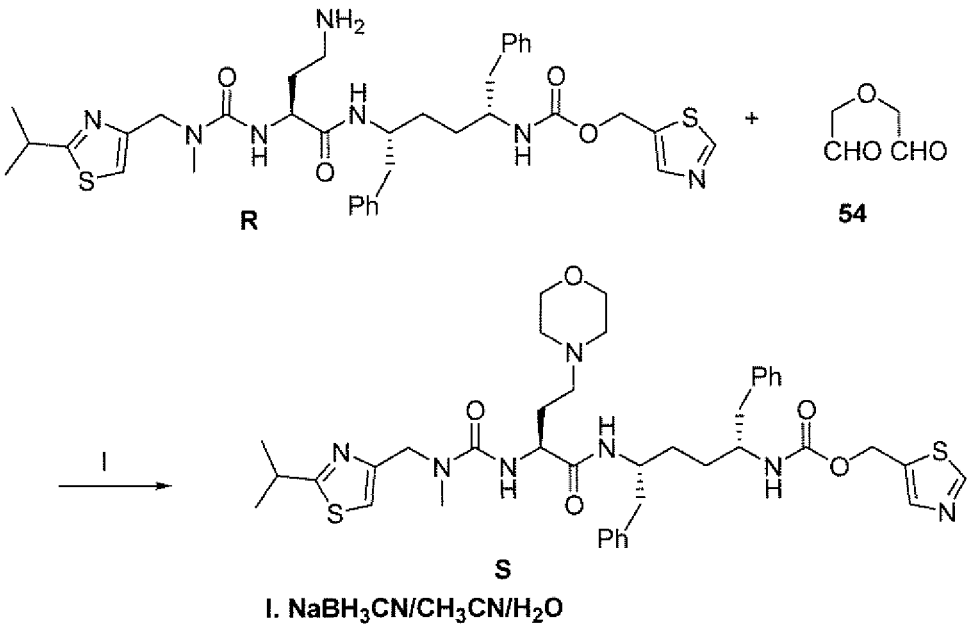
I. $NaIO_4$, H_2O

Compound 54

Compound **54** was prepared following the procedure described in J. Med. Chem. 1993, *36*, 1384 (herein incorporated by reference in its entirety for all purposes).

To solution of Compound **53** (0.550 g, 5.28 mmol) (Sigma-Aldrich) in H_2O (8.8 mL) at 0°C was added $NaIO_4$ (1.016 g, 4.75 mmol). The mixture was allowed to slowly warm to 25°C and stirred for 12 hours. Solid $NaHCO_3$ was added to the reaction mixture until pH 7. $CHCl_3$ (16 mL) was added and the mixture was allowed to stir for 5 minutes. The mixture was filtered and the solid was washed with $CHCl_3$ (6 mL). The combined $H_2O/CHCl_3$ solution was used directly in the next step without further purification.

Scheme 21

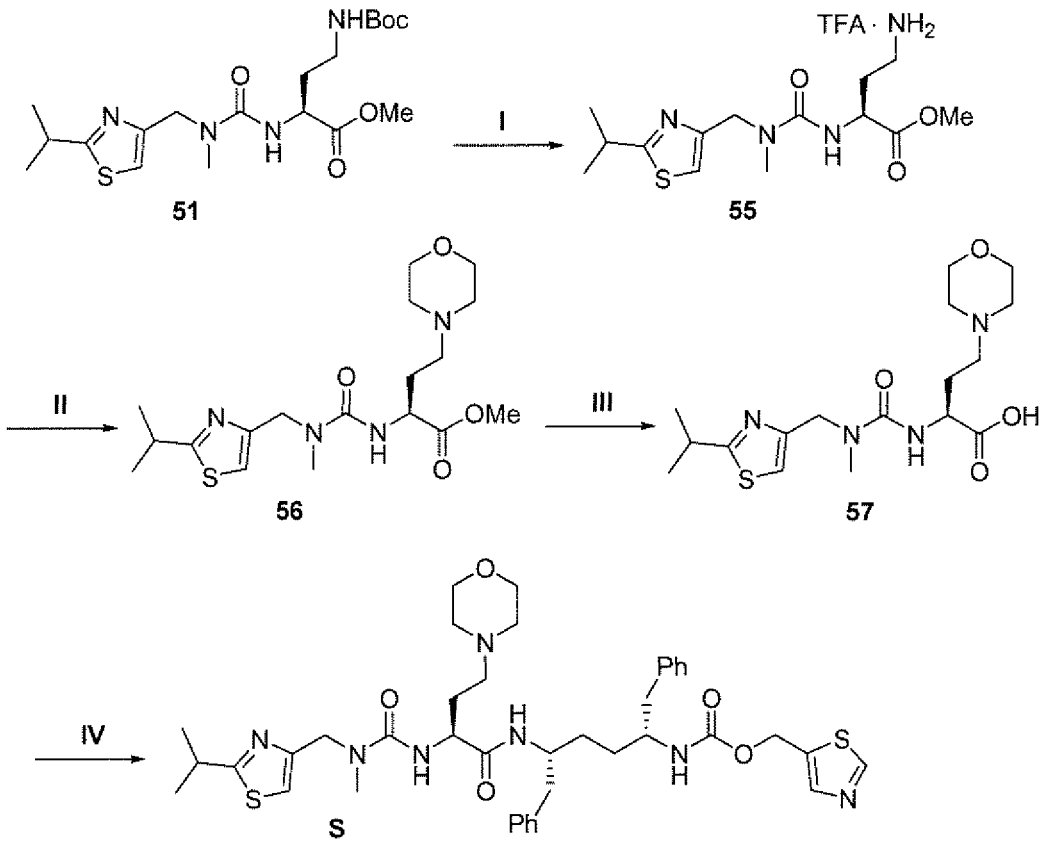


Example S

To a solution of Example **R** (70 mg, 0.1 mmol) in CH_3CN (5 mL) was added sodium cyanoborohydride (50 mg) in water (5 mL). To the above mixture was added a solution of dialdehyde Compound **54** (0.6 mmol) in $CHCl_3/H_2O$) (4 mL/ 1 mL). The mixture was stirred for 12 hours, and basified with saturated Na_2CO_3 solution. The mixture was extracted with EtOAc, and organic phase was washed with water and brine, and dried over Na_2SO_4. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column) gave Example **S** (57 mg).

Method III

Scheme 22



I. TFA, CH_2Cl_2; II. Cmpd 54, $NaBH_3CN$, H_2O/CH_3CN; III. LiOH, THF/H_2O; IV. amine Cmpd 8, DIPEA, EDC, HOBt, THF

Compound 55

Compound **51** (0.28 g, 0.66 mmol) was dissolved in CH_2Cl_2 (4 mL) and TFA (1 mL) was added dropwise. The reaction was allowed to stir at 25°C for 1 hour. The solvent was removed under reduced pressure to afford Compound **55** (0.39 g). m/z: 329.0 $(M+H)^+$.

Compound 56

To a solution of Compound **55** (0.39 g, 0.89 mmol) in CH_3CN (45 mL) was added $NaBH_3CN$ (0.45 g, 7.12 mmol) and H_2O (45 mL). A solution of Compound **54** (0.55 g, 5.34 mmol) in $CHCl_3/H_2O$ (40 mL) was added. The mixture was stirred at 25°C for 12 hours. The reaction mixture was made basic with saturated aqueous

Na_2CO_3 and extracted sequentially with ethyl acetate and dichloromethane. The combined organic layers were washed sequentially with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Compound **56** (0.17 g). m/z: 399.1 $(M+H)^+$.

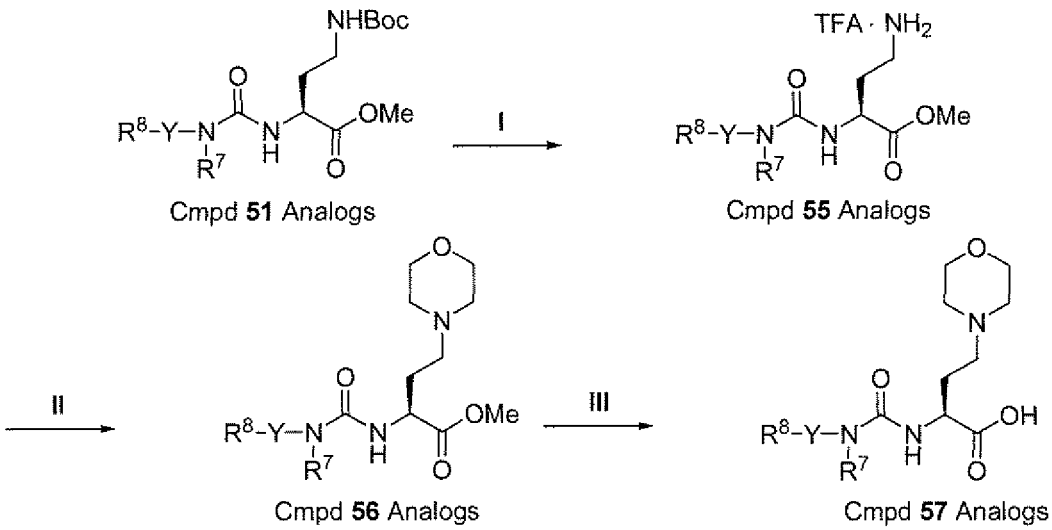
Compound 57

Compound **56** (377 mg, 0.95 mmol) was dissolved in THF (4 mL) and 1M aqueous LiOH (1.90 mL) was added. The mixture was stirred at 25°C for 1 hour. The reaction was neutralized with 1M HCl. THF was removed under reduced pressure and the aqueous solution was lyophilized to afford Compound **57** (365 mg). The material was used directly in the next step without further purification. m/z: 385.1 $(M+H)^+$.

Example S

Example **S** (185 mg, 57%) was prepared following the same procedure as for Example **Q**, except that Compound **57** (160 mg, 0.42 mmol) was used instead of Compound **52**. mass m/z: 776.2 $(M+H)^+$.

The skilled practitioner will recognize that the procedure outlined in Scheme **22** can be used to prepare a variety of compounds analogous to Compounds **55-57**:



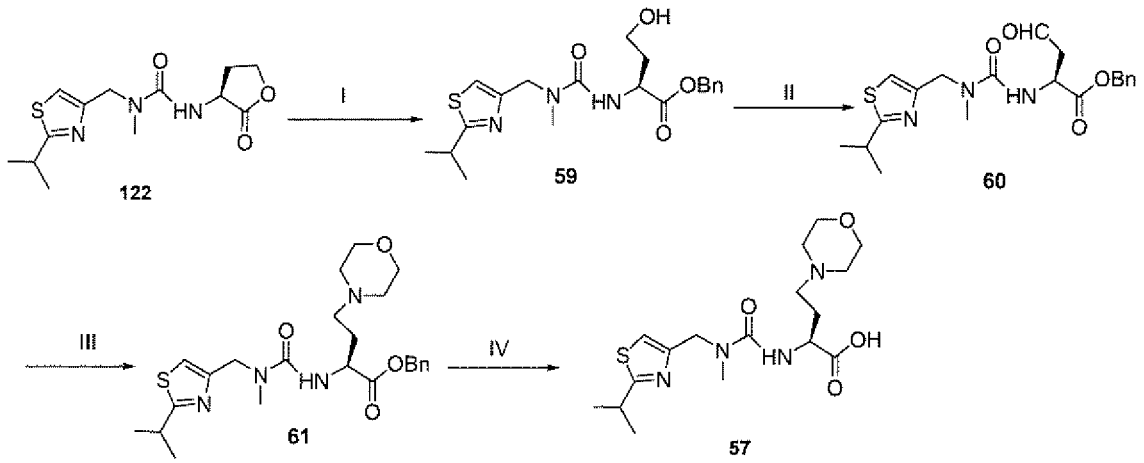
I. TFA, CH_2Cl_2; II. Ex. R, $NaBH_3CN$, H_2O/CH_3CN; III. LiOH, THF/H_2O

wherein R^7, R^8 and Y are as defined herein.

It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **51** having the appropriate stereochemical configuration at the chiral center.

Method IV

Scheme 23



I. a. NaOH/H2O; b. BnBr; II. SO3/pyridine; III. morpholine/NaBH(OAc)3; IV. a. NaOH; b. HCl

Compound 59

To a solution of Compound **122** (33 g, 112 mmol) (see Scheme **69**) in ethanol (366 mL) at 0°C was added a solution of sodium hydroxide (4.7 g, 117 mmol) in water (62 mL). The mixture was stirred for one hour at 25°C, and solvents were removed under reduced pressure. The mixture was coevaporated with ethanol (3x400 mL), and dried at 60°C for two hours under high vacuum to give a white solid. To the solution of above solid in DMF (180 mL) was added benzyl bromide (16.2 mL, 136 mmol). The mixture was stirred for 16 hours under darkness, and was quenched with water (300 mL). The mixture was extracted with EtOAc (4x300 mL). The combined organic phase was washed with water (5x) and brine, and dried over Na_2SO_4. Concentration gave Compound **59** (48 g), which was used in the next step without further purification.

Compound 60

A mixture of Compound **59** (33 g, 74 mmol) in DMSO (225 mL) and Et_3N (36 mL) was stirred for 30 minutes. The mixture was cooled to 0-10°C, SO_3-pyridine (45 g) was added, and the stirring was continued for 60 minutes. Ice (300

g) was added, and the mixture was stirred for 30 minutes. EtOAc (300 mL) was added and sat. Na_2CO_3 was added until pH was 9~10. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with EtOAc (2x300ml). The combined organic phases were washed with sat Na_2CO_3 (2x), water (3x), and brine. The mixture was dried over Na_2SO_4 and concentrated to give Compound **60** (32 g), which was used directly in next step without further purification.

Compound 61

To a solution of Compound **60** (32 g) in CH_3CN (325 mL) was added morpholine (12.9 mL, 148 mmol), with a water bath around the reaction vessel, followed by HOAc (8.9 mL, 148 mmol), and $NaBH(OAc)_3$ (47 g, 222 mmol). The mixture was stirred for 12 hours. CH_3CN was removed under reduced pressure, and the mixture was diluted with EtOAc (300 mL). Sat. Na_2CO_3 was added until the pH was 9~10. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with EtOAc (2x300 mL). The combined organic phases were washed with sat Na_2CO_3 (2x), water (1x), and brine (1x). The mixture was dried over Na_2SO_4. The resulting residue was concentrated and purified by silica gel column chromatography (EtOAc to DCM/iPrOH =10/1) to give Compound **61** (30 g).

Compound 57

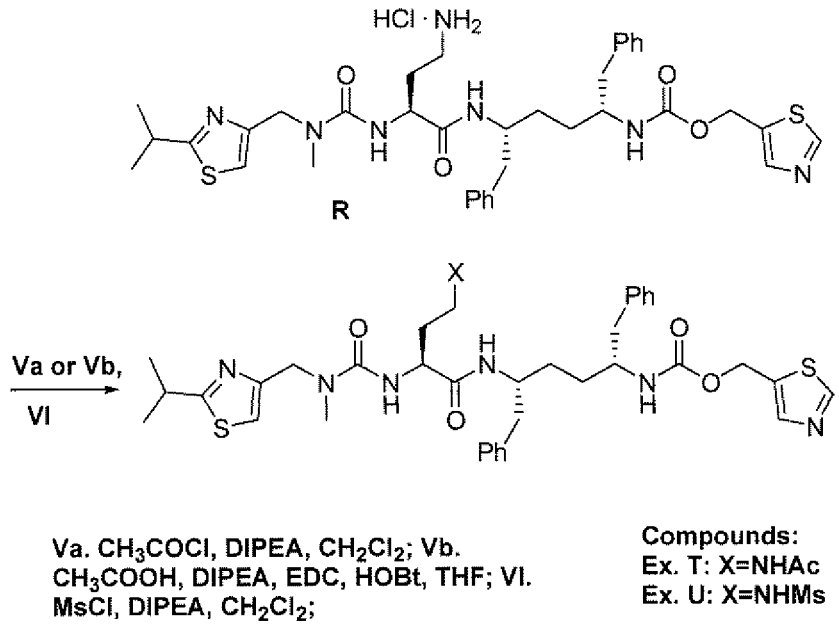
To a solution of Compound **61** (26.5 g, 56 mmol) in ethanol (160 mL) at 0°C was added a solution of sodium hydroxide (2.5 g, 62 mmol) in water (30 mL). The mixture was stirred for one hour at 25°C, and solvents were removed under reduced pressure. The mixture was diluted with water (200 mL), and was washed with CH_2Cl_2 (6x100 mL). The water phase was acidified with 12 N HCl (5.2 mL), and was dried under reduced pressure to give Compound **57** (22 g).

Example S

Compound **57** was converted to Example **S** using the procedure described in Method III, above.

Preparation of Compounds T and U

Scheme 24



Example T

Method I

The hydrochloride salt of Example **R** (100 mg, 0.13 mmol) was suspended in CH_2Cl_2 (2 mL) and dissolved by addition of iPr_2NEt (69 μL). Acetyl chloride (11 μL) was added dropwise and the mixture was allowed to stir at 25°C for 4 hours. The solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **T** (39 mg, 40%). m/z: 748.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.85 (s, 1H); 7.87 (s, 1H); 7.73 (s, 1H); 7.40-7.00 (m, 13H); 6.45 (br s, 1H); 5.70 (m, 1H); 5.32, 5.22 (d_{AB}, *J*=13 Hz, 2H); 4.51 (s, 2H); 4.20-3.90 (m, 4H); 3.78 (m, 1H); 3.38 (m, 2H); 3.20-2.50 (m, 8H); 1.95 (s, 4H); 1.82 (m, 2H); 1.41 (m, 6H).

Method II

Saturated aqueous Na_2CO_3 solution was added to the hydrochloride salt of Example **R** (3.18 g, 3.46 mmol) while stirring until the solid disappeared. The

aqueous solution was extracted with ethyl acetate. The organic phases were dried over Na_2SO_4, filtered, and evaporated to afford Example **R** as a yellow foam (2.44g, 81%). This material was used without further purification in the next step. m/z: 706.1 $(M+H)^+$.

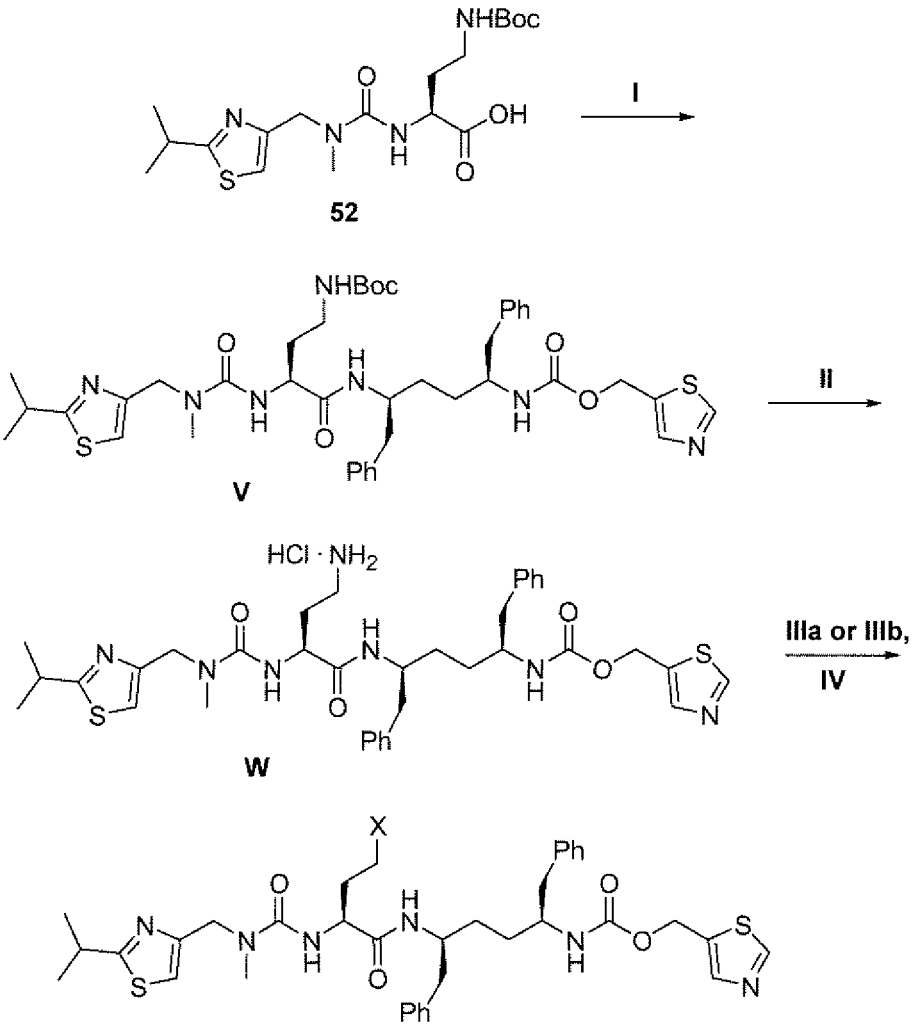
Example **R** (300 mg, 0.43 mmol) was dissolved in THF (5.5 mL). Acetic acid (37 μL, 0.64 mmol) was added, followed by HOBt (85 mg, 0.64 mmol), iPr_2NEt (304 μL, 1.70 mmol), and EDC (151 μL, 0.85 mmol). The reaction mixture was allowed to stir at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 10% MeOH/CH_2Cl_2) gave Example **T** (249 mg, 77%). m/z: 748.2 $(M+H)^+$.

Example U

Example **R** (100 mg, 0.13 mmol) was suspended in CH_2Cl_2 (2 mL) and dissolved by addition of iPr_2NEt (69 μL). Methanesulfonyl chloride (12 μL) was added dropwise and the mixture was allowed to stir at 25°C for 4 hours. The solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **U** (55 mg, 54%). m/z: 784.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.90 (s, 1H); 7.88 (s, 1H); 7.40-7.00 (m, 12H); 6.54 (br s, 1H); 6.19 (br s, 1H); 5.25 (s, 2H); 4.53 (s, 2H); 4.38 (m, 1H); 4.12 (m, 1H); 3.79 (m, 1H); 3.79 (m, 1H); 3.48 (m, 1H); 2.99 (s, 3H); 2.90 (m, 3H); 2.73 (m, 6H); 2.00 (m, 1H); 1.79 (m, 1H); 1.60-1.18 (m, 10H).

Preparation of Examples V, W, X and Y

Scheme 25



I. Cmpd. 46, DIPEA, EDC, HOBt, THF; II. HCl/dioxane; IIIa. CH_3COCl, DIPEA, CH_2Cl_2; IIIb. CH_3COOH, DIPEA, EDC, HOBt, THF; IV. MsCl, DIPEA, CH_2Cl_2

Compounds:
Ex. X: X=NHAc
Ex. Y: X=NHMs

Example V

Example **V** (692 mg) was prepared following the same procedure used for preparing Example **Q**, except that Compound **46** was used instead of Compound **8**. m/z: 806.2 $(M+H)^+$.

Example W

Example **W** (770 mg, quantitative yield) was prepared following the same procedure for Example **R** except that Example **V** was used instead of Example **Q**.

m/z: 706.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 9.86 (s, 1H); 8.23 (s, 1H); 7.66 (s, 1H); 7.40-7.00 (m, 10H); 5.29, 5.17 (d_{AB}, *J*=13 Hz, 2H); 4.80-4.60 (m, 2H); 4.18 (s, 2H); 4.26 (m, 2H); 3.67 (br s, 1H); 3.55 (m, 2H); 3.03 (m, 3H); 2.90-2.60 (m, 8H); 2.53 (s, 2H); 2.00-1.80 (m, 2H); 1.85-1.30 (m, 10H).

Example X

Method I

Example **X** (107 mg, 55%) was prepared following the Method I procedure for Example **T** except that Example **W** was used instead of Example **R**. m/z: 748.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H); 7.85 (s, 1H); 7.40 (m, 1H); 7.38-7.00 (m, 10H), 6.94 (s, 1H); 6.30 (m, 2H); 5.75 (m, 1H); 5.30, 5.23 (d_{AB}, J=13 Hz, 2H); 4.54, 4.46 (d_{AB}, *J*=8 Hz, 2H); 4.20-3.90 (m, 2H); 3.74 (br s, 1H); 3.46 (br s, 1H); 3.28 (m, 1H); 2.98 (s, 3H); 2.83 (m, 3H); 2.72 (m, 1H); 2.62 (m, 1H); 2.05-1.20 (m, 15H).

Method II

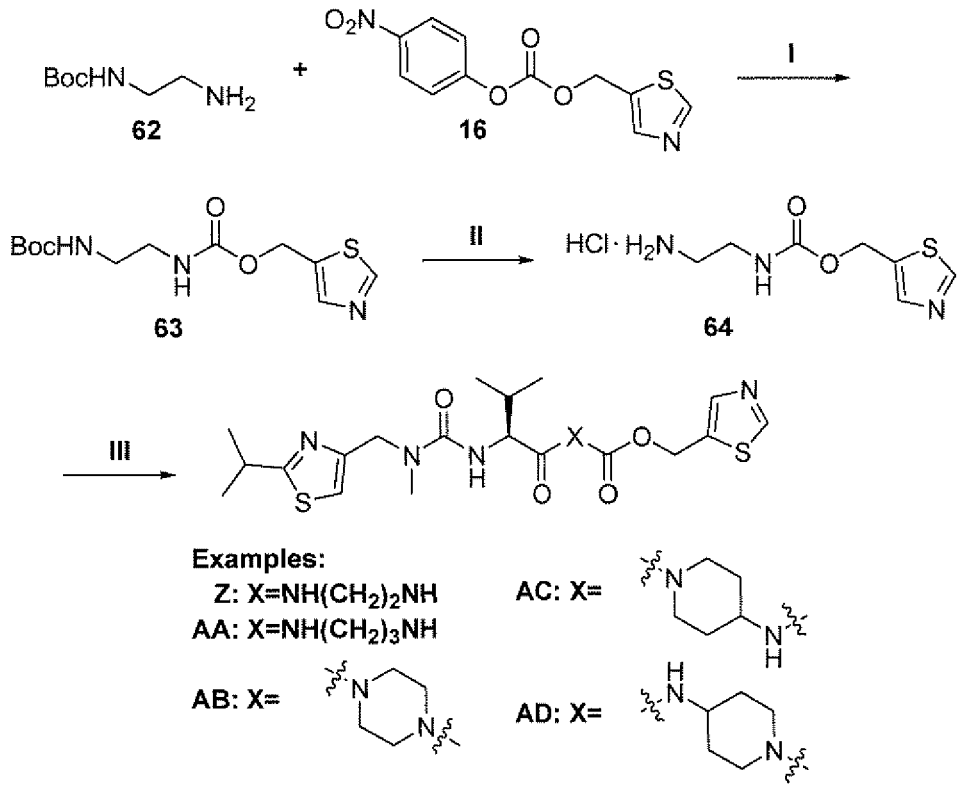
Example **X** (205 mg, 65%) was prepared following the Method II procedure for Example **T** except that Example **W** was used instead of Example **R**. m/z: 748.2 $(M+H)^+$.

Example Y

Example **Y** (106 mg, 50%) was prepared following the same procedure for Example **U**, except that Example **W** was used instead of Example **R**. m/z: 784.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.81 (s, 1H); 7.85 (s, 1H); 7.40-7.05 (m, 10H), 6.98 (s, 1H); 6.22 (br s, 1H); 5.78 (s, 1H); 5.25 (m, 4H); 4.29 (m, 2H); 4.33 (br s, 1H); 4.12 (br s, 1H); 3.77 (br s, 1H); 3.10 (br s, 1H); 2.98 (s, 3H); 2.90 (s, 3H); 2.73 (m, 6H); 2.00-1.20 (m, 12H).

Preparation of Examples Z-AD

Scheme 26



I. DIPEA, CH_3CN; II. HCl/dioxane, EtOAc; III. acid 29, DIPEA, EDC, HOBt, THF

Compound 62

Tert-butyl 2-aminoethylcarbamate (**62**) is commercially available from Aldrich, and was used without further purification.

Compound 63

To a solution of Compound **62** (2.0 mmol) in CH_3CN (15 mL) was added Compound **16** (1.82 mmol), followed by the addition of *N,N*-diisopropylethylamine (0.61 mL). The mixture was stirred at 25°C for 12 hours. The solvent was removed *in vacuo*, and the residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic layers were dried with Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 25-100% EtOAc/hexane gradient) gave Compound **63**. m/z: 301.9 $(M+H)^+$.

Compound 64

To a solution of Compound **63** (1.05 mmol) in EtOAc (3 mL) was added 4N HCl/dioxane solution (1.1 mL). The mixture was allowed to stir at 25°C for 12 hours. The solvent was removed under reduced pressure, and Compound **64** was obtained as a white powder. This material was used in the next step without further purification. m/z: 216.0 $(M+H)^+$.

Example Z

Compound **64** (70 mg, 0.29 mmol) was dissolved in THF (2.2 mL). Compound **29** (91 mg, 0.29 mmol) was added to the reaction flask as a 1.0M solution in THF, followed by HOBt (59 mg, 0.44 mmol), *N,N*-diisopropylethylamine (207 μL, 1.16 mmol), and EDC (103 μL, 0.58 mmol). The reaction was allowed to stir for 12 hours at 25°C and concentrated under reduced pressure. The residue was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic layers were dried with Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Example **Z** (54 mg, 38%). m/z: 497.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H); 7.83 (s, 1H); 6.99 (s, 1H); 6.80 (br s, 1H); 6.22 (br s, 1H); 5.87 (br s, 1H); 5.25 (s, 2H); 4.43 (s, 2H); 3.97 (m, 1H); 3.34 (m, 4H); 2.95 (s, 3H); 2.22 (m, 2H); 1.38 (d, *J*=7 Hz, 6H); 0.97 (d, *J*=7 Hz, 6H).

Example AA

Example **AA** was prepared following the procedures for steps I-III (**Scheme 20**) for Example **Z**, with the exception that tert-butyl 3-aminopropylcarbamate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62**). After Combiflash® purification, 38 mg (34%) of Example **AA** was obtained. m/z: 511.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H); 7.84 (s, 1H); 6.96 (s, 2H); 6.17 (br s, 1H); 5.80 (m, 1H); 5.26 (m, 2H); 4.44 (s, 2H); 4.09 (m, 1H); 3.40-3.10

(m, 5H); 2.97 (s, 3H); 2.20 (m, 1H); 1.60 (m, 2H); 1.36 (d, *J*=7 Hz, 6H); 0.96 (d, *J*=7 Hz, 6H).

Example AB

Example **AB** was prepared following the procedures for steps I-III (**Scheme 20**) for Example **Z**, with the exception that tert-butyl 1-piperazinecarboxylate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62**). After Combiflash® purification, 64 mg (45%) of Example **AB** was obtained. m/z: 523.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.82 (s, 1H); 7.89 (s, 1H); 6.96 (s, 1H); 5.93 (br s, 1H); 5.35 (s, 2H); 4.62 (m, 1H); 4.50 (m, 2H); 3.80-3.40 (m, 8H); 3.34 (m, 1H); 3.00 (s, 3H); 1.97 (m, 1H); 1.40 (d, *J*=7 Hz, 6H); 0.96, 0.93 (d, *J*=7 Hz, 6H).

Example AC

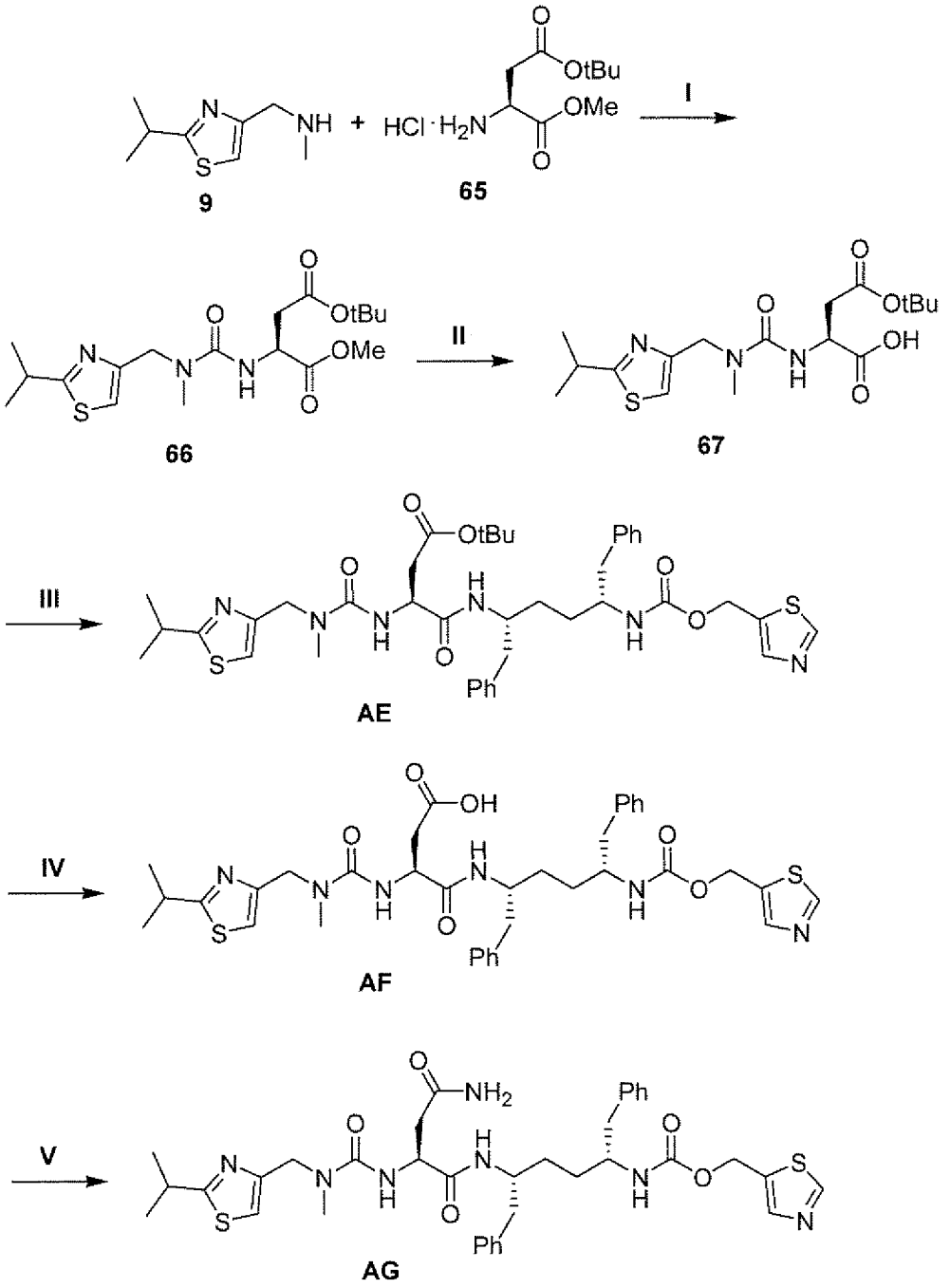
Example **AC** was prepared following the procedures for steps I-III (**Scheme 20**) for Example **Z**, with the exception that tert-butyl 4-amino-1-piperidinecarboxylate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62**). After Combiflash® purification, 60 mg (44%) of Example **AC** was obtained. m/z: 537.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.82 (s, 1H); 7.87 (s, 1H); 6.97 (s, 1H); 5.82 (br s, 1H); 5.30 (m, 3H); 4.80-4.40 (m, 5H); 4.03 (m, 1H); 3.72 (br s, 1H); 3.34 (m, 1H); 3.18 (m, 1H); 3.01 (s, 3H); 2.79 (m, 1H); 2.20-1.90 (m, 4H); 1.40 (d, *J*=7 Hz, 6H); 0.97, 0.90 (d, *J*=7 Hz, 6H).

Example AD

Example **AD** was prepared following the procedures I-III for Example **Z**, with the exception that tert-butyl 4-piperidinylcarbamate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62**). After Combiflash® purification, 49 mg (36%) of Example **AD** was obtained. m/z: 537.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.82 (s, 1H); 7.87 (s, 1H); 7.01 (s, 1H); 6.33 (br s, 1H); 6.11 (br s, 1H); 5.32 (s, 2H); 4.47 (s, 2H); 4.20-3.80 (m, 4H); 3.35 (m, 1H); 3.10-2.80 (m, 6H); 2.21 (m, 2H); 1.90 (m, 2H); 1.40 (d, *J*=7 Hz, 6H); 0.97 (d, *J*=7 Hz, 6H).

Preparation of Examples AE-AG

Scheme 27



I. CDI, DIPEA, CH_2Cl_2; II. NaOH, THF/H_2O; III. Cmpd. 8, DIPEA, EDC, HOBt, THF; IV. neat TFA; V. $(Boc)_2O$, NH_4HCO_3, pyridine, dioxane, DMF

Compound 65

Compound **65** is commercially available from Chem Impex International, and was used without further purification.

Compound 66

Compound **65** (956 mg, 4.0 mmol) was dissolved in CH_2Cl_2 (45 mL) and 1,1-carbonyldiimidiazole (648 mg, 4.0 mmol) was added, followed by i-Pr_2NEt (2.8 mL, 16 mmol). The solution was stirred at 25°C for 12 hours. Compound **9** (679 mg, 4.0 mmol) was dissolved in CH_2Cl_2 (5 mL) and added to the reaction. The mixture was allowed to stir for 5 hours. Then, the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and filtered through celite. The ethyl acetate was then removed *in vacuo*. Purification by flash column chromatography (stationary phase: silica gel; eluent: EtOAc) gave Compound **66** (841 mg). m/z: 400.0 $(M+H)^+$.

Compound 67

Compound **66** (841 mg, 2.11 mmol) was dissolved in THF (9 mL) and 2N aqueous NaOH was added. The solution was stirred at 25°C for 2 hours. The reaction was adjusted to pH 2 with 1N HCl. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and evaporated. Compound **67** (772 mg) was used directly in the next step without further purification. m/z: 386.0 $(M+H)^+$.

Example AE

Compound **67** (569 mg, 1.48 mmol) was dissolved in THF (17 mL). Compound **8** (970 mg, 2.37 mmol) was added, followed by HOBt (300 mg, 2.22 mmol), i-Pr_2NEt (1.06 mL, 5.92 mmol), and EDC (0.52 mL, 2.96 mmol). The mixture was stirred at 25°C for 36 hours. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **AE** (3.02 g). m/z: 777.2 $(M+H)^+$.

Example AF

Example **AE** (100 mg, 0.13 mmol) was dissolved in neat TFA (3 mL). The mixture was stirred at 25°C for 2 hours. The solvent was removed under reduced pressure. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/H_2O gradient) gave Example **AF** (20 mg, 21%). m/z: 721.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.92 (s, 1H); 7.91 (s, 1H); 7.40-7.00 (m, 11H); 6.41 (br s, 1H); 6.12 (br s, 1H); 5.40-5.00 (m, 3H); 4.70-4.50 (m, 3H); 4.05 (br s, 1H); 3.81 (br s, 1H); 3.51 (br s, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 6H); 1.41 (d, *J*=7 Hz, 10H).

Example AG

Example **AF** (70 mg, 0.10 mmol) was dissolved in dioxane (0.5 mL). DMF (83 μL), pyridine (25 μL, 0.29 mmol), di-*tert*-butyldicarbonate (27 mg, 0.13 mmol), and ammonium bicarbonate (15 mg, 0.19 mmol) were added. The mixture was stirred at 25°C for 48 hours, then diluted with ethyl acetate and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/H_2O gradient) gave Example **AG** (35 mg, 50%). ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 7.08 (s, 1H); 6.83 (m, 1H); 6.65 (m, 1H); 5.40-5.10 (m, 4H); 4.60-4.40 (m, 3H); 4.06 (m, 1H); 3.79 (m, 1H); 3.36 (m, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 6H); 2.45 (m, 1H); 1.70-1.20 (m, 10H).

Preparation of Compounds 68 and 69

Scheme 28

15 **68: R=methyl**
69: R=cyclopropyl

I. a. MsCl, TEA, CH_3CN; b. $MeNH_2/H_2O$; c. cyclopropyl amine

Compound 15

Compound 15 is commercially available from Molekula, and was used without further purification.

Compound 68

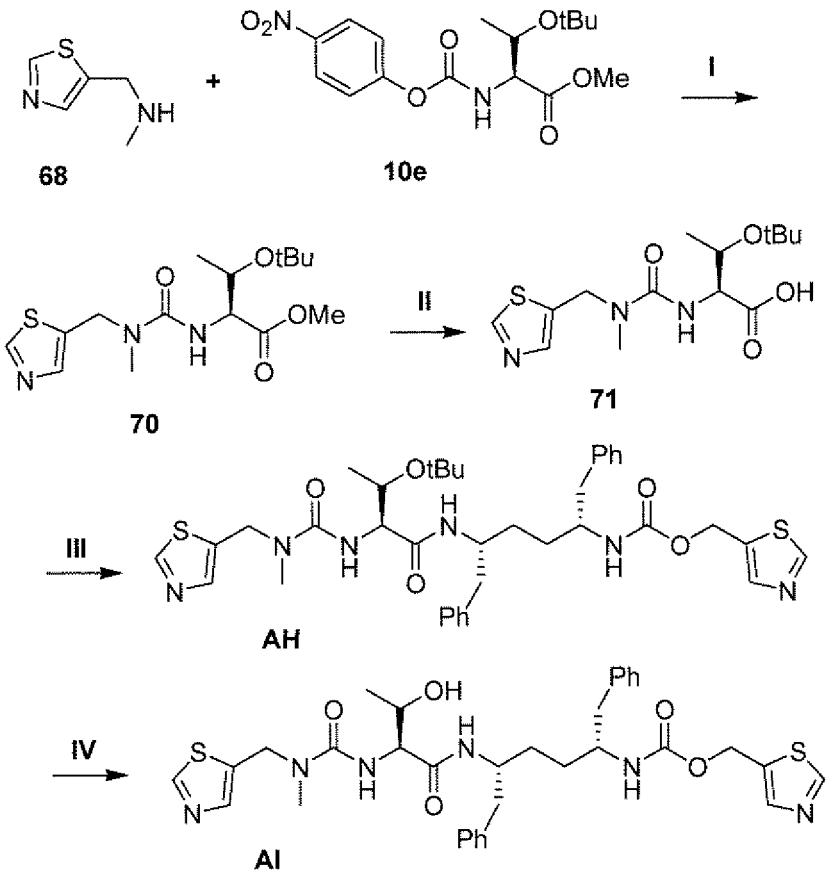
Compound **15** (6.81 g, 59.1 mmol) was dissolved in CH_3CN (340 mL) and methanesulfonyl chloride (7.03 mL, 65.1 mmol) was added, followed by triethylamine (9.03 mL, 65.1 mmol). After the mixture was stirred for 20 min, 40% wt. methylamine/water (516 mL) was added to the reaction mixture. The solution was stirred for 12 hours at 25°C. Solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Compound **68** (5.07 g). m/z: 128.9 $(M+H)^+$.

Compound 69

Compound **15** (10.0 g, 80 mmol) was dissolved in CH_3CN (500 mL) and methanesulfonyl chloride (7.0 mL, 88 mmol) was added, followed by triethylamine (12.3 mL, 88 mmol). After the mixture was stirred for 2h, cyclopropylamine (140 mL, 2000 mmol) in CH_3CN (500 mL) was added to the reaction mixture. The solution was stirred for 36 hours at 25°C. Solvent was removed under reduced pressure and the slurry was partitioned between saturated aqueous Na_2CO_3 and 3:1 CH_2Cl_2:i-PrOH. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. Compound **69** (12.81 g) was used in the next step without further purification. m/z: 155.0 $(M+H)^+$.

Preparation of Examples AH and AI

Scheme 29



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF;
IV. a. neat TFA; b. NaOH, THF, H_2O

Compound 70

Compound **68** (1.00 g, 7.80 mmol) was dissolved in THF (25 mL) and Compound **10e** (2.51 g, 7.09 mmol) was added, followed by *N,N*-dimethaminopyridine (200 mg, 1.63 mmol), and triethylamine (4.34 mL, 31.2 mmol). The mixture was allowed to stir at 60 °C for 6 hours. Solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The resulting residue was purified by Combiflash® (stationary phase: silica gel; eluent: 20-100% EtOAc/Hexane gradient) to give Compound **70** (2.14 g). m/z: 343.9 $(M+H)^+$.

Compound 71

Compound **70** (2.14 g, 6.23 mmol) was dissolved in THF (25 mL) and 1M aqueous LiOH (12.5 mL) was added. The mixture was stirred at 25°C for 2 hours. The reaction was quenched with 1M HCl (15 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to provide Compound **71** (1.96 g). This material was used in the next step without further purification. m/z: 330.0 $(M+H)^+$.

Example AH

Compound **71** (43 mg, 0.13 mmol) was dissolved in THF (1.5 mL). Compound **8** (50 mg, 0.12 mmol) was added, followed by HOBt (24 mg, 0.18 mmol), iPr_2NEt (86 μL, 0.48 mmol), and EDC (42 μL, 0.24 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure, and the resulting residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 1-10% MeOH/CH_2Cl_2 gradient) gave Example **AH** (66 mg). m/z: 721.2 $(M+H)^+$.

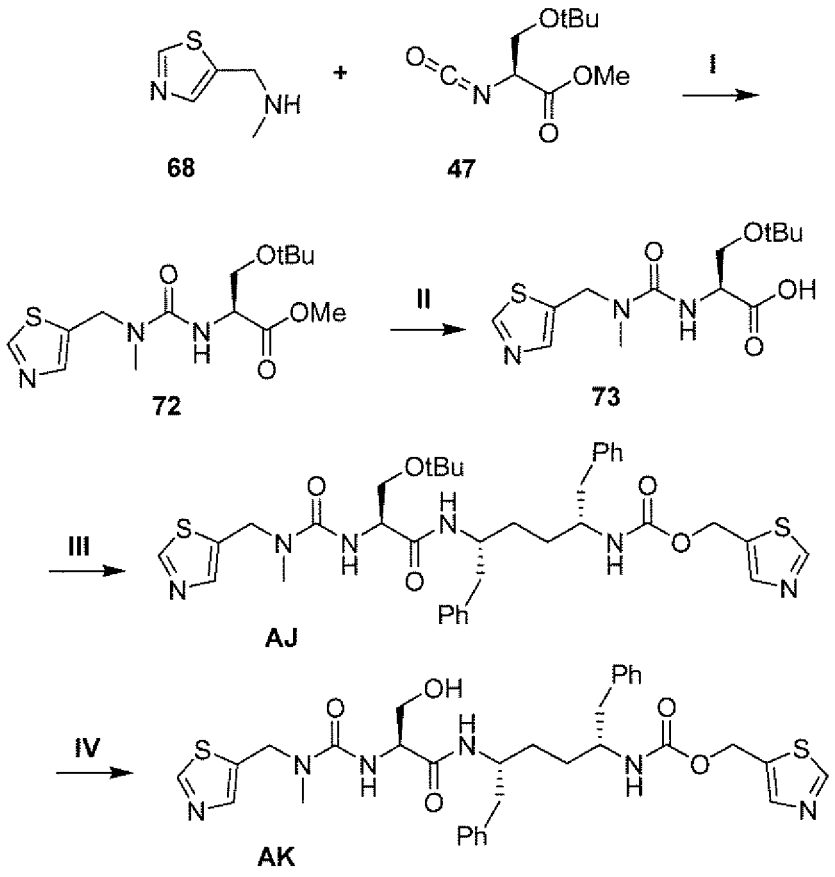
Compound AI

Example **AH** (66 mg, 0.09 mmol) was dissolved in TFA and allowed to stir at 25 °C for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with THF (3 mL) and 2N aqueous NaOH was added until pH 12. The mixture was allowed to stir for 20 min and extracted with EtOAc. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-20% i-PrOH/CH_2Cl_2 gradient) gave Example **AI** (71 mg, 97%). m/z: 665.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.84 (s, 1H); 8.80 (s, 1H); 7.85 (s, 1H); 7.79 (s, 1H); 7.40-7.00 (m, 10H); 6.69 (m, 1H); 5.34 (m, 1H); 5.24 (s, 2H); 4.86 (m, 2H); 4.73,

4.59 (d_{AB}, J=16 Hz, 2H); 4.30 (s, 1H); 4.15 (m, 2H); 3.86 (br s, 1H); 2.88 (s, 3H); 2.85-2.60 (m, 4H); 2.01 (s, 1H); 1.58 (s, 2H); 1.44 (s, 2H); 1.09 (d, J= 6 Hz, 3H).

Preparation of Examples AJ and AK

Scheme 30



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF;
IV. a. neat TFA; b. NaOH, THF, H_2O

Compound 47

Compound **47** is commercially available from TCI America, and was used without further purification.

Compound 72

Compound **72** was prepared following procedure for Compound **48** (Method II), except that Compound **68** was used instead of Compound **9**.

Compound 73

Compound **73** was prepared following procedure for Compound **49**, except that Compound **72** was used instead of Compound **48**.

Example AJ

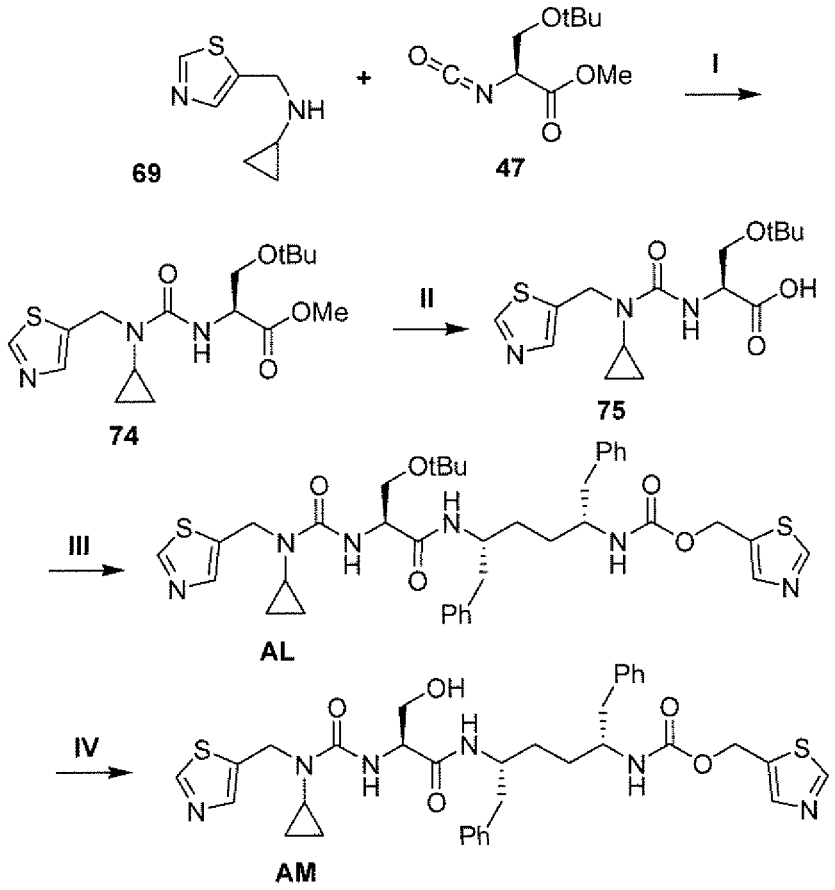
Example **AJ** (70 mg) was prepared following the same procedure used to prepare Example **AH**, with the exception that Compound **73** (41 mg, 0.13 mmol) was used instead of Compound **71**. m/z: 707.2 $(M+H)^+$.

Example AK

Example **AK** (43 mg, 67%) was prepared following the same procedure used to prepare Example **AI**, with the exception that Example **AJ** (70 mg, 0.10 mmol) was used instead of Example **AH**. m/z: 651.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.83 (s, 2H); 7.84 (s, 1H); 7.79 (s, 1H); 7.40-7.00 (m, 10H); 6.65 (br s, 1H); 5.47 (br s, 1H); 5.24 (s, 2H); 4.90 (m, 1H); 4.82-4.50 (m, 2H); 4.30-4.00 (m, 3H); 3.84 (br s, 1H); 3.49 (m, 1H); 2.87 (s, 3H); 2.75 (br s, 5H); 1.60-1.20 (m, 4H).

Preparation of Examples AL and AM

Scheme 31



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF;
IV. a. neat TFA; b. NaOH, THF, H_2O

Compound 74

Compound **69** (1.56 g, 10.1 mmol) was dissolved in CH_2Cl_2 (10 mL). Compound **47** (1.7 g, 8.5 mmol) in CH_2Cl_2 (20 mL) was added, followed by iPr_2NEt (3.02 mL, 16.9 mmol). The reaction was stirred at 25 °C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 50-100% EtOAc/hexane gradient) gave Compound **74** (2.92 g). m/z: 356.0 $(M+H)^+$.

Compound 75

Compound **74** (0.97 mmol) was taken up in THF (3 mL) and treated with freshly prepared 1M LiOH (2 mmol) and stirred vigorously for 1 h. The reaction was quenched with 1M HCl (2.5 mmol) and extracted with EtOAc (3 X 15 mL). The combined organics were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to produce 0.331 g (quant) of Compound **75** as a colorless film (*m/z* 342.0 $(M+H)^+$).

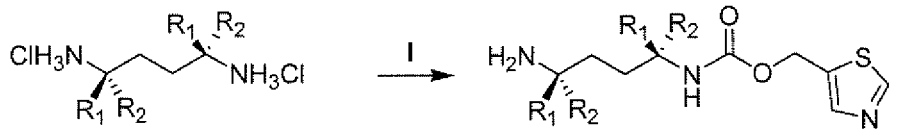
Example AL

Example **AL** (2.20 g) was prepared following the same procedure used to prepare Example **AH**, with the exception that Compound **75** (2.00 g, 4.88 mmol) was used instead of Compound **71**. m/z: 733.2 $(M+H)^+$.

Example AM

Example **AM** (1.88 g, 92%) was prepared following the same procedure used to prepare Example **AI**, with the exception that Example **AL** (2.20 g, 3.01 mmol) was used instead of Example **AH**. m/z: 677.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H); 8.72 (s, 1H); 7.82 (s, 1H); 7.77 (s, 1H); 7.40-7.00 (m, 10H); 6.59 (m, 1H); 6.31 (m, 1H); 5.23 (s, 2H); 5.00 (m, 1H); 4.72, 4.60 (d_{AB}, *J*=15 Hz, 2H); 4.18 (s, 2H); 4.03 (m, 1H); 3.84 (br s, 1H); 3.48 (m, 1H); 2.85-2.60 (m, 4H); 2.37 (br s, 2H); 1.58 (s, 2H); 1.41 (s, 2H); 0.93 (m, 2H); 0.76 (m, 2H).

Scheme 32



76: R_1 = H, R_2 = CH_3
77: R_1 = H, R_2 = CH_2CH_3

78: R_1 = H, R_2 = CH_3
79: R_1 = H, R_2 = CH_2CH_3

I. compound 16, DIPEA, MeCN

Compound 76

Compound **76** (*m/z* 117.0 $(M+H)^+$ of diamine) was prepared using a procedure similar to that used to prepare Compound **22** (described in Scheme **12**) except that CBZ-L-alininol was used instead of CBZ-L-phenylalininol and Step **III** was performed with 1 M HCl added.

Compound 77

Compound **77** (*m/z* 145.0 $(M+H)^+$ of diamine) was prepared using a procedure similar to that used to prepare Compound **76** except that (S)-(+)-2-CBZ-amino-1-butanol was used instead of CBZ-L-alininol.

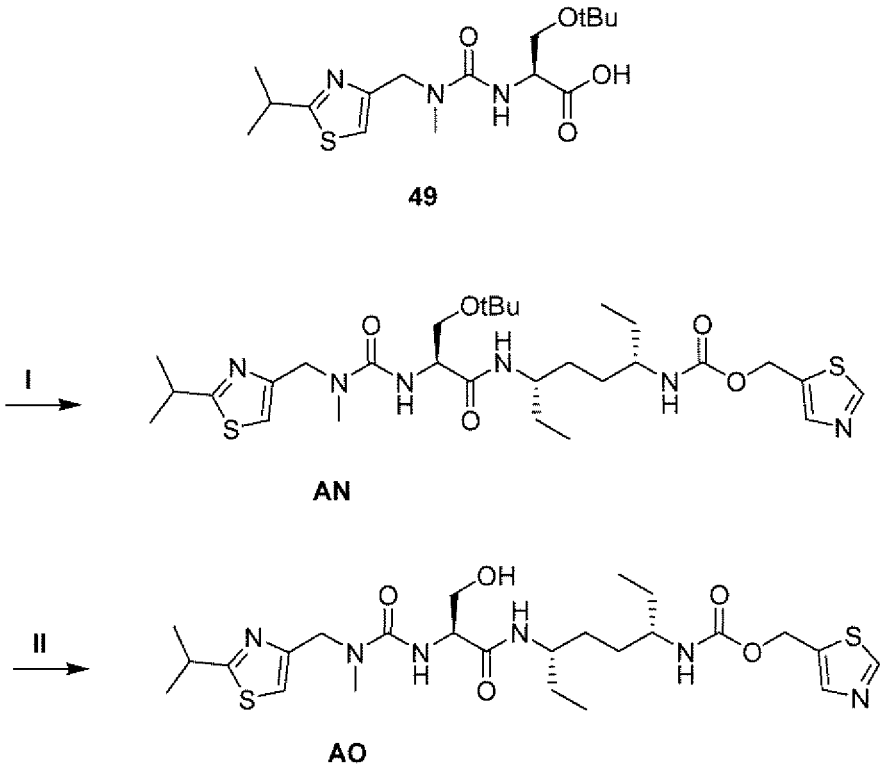
Compound 78

Compound **76** (7.93 mmol) is added to a solution of NaOH (16.7 mmol) in H_2O (5 mL) that is cooled to 0 °C and diluted with MeCN (40 mL). DIPEA is added (2.1 mL, 11.9 mmol). Compound **16** (7.9 mmol) is taken up in MeCN (40 mL) and added to the reaction solution dropwise via an addition funnel over 1 h. The resulting solution is allowed to warm to room temperature overnight. The solvent is removed *in vacuo* and the residue taken up in 3/1 $CHCl_3$/IPA (50 mL). The resulting solution is washed with sat. Na_2CO_3 (50 mL) and water is added until the aqueous layer is homogeneous. The aqueous layer is extracted with 3/1 $CHCl_3$/IPA (3 X 25 mL). The combined organics are washed with saturated Na_2CO_3 (50 mL), water (50 mL) and brine (50 mL) and are dried over anhydrous Na_2SO_4. The solvent is removed *in vacuo* and the residue purified by column chromatography on SiO_2 (100% EtOAc, then 0 to 20% MeOH/DCM) to produce 0.63 g (31%) of **78** as an off-white solid. (*m/z* 258.0 $(M+H)^+$).

Compound 79

Compound **79** (*m/z* 286.1 (M+H)+) was prepared following the procedure for Compound **78** except that Compound **77** was used instead of Compound **76**.

Scheme 33



I. Cmpd. 79, HOBt, EDC, DIPEA, THF;
II. a. neat TFA; b. NaOH, THF, H_2O

Example AN

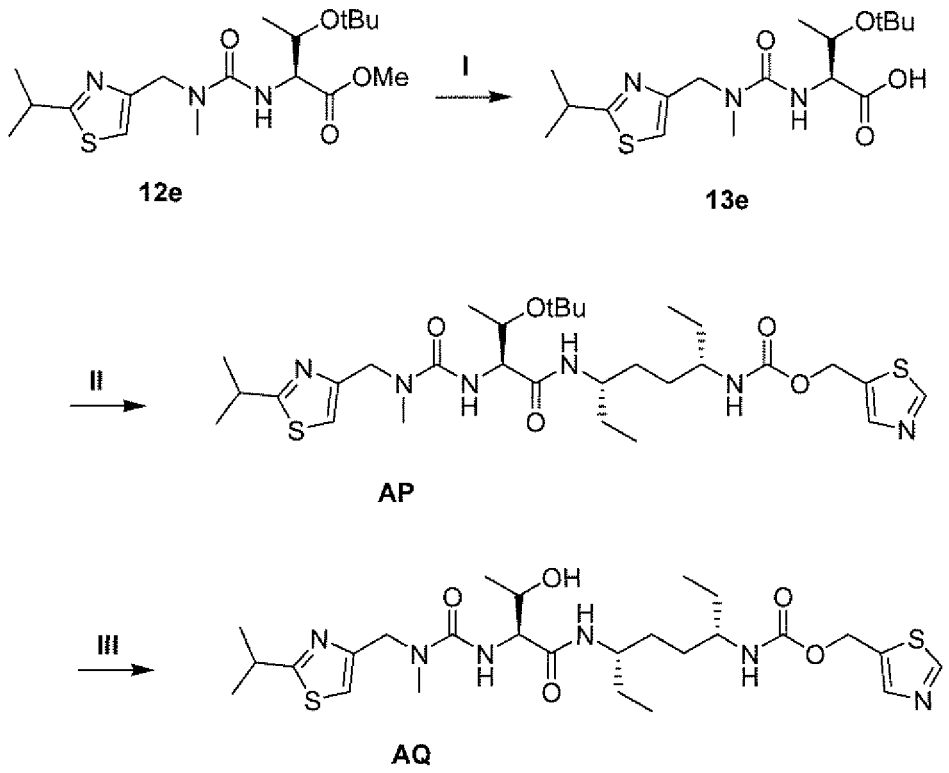
Example **AN** (68 mg) was prepared following the same procedure used to prepare Example **AH**, with the exceptions that Compound **49** (68 mg, 0.19 mmol) was used instead of Compound **71**, and Compound **79** (50 mg, 0.18 mmol) was used instead of Compound **8**. m/z: 625.2 $(M+H)^+$.

Example AO

Example **AO** (66 mg, 76%) was prepared following the same procedure used to prepare Example **AI**, with the exception that Example **AN** (43 mg, 0.13 mmol) was used instead of Example **AH**. m/z: 569.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.85 (s, 1H); 7.89 (s, 1H); 7.08 (s, 1H); 6.81 (m, 1H); 5.29 (s, 2H); 4.87 (m, 1H); 4.63, 4.48 (d_{AB}, J=16 Hz, 2H); 4.31 (m, 1H); 4.11 (m, 1H); 3.76 (m, 2H); 3.44 (m, 2H); 3.02 (m, 4H); 1.60-1.20 (m, 14H); 1.00-0.70 (m, 6H).

Preparation of Examples AP and AQ

Scheme 34



I. LiOH, THF/H_2O; II. Cmpd. 79, HOBt, EDC, DIPEA, THF; III. a. neat TFA; b. NaOH, THF, H_2O

Compound 13e

Compound **13e** (1.39 g) was prepared following the same procedure used to prepare Compound **71**, with the exception that Compound **12e** (1.53 g, 3.97 mmol) was used instead of Compound **70** m/z: 372.0 $(M+H)^+$.

Example AP

Example **AP** (87 mg) was prepared following the same procedure used to prepare Example **AH**, with the exception that Compound **13e** (71 mg, 0.19 mmol) was used instead of Compound **71**, and Compound **79** (50 mg, 0.18 mmol) was used instead of Compound **8**. m/z: 639.2 $(M+H)^+$.

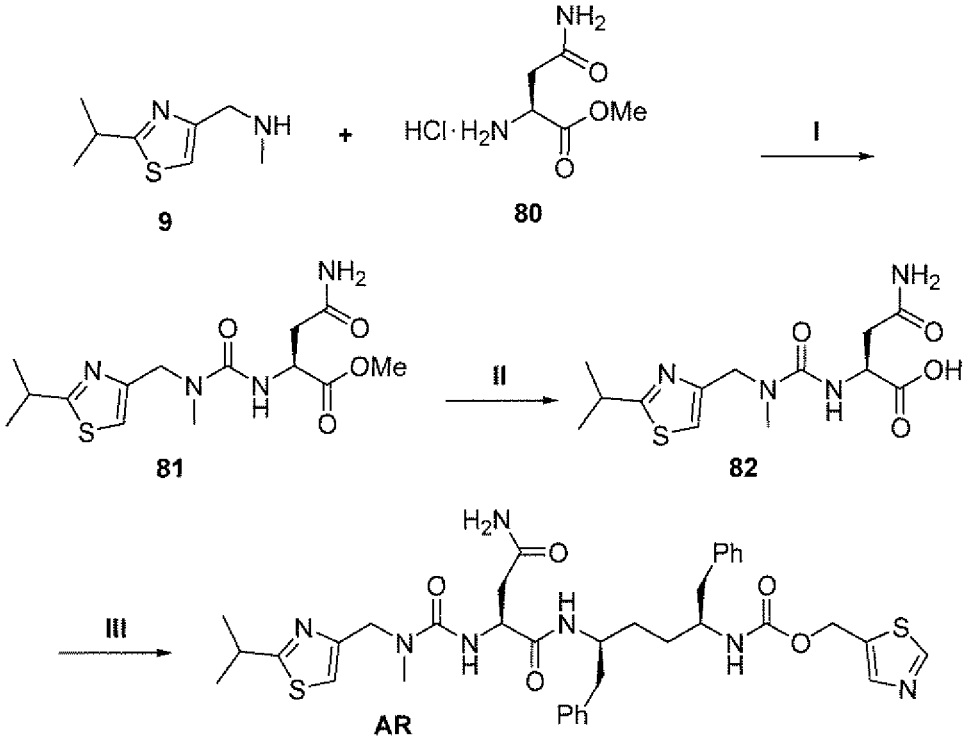
Compound AQ

Example **AQ** (61 mg, 76%) was prepared following the same procedure used to prepare Example **AI**, with the exception that Example **AP** (87 mg, 0.14

mmol) was used instead of Example **AH**. m/z: 583.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.81 (s, 1H); 7.87 (s, 1H); 7.01 (s, 1H); 6.87 (m, 1H); 6.52 (s, 1H); 5.28 (m, 2H); 4.47 (m, 1H); 4.59, 4.43 (d_{AB}, J=16 Hz, 2H); 4.45 (m, 1H); 4.17 (br s, 1H); 3.75 (br s, 1H); 3.52 (br s, 1H); 3.35 (br s, 1H); 3.01 (m, 3H); 2.07 (br s, 1H); 1.60-1.10 (m, 17H); 1.00-0.70 (m, 6H).

Preparation of Example AR

Scheme 35



I. CDI, DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 46, DIPEA, EDC, HOBt, THF

Compound 80

Compound **80** is commercially available from Chem Impex International, and was used without further purification.

Compound 81

Compound **80** (2.0 g, 11.0 mmol) was dissolved in CH_2Cl_2 (170 mL) and 1,1-carbonyldiimidazole (1.78 g, 11.0 mmol) was added, followed by iPr_2NEt (7.83 mL, 43.8 mmol). The solution was allowed to stir at 25°C for 12 hours. Compound

9 (1.86 g, 11.0 mmol) was dissolved in 20 mL of CH_2Cl_2 and added to the reaction mixture. The solution was stirred at 25°C for 12 hours. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate and washed water and brine. The organic layers were dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 66-100% EtOAc/Hexane gradient) gave Compound **81** (0.252 mg). m/z: 343.0 $(M+H)^+$.

Compound 82

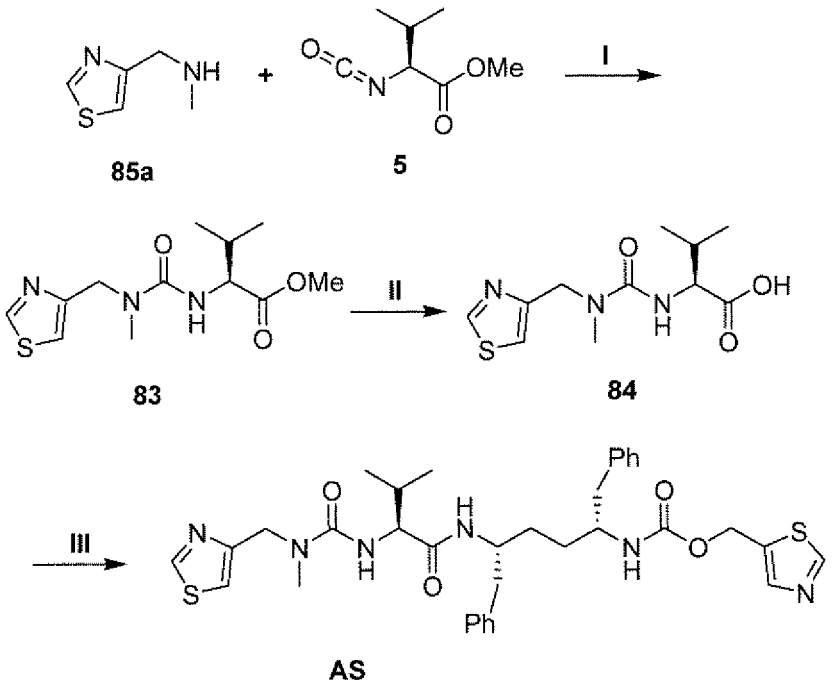
Compound **82** (0.252 g, 0.74 mmol) was dissolved in THF (4 mL) and 1M aqueous LiOH (1.48 mL) was added. The mixture was stirred at 25°C for 3 hours. The reaction was quenched with 1M HCl (2 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to afford Compound **82** (0.18 g). This material was used in the next step without further purification. m/z: 329.1 $(M+H)^+$.

Example AR

Compound **82** (182 mg, 0.55 mmol) was dissolved in THF (7.15 mL). Compound **46** (225 mg, 0.55 mmol) was added, followed by HOBt (112 mg, 0.83 mmol), iPr_2NEt (393 μL, 2.20 mmol), and EDC (194 μL, 1.10 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5-10% MeOH/CH_2Cl_2 gradient) gave Example **AR** (208 mg, 53%). m/z: 720.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 6.97 (s, 1H); 6.83 (m, 1H); 6.65 (br s, 1H); 5.99 (m, 1H); 5.40-5.10 (m, 4H); 4.52 (m, 3H); 4.06 (m, 1H); 3.79 (m, 1H); 3.34 (m, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 5H); 2.50-2.40 (br s, 1H); 1.80-1.20 (m, 10H).

Preparation of Example AS

Scheme 36



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O; III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 85a

Compound **85a** was prepared following the same procedure as Compound **4**, except that 4-chloromethylthiazole (purchased from TCI America) was used instead of Compound **3**, and methylamine was used instead of isopropylamine.

Compound 83

To compound **85a** (0.40 g, 3.12 mmol) in CH_2Cl_2 (9 mL) was added *N,N*-diisopropylethylamine (1.04 mL, 5.85 mmol), followed by Compound **5** (280 μL, 1.95 mmol). The reaction mixture was stirred for 3.5 hours at 25 °C. Solvent was removed under reduced pressure. Purification by Combiflash® (stationary phase: silica gel; eluent: 90-100% EtOAc/Hexane gradient) gave Compound **83** (0.51 g). m/z: 286.0 $(M+H)^+$.

Compound 84

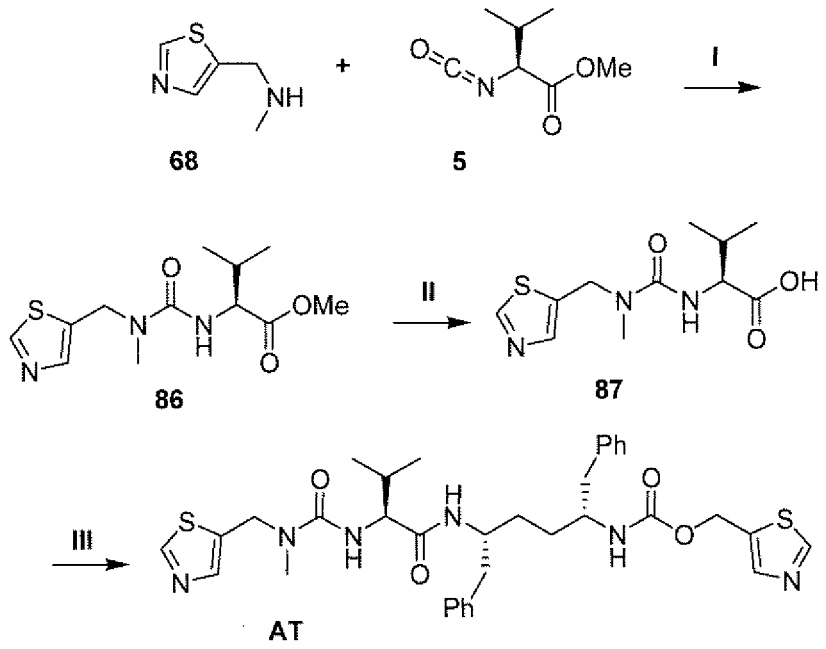
Compound **83** (0.51 g, 1.77 mmol) was dissolved in THF (10 mL) and 1M aqueous LiOH (3.54 mL) was added. The mixture was stirred at 25°C for 2 hours. The reaction was quenched with 1M HCl (4.8 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to afford Compound **84** (0.430 g). This material was used in the next step without further purification. m/z: 272.0 $(M+H)^+$.

Example AS

Compound **84** (150 mg, 0.55 mmol) was dissolved in THF (7.15 mL). Compound **8** (225 mg, 0.55 mmol) was added, followed by HOBt (112 mg, 0.83 mmol), iPr_2NEt (393 μL, 2.20 mmol), and EDC (198 μL, 1.11 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 7% i-PrOH/CH_2Cl_2) gave Example **AS** (219 mg, 60%). m/z: 663.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.87 (s, 1H); 8.76 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 6.22 (br s, 1H); 5.73 (br s, 1H); 5.22 (m, 2H); 4.50 (m, 2H); 4.16 (br s, 1H); 4.05 (br s, 1H); 3.75 (m, 1H); 2.93 (s, 3H); 2.90-2.60 (m, 5H); 2.90 (m, 1H); 2.31 (m, 1H); 1.60-1.30 (m, 4H); 1.00-0.80 (m, 6H).

Preparation of Example AT

Scheme 37



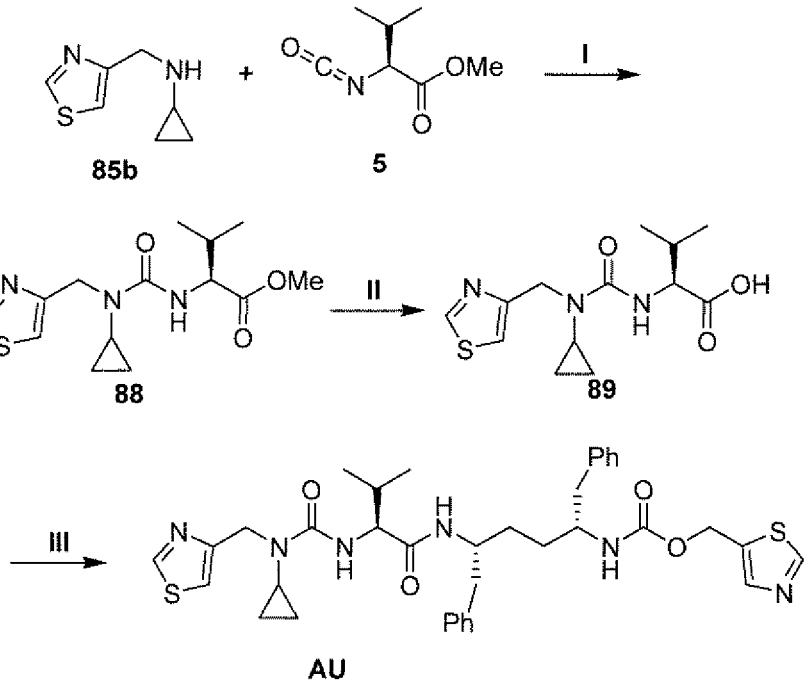
I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd 8, HOBt, EDC, DIPEA, THF

Compound 87

Compound **87** (386 mg) was prepared from Compound **86** following the same procedure used to prepare Compound **7** from Compound **6**, except that Compound **68** was used was used instead of Compound **4**. m/z 286.0 $(M+H)^+$

Preparation of Example AU

Scheme 38



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O; III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 85b

Compound **85b** was prepared following the same procedure as Compound **4**, except that 4-chloromethylthiazole (obtained from TCI America) was used instead of Compound **3**.

Compound 88

Compound **88** (341 mg) was prepared following the same procedure used to prepare Compound **83**, with the exception that Compound **85b** (300 mg, 1.95 mmol) was used instead of Compound **85a**. m/z: 312.0 $(M+H)^+$.

Compound 89

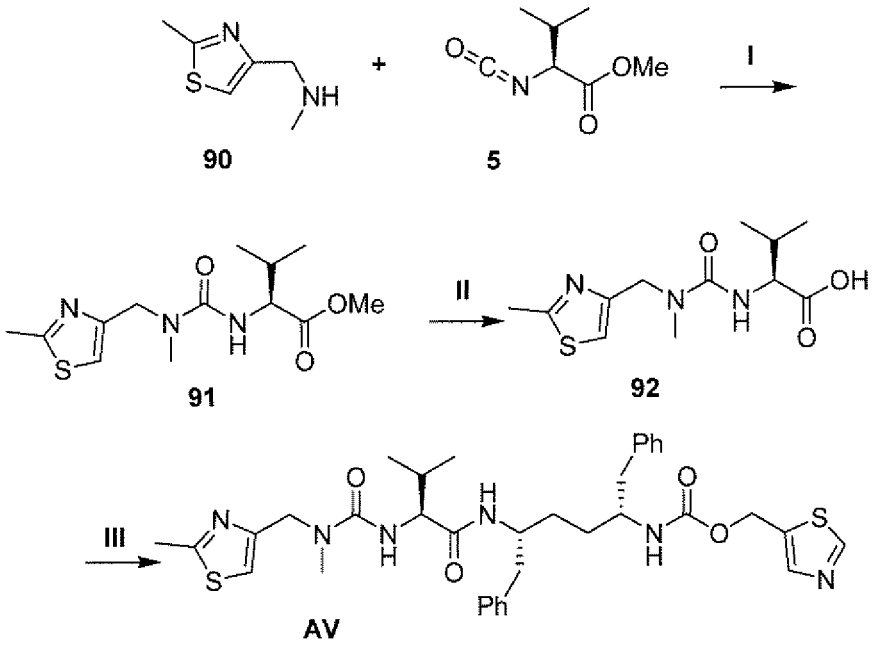
Compound **89** (341 mg) was prepared following the same procedure for **84**, with the exception that Compound **88** (293 mg, 0.99 mmol) was used instead of Compound **83**. m/z: 298.0 $(M+H)^+$.

Example AU

Example **AU** (226 mg, 64%) was prepared following the same procedure used to prepare Example **AS**, with the exception that Compound **89** (150 mg, 0.51 mmol) was used instead of Compound **84**. m/z: 689.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.87 (s, 1H); 8.74 (s, 1H); 7.83 (s, 1H); 7.40-7.00 (m, 10H); 6.21 (m, 1H); 5.73 (m, 1H); 5.29 (m, 1H); 5.17 (m, 2H); 4.88 (d, *J*=16 Hz, 1H); 4.47 (d, *J*=16 Hz, 1H); 4.18 (m, 1H); 3.75 (br s, 1H); 2.90-2.60 (m, 6H); 2.51 (br s, 1H); 2.31 (m, 1H); 1.60-1.30 (m, 4H); 1.00-0.80 (m, 10H).

Preparation of Example AV

Scheme 39



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 90

Compound **90** (190 mg) was prepared following the procedure used to prepare Compound **4**, except that 4-(chloromethyl)-2-methylthiazole was used instead of Compound **3**. m/z 141.1 (M-H)

Compound 91

Compound **91** (400 mg) was prepared following the same procedure used to prepare Compound **6** except that Compound **90** was used instead of Compound **4**. m/z 300.0 $(M+H)^+$

Compound 92

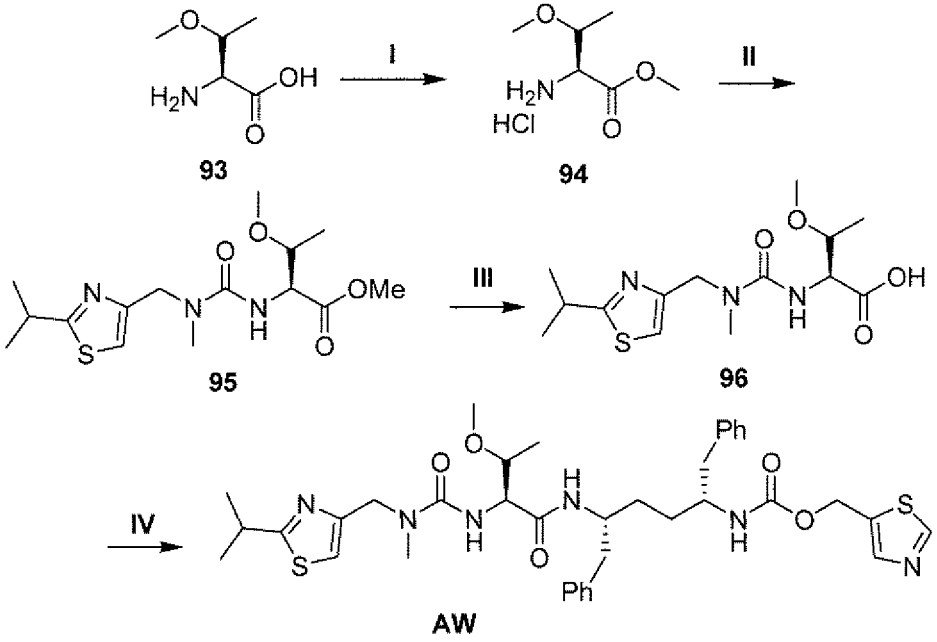
Compound **92** (188 mg) was prepared following the same procedure as Compound **7** except that Compound **91** was used instead of Compound **6**. m/z 284.0 $(M-H)^-$

Example AV

Example **AV** (107 mg) was prepared following the procedure used to prepare Example **C**, except Compound **92** was used instead of Compound **7**. ^1H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.78 (s, 1H), 7.27-7.07 (m, 10H), 6.93 (s, 1H), 6.25 (m, 2H), 5.39 (m, 1H), 5.19 (m, 2H),4.37-4.32(m, 2H),4.06 (m, 1H), 3.81 (br s, 1H), 2.83 (m, 4H), 2.65 (br s, 7H), 2.28-2.22 (m, 1H), 1.51-1.37 (m, 4H), 0.82 (m, 6 H): m/z 677.2 $(M+H)^+$

Preparation of Example AW

Scheme 40



I.$SOCl_2$/MeOH; II.DIPEA,CH_2Cl_2; III.LiOH,THF/H_2O;
IV. Cmpd 8, HOBt, EDC, IPEA,THF

Compound 93

Compound **93** is commercially available from TCI, and was used without further purification.

Compound 94

To a solution of Compound **93** (500 mg, 3.76 mmol) in methanol (20 mL) was added thionyl chloride (0.5 mL, 6.6 mmol) dropwise. The mixture was stirred at 60 ºC for 20 minutes, and concentrated *in vacuo* to gave Compound **94**.

Compound 95

To a stirred solution of Compound **94** (3.7 mmol) and diisopropylethylamine (1.4 mL, 8.3 mmol) in dichloromethane (50 mL) was added CDI (609 mg, 3.7 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (0-100%: EtOAc/hexane) gave Compound **95** (100 mg). m/z 344.3 $(M+H)^+$

Compound 96

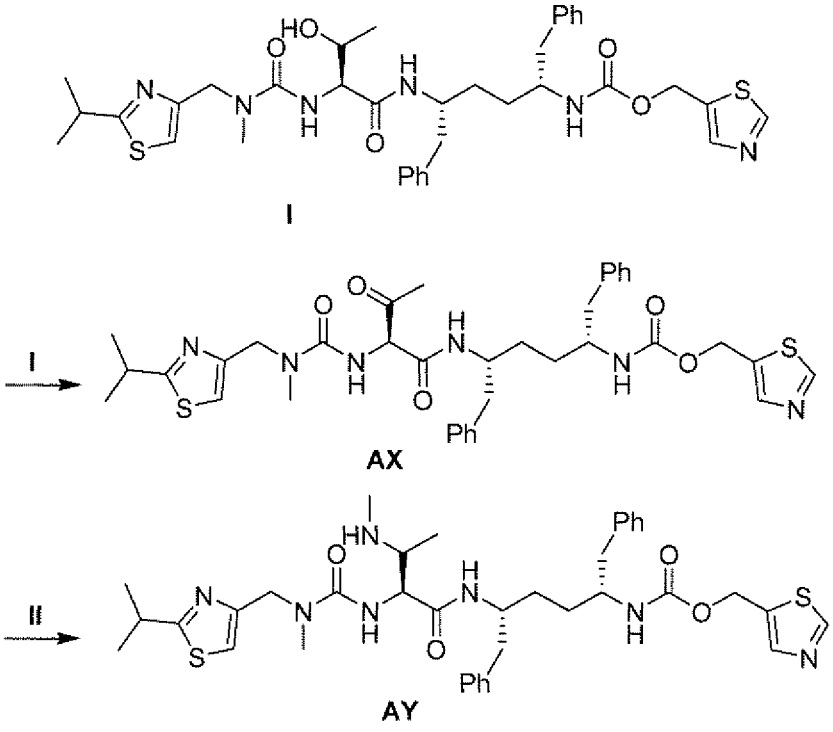
Compound **96** (39 mg) was prepared following the same procedure used to prepare Compound **7** except that Compound **95** was used instead of Compound **6**. m/z 328.3 $(M-H)^-$

Example AW

Example **AW** (107 mg) was prepared following the procedure for Example **C**, except that Compound **96** was used instead of Compound **7**. ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H), 7.82 (s, 1H), 7.27-7.09 (m, 10H), 6.95 (s, 1H), 6.23 (m, 1H), 6.14 (s, 1H), 5.22 (s, 3H), 4.45 (m, 2 H), 4.35-4.0 (m, 3 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 3.25 (s, 3H), 3.21 (m, 2H), 2.95 (s, 3 H), 2.8-2.6 (m, 4 H), 2.0-1.4 (m, 4 H), 1.25 (m, 4 H), 1.05 (m,4H): m/z 721.3 $(M+H)^+$

Preparation of Examples AX and AY

Scheme 41



Example AX

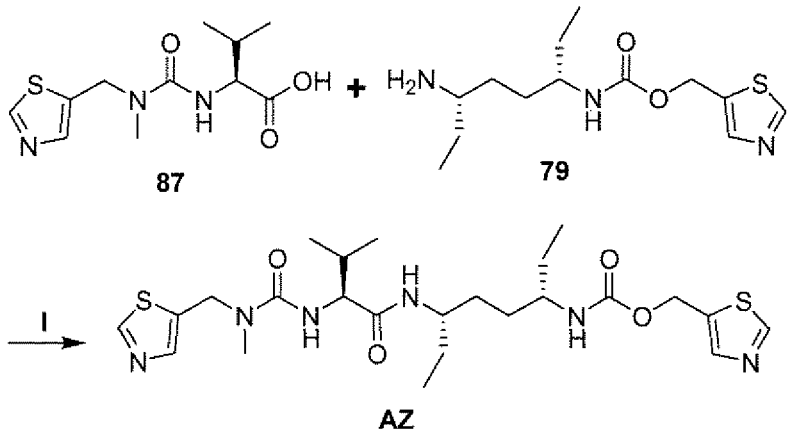
To a solution of Example **I** (650 mg, 1.00 mmol) in DMSO (3.5 mL) was added triethylamine (0.5 mL). The mixture was stirred for 30 minutes. Pyridine SO_3 was added to the mixture at 5°C then stirred for 60 minutes. The mixture was poured on to ice-water, then stirred for 30 minutes. The mixture was diluted with EtOAc and washed with water, sat. $NaHCO_3$, and brine. Concentration gave Example **AX**. m/z 705.2 $(M+H)^+$

Example AY

To a stirred solution of Example **AX** (70 mg, 0.099 mmol) and methylamine (1.5 mL, 2M) in MeOH (1.5 mL) was added AcOH (119 mg, 1.99 mmol). The mixture was stirred for 2 hours. $NaBH(OAc)_3$ (94 mg) was added, and the mixture was stirred for 2 hours. Concentration and purification by prep. HPLC gave Example **AY** (30 mg). ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H), 7.82 (s, 1H), 7.27-7.09 (m, 10H), 6.95 (s, 1H), 6.23 (m, 1H), 6.14 (s, 1H), 5.22 (s, 2 H), 4.45 (m, 1 H), 4.35-4.0 (m, 4 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 3.21 (m, 1 H), 2.95 (s, 3 H), 2.93 (s, 3H), 2.8-2.6 (m, 4 H), 2.0-1.4 (m, 4 H), 1.25 (m, 4 H), 1.05 (m, 4H): m/z 720.3 $(M+H)^+$

Preparation of Example AZ

Scheme 42



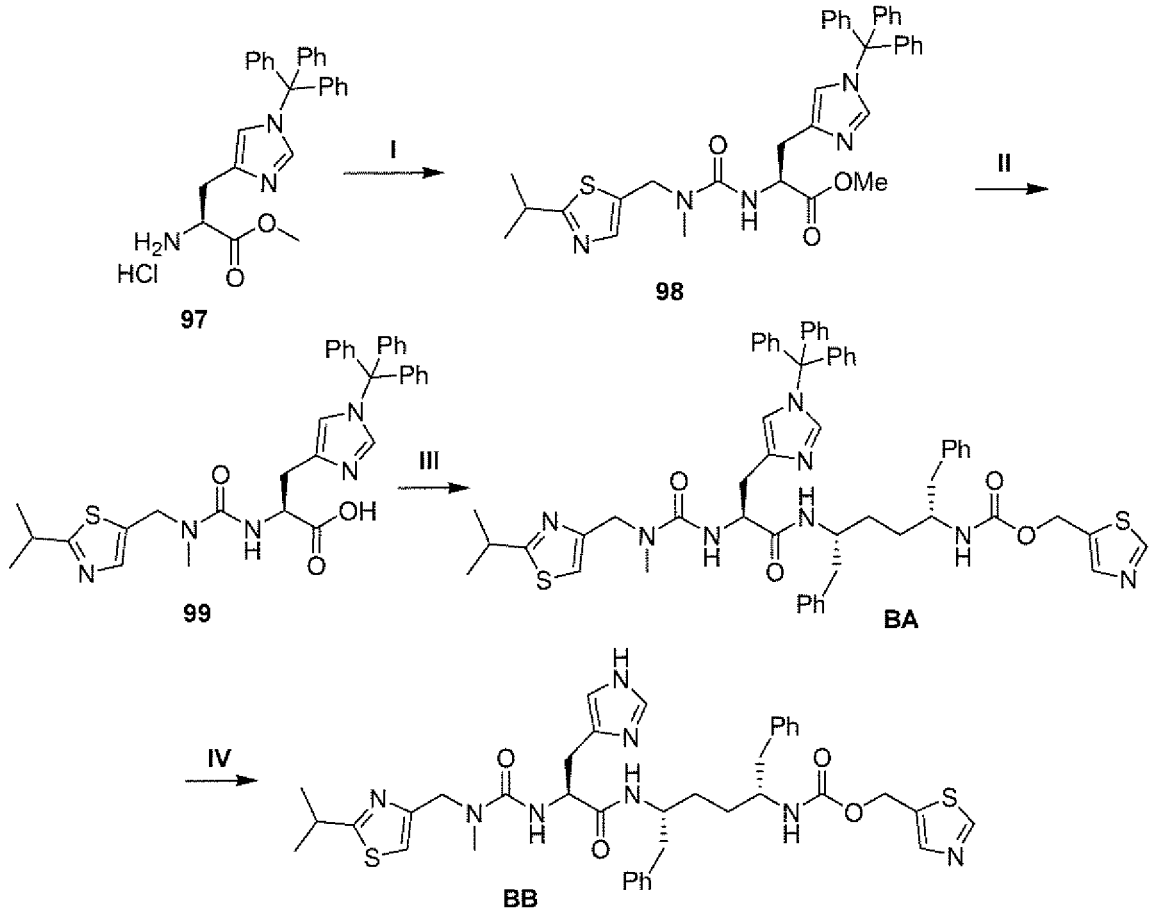
I. HOBt, EDC, DIPEA, THF

Example AZ

Compound **AZ** (61 mg) was prepared following the procedure for Example **C**, except that Compound **87** was used instead of Compound **7** and Compound **79** was used instead of Compound **8**. ^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.72 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 6.23 (d, 1H), 5.28-5.24 (m, 2H), 4.85 (d, 1H), 4.71-4.57 (m, 2H), 4.08-4.03 (m, 1H), 3.78 (br s, 1H), 3.51 (br s, 1H), 2.87 (s, 3H), 2.33 (br s, 1H), 2.13-2.06 (m, 1H), 1.49-1.33 (m, 8H), 0.93-0.80 (m, 12 H): m/z 539.2 $(M+H)^+$

Preparation of Examples BA and BB

Scheme 43



I. a. CDI/iPr_2NEt; b. Compound 9; II.a. NaOH/THF/H_2O; b. HCl; III. Cmpd 8/EDC/HOBt, IPEA, THF: IV. Et_3SiH, TFA

Compound 97

Compound 97 is commercially available from TCI, and was used as received.

Compound 98

To a stirred solution of Compound **97** (1 g, 2.2 mmol) and diisopropylethylamine (1.6 mL, 8.9 mmol) in dichloromethane (26 mL) was added CDI (362 mg, 2.2 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (0-8%: MeOH/DCM) gave Compound **98** (1.2 g). m/z 608.1 $(M+H)^+$

Compound 99

Compound **99** (1.2 g) was prepared following the same procedure used to prepare Compound 67, with the exception that Compound **98** was used instead of Compound **66**. m/z 592.2 $(M-H)^-$

Example BA

Example **BA** (111 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **99** was used instead of Compound 7. m/z 986.1 $(M+H)^+$

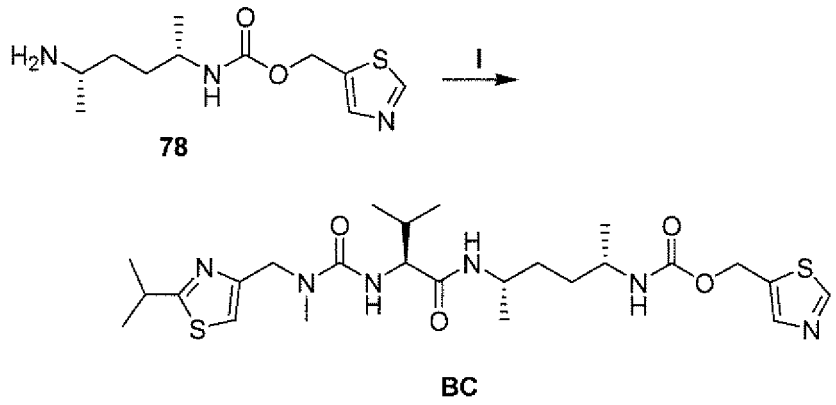
Example BB

To a stirred solution of Example **BA** (111 mg, 0.113 mmol) and TFA (1.4 mL) was added Et_3SiH (0.1 mL). The mixture was stirred for 60 minutes, then concentrated and partitioned with EtOAc and sat. $NaHCO_3$, followed by extraction with EtOAc (2X) and drying over Na_2SO_4. Concentration and purification by flash column chromatography (0-15%: MeOH/DCM) gave Example **BB** (50 mg).

^{1}H-NMR ($CDCl_3$) δ 8.75 (s, 1 H), 7.79 (s, 1 H), 7.42 (s, 1 H), 7.22-7.12 (m, 9H), 6.99-6.96 (m, 2H), 6.86 (s, 1H), 6.71 (m, 2H), 5.51 (br s, 1 H), 5.17 (m, 2H), 4.57-4.52 (m, 1 H), 4.39-4.35 (m, 2 H), 4.07 (m, 1 H), 3.74 (br s 1 H), 3.28-3.19 (m, 1H,), 3.09-2.76 (m, 6 H), 3.65-2.58 (m, 3 H), 1.49 (m, 2 H), 1.36-1.20 (m, 8 H); m/z 743.2 $(M+H)^+$

Preparation of Example BC

Scheme 44

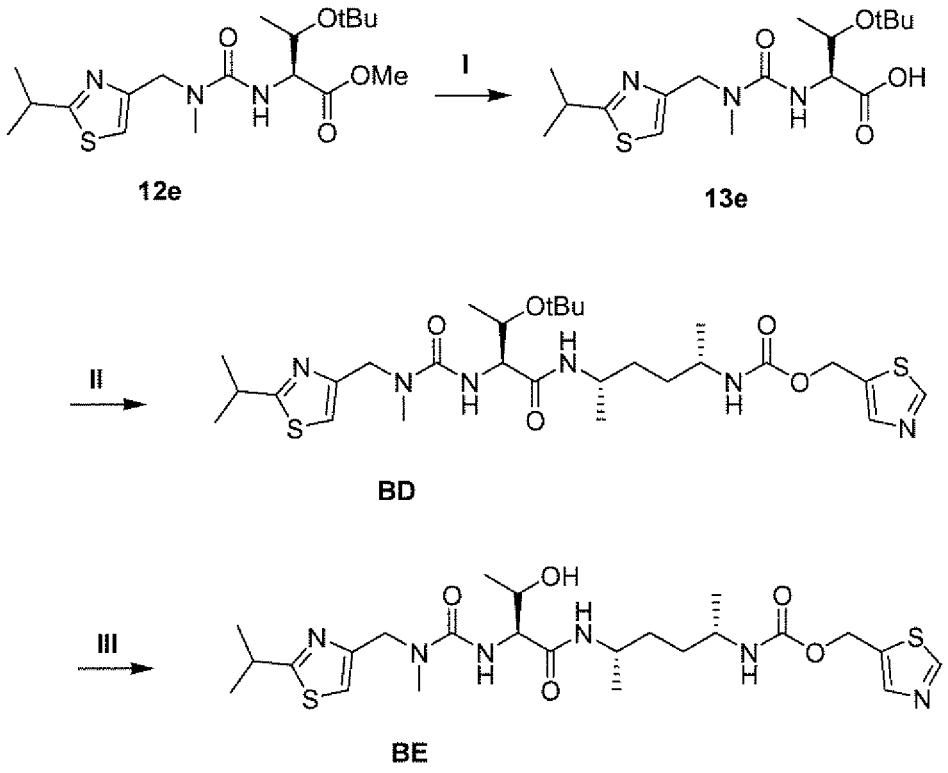


Example BC

Example **BC** (95 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **29** was used instead of Compound **7**, and Compound **78** was used instead of Compound **8**. ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.80 (s, 1H), 6.93 (s, 1H), 6.28 (d, 1H), 6.18 (m, 1H), 5.26-5.21 (m, 3H), 4.47-4.30 (m, 2H), 4.11-4.00 (m, 1H), 3.91 (br s, 1H), 3.59 (br s, 1H), 3.28 (m, 1H), 2.97-2.90 (m, 3H), 2.26-2.19 (m, 1H), 1.39-1.24 (m, 10H), 1.09-1.01 (m, 6 H), 0.94-0.86 (m, 6 H): m/z 553.1 $(M+H)^+$

Preparation of Examples BD and BE

Scheme 45



I. LiOH, THF/H_2O; II. Cmpd. 78, HOBt, EDC, DIPEA, THF; III. a. neat TFA; b. NaOH, THF, H_2O

Example BD

Example **BD** (148 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **13e** was used instead of Compound **7**, and Compound **78** was used instead of amine **8**. m/z 611.1 $(M+H)^+$

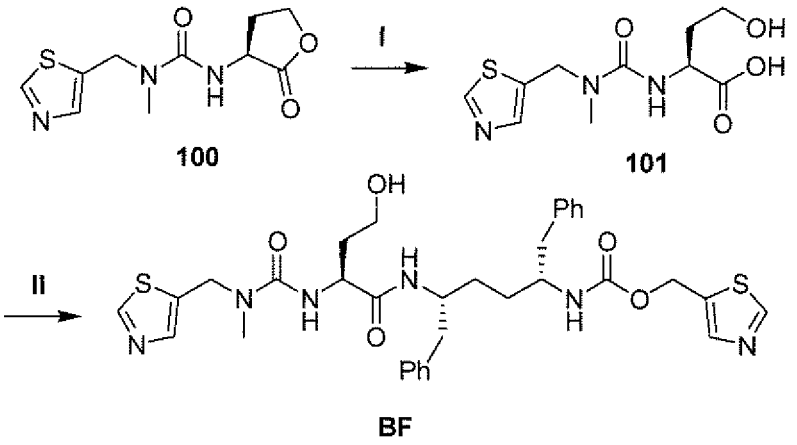
Example BE

Example **BD** (148 mg, 0.242 mmol) was dissolved in TFA (3 mL) and allowed to stir at 25 °C for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with THF (3 mL) and 2N aqueous NaOH was added until pH 10. The mixture was allowed to stir for 20 min and extracted with EtOAc. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography

(0-10% MeOH/CH_2Cl_2) gave Example **BE** (109 mg). ^1H NMR ($CDCl_3$) δ 8.75 (s, 1H), 7.80 (s, 1H), 6.97-6.94 (d, 1 H), 6.90 (s, 1H), 6.32 (br s, 1 H), 5.26-5.22 (m, 2H), 5.12 (d, 1H), 4.51-4.39 (m, 3H), 4.25-4.22 (m, 2 H), 3.87 (br s, 1H), 3.62 (br s, 1 H), 3.27-3.18 (m, 1 H), 2.94 (s, 3 H), 1.41-1.31 (m, 10 H), 1.13-1.00 (m, 9 H). m/z: 555.1 $(M+H)^+$.

Preparation of Example BF

Scheme 46



I. LiOH, THF/H_2O; II. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 100

Compound **100** was prepared using the same method used to prepare Compound **122**, except that Compound **9** was replaced with Compound **68** (*see* Scheme 70).

Compound 101

Compound **100** (108 mg, 0.423 mmol) was dissolved in THF (2 mL), then 847 µl of 1 M LiOH/H_2O was added. After stirring overnight, 843 µl of 1 N HCl was added. Concentration gave Compound **101**.

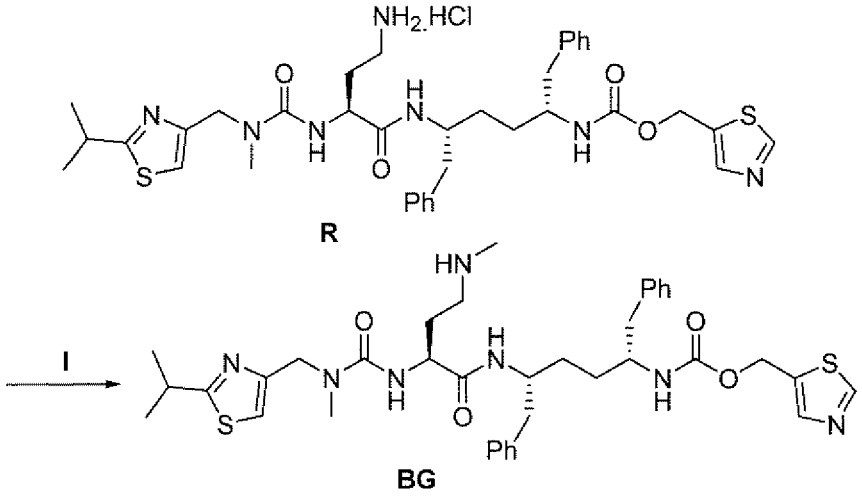
Example BF

Example **BF** (24 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **101** was used instead of Compound **7**.

^{1}H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.73 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.27-7.10 (m, 10H), 6.55-6.52 (d, 1H), 5.84 (d, 1 H), 5.21-5.19 (m, 3 H), 4.77-4.53 (m, 2H), 4.39 (br s, 1 H), 4.11-3.99 (m, 2 H), 3.81 (br s, 1H), 3.58 (m, 2 H), 2.86 (s, 3 H), 2.81-1.72 (m, 5H), 2.04 (m, 1 H), 1.85 (m, 1 H), 1.66-1.37 (m, 6 H): m/z 665.2 $(M+H)^+$

Preparation of Example BG

Scheme 47



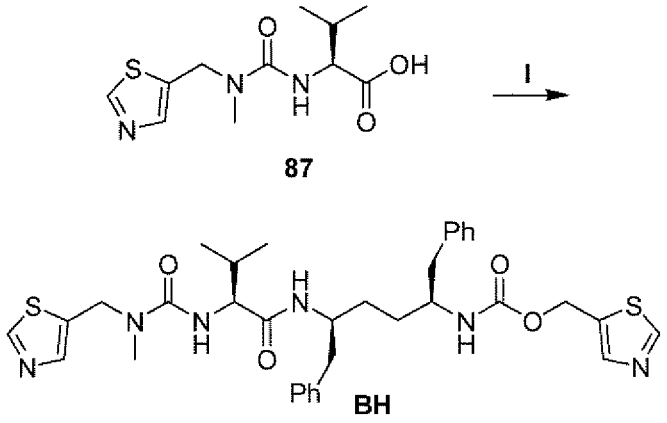
I. Ethyltrifluoroacetate, MeI, Cs_2CO_3, THF

Example BG

Example **R** (102 mg, 0.137 mmol) was dissolved in THF (2 mL), then 2 mL of ethyltrifluoroactate was added. Then 1.3 eq of MeI and excess Cs_2CO_3 were added. After stirring for 1 day, the mixture was partitioned with EtOAc and sat. Na_2CO_3, extracted with EtOAc (2X), and dried over Na_2SO_4. Purification by flash chromatography (0-20% MeOH/CH_2Cl_2) gave Example **BG** (6.5 mg). ^{1}H NMR (CD_3OD) δ 9.94 (s, 1H), 8.27 (s, 1H), 7.73 (s, 1H), 7.30-7.10 (m, 10H), 5.29, 5.17 (d 2H), 4.72 (s, 3H), 4.29 (m, 1H), 4.15 (br s, 1H), 3.83 (br s, 1H), 3.61 (m, 2H), 3.07 (s, 3H), 2.93 (m, 2H), 2.82-2.70 (m, 4H), 2.68-2.58 (m, 2H), 2.42 (s, 3H), 2.05 (m, 2H), 1.70-1.40 (m, 10H). m/z: 720.2 $(M+H)^+$.

Preparation of Example BH

Scheme 48



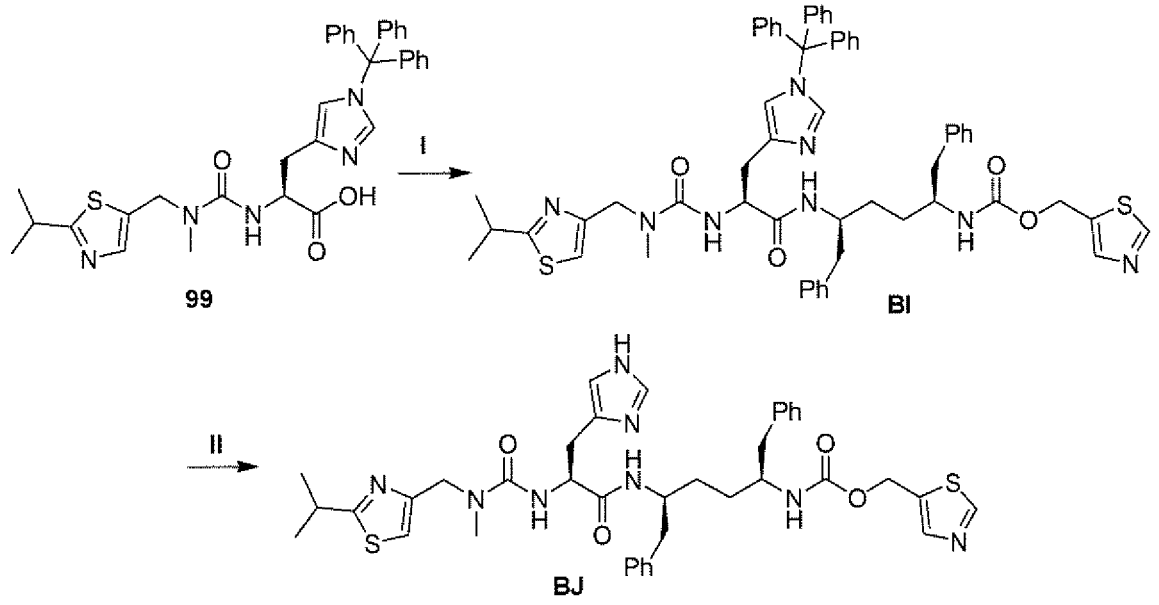
I. amine 59, HOBt, EDC, DIPEA, THF

Example BH

Example **BH** (78 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **87** was used instead of Compound **7**, and Compound **46** was used instead of Compound **8**. ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.68 (s, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 7.18-7.09 (m, 10H), 6.26 (m, 1H), 5.76 (m, 1H), 5.22-5.18 (m, 4H), 4.71-4.65 (d, 1H), 4.46-4.40 (d, 1H), 4.11-4.04 (m, 2H), 3.81 (br s, 1H), 3.14 (br s, 1H), 2.83 (s, 3H), 2.76-2.52 (m, 4H), 1.88 (m, 1H), 1.51-1.37 (m, 2H), 0.73-0.69 (m, 6 H) m/z 663.2 $(M+H)^+$

Preparation of Examples BI and BJ

Scheme 49



I. Cmpd. 46/EDC/HOBt, IPEA, THF: II. Et_3SiH, TFA

Example BI

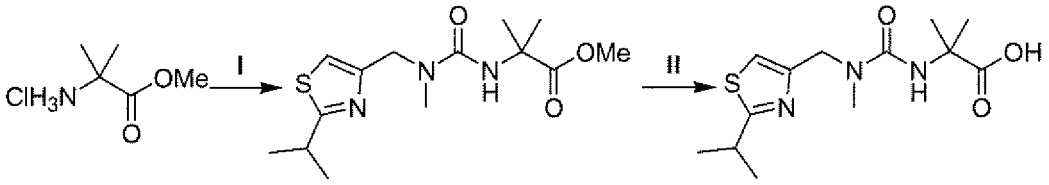
Example **BI** (1.78 g) was prepared following the procedure used to prepare Example **C**, except that Compound **99** was used instead of Compound **7**, and Compound **46** was used instead of Compound **8**. m/z 986.1 $(M+H)^+$

Example BJ

Example **BJ** (728 mg) was prepared following the procedure used to prepare Example **BB**, except that Example **BI** was used instead of Example **BA**. ^{1}H-NMR (CDCl3) δ 8.75 (s, 1 H), 7.79 (s, 1 H), 7.42 (s, 1 H), 7.22-7.12 (m, 9H), 6.99-6.96 (m, 2H), 6.86 (s, 1H), 6.71 (m, 2H), 5.51 (br s, 1 H), 5.17 (m, 2H), 4.57-4.52 (m, 1 H), 4.39-4.35 (m, 2 H), 4.07 (m, 1 H), 3.74 (br s 1 H), 3.28-3.19 (m, 1H,), 3.09-2.76 (m, 6 H), 3.65-2.58 (m, 3 H), 1.49 (m, 2 H), 1.36-1.20 (m, 8 H); m/z 743.2 $(M+H)^+$

Preparation of Compounds 104-115

Scheme 50



102 **103** **104**

I. a. CDI, DIPEA, MeCN; b. Cmpd. 9, MeCN. II. 1M LiOH, THF.

Compound 102

Compound **102** is commercially available from Aldrich Chemical Co., and was used without further purification.

Compound 103

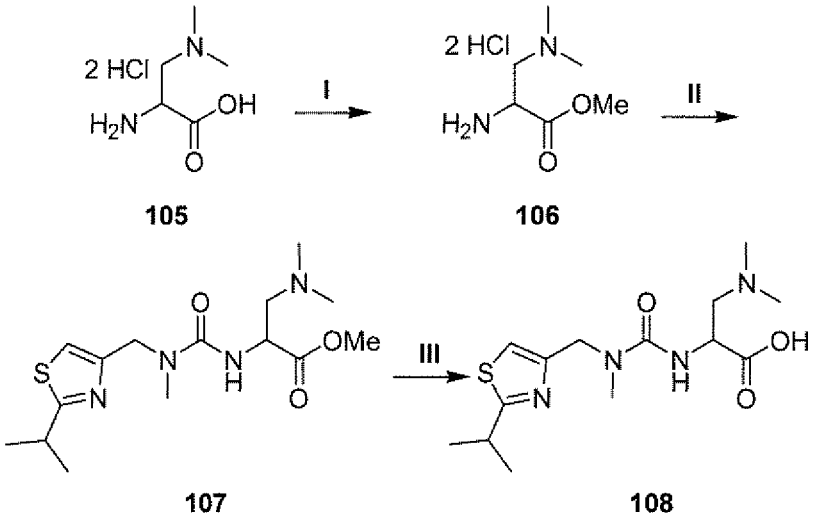
Compound **102** (5.5 mmol) was suspended in MeCN (55 mL) and DIPEA (8.25 mmol) was added. Carbonyl diimidazole (5.5 mmol) was diluted in MeCN (20 mL) and the solution added slowly to the reaction mixture over 45 min. The resulting mixture was allowed to age overnight. Compound **9** (5.5 mmol) was diluted in MeCN (10 mL) and treated with DIPEA (8.25 mmol) before being added to the reaction mixture, which was then allowed to age overnight. The volatiles were removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with 1M HCl (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with sat. Na_2CO_3 until the pH of the washes was ~ pH 8. A brine wash (30 mL) was followed by drying over anhydrous $MgSO_4$. Following concentration *in vacuo*, the residue was purified on SiO_2 (0-65% EtOAc/hex) to provide 0.340 g (20%) of Compound **103** as an amorphous white solid (*m/z* 314.0 $(M+H)^+$).

Compound 104

Compound **103** (1.1 mmol) was diluted in THF (5 mL) and treated with freshly prepared 1M LiOH (2.2 mmol). The biphasic reaction was stirred vigorously for 2 h before being quenched with 1M HCl (3 mmol). The reaction

was extracted with EtOAc (5 X 15 mL) and the combined organics were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to provide 0.282 g (86%) of Compound **104** as an amorphous white powder that was used with further purification ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.06 (s, 1H); 4.37 (s, 1H); 3.28 (p, J = 6.9 Hz, 1H); 3.00 (s, 3H); 1.62 (s, 6H); 1.39 (d, J = 6.9 Hz, 6H).

Scheme 51



I. HCl, MeOH; II. a. CDI, DIPEA, MeCN; b. Cmpd. 9, MeCN. III. 1M LiOH, THF.

Compound 105

Compound **105** is commercially available from Aldrich Chemical Co., and was used without further purification.

Compound 106

Racemic Compound **105** (12.2 mmol) was diluted in MeOH (100 mL). HCl/dioxane solution (4M, 25 mmol) was added and the solution was refluxed overnight. Volatiles were removed *in vacuo* to produce 2.60 g (97%) of Compound **106** as a racemic mixture. The foamy white solid was used without further purification (*m/z* 147.0 $(M+H)^+$).

Compound 107

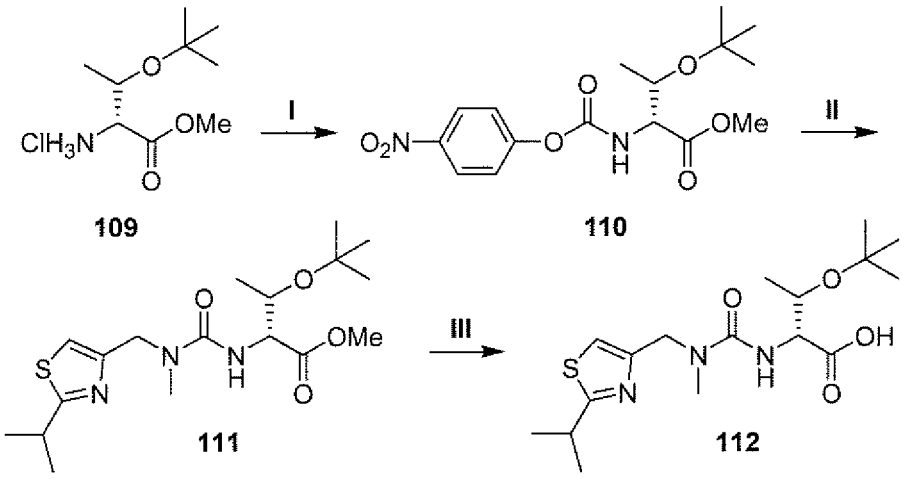
Compound **106** (5 mmol) was diluted in MeCN (65 mL) and treated with DIPEA (25 mmol). The resulting solution was added slowly via addition funnel

to a solution of CDI (5 mmol) in MeCN (30 mL) and allowed to age overnight. Compound **9** (5 mmol) and DIPEA (3 mmol) were added to the reaction solution which was allowed to age overnight. The volatiles were removed *in vacuo* and the residue was taken up in EtOAc and sat. Na_2CO_3 (30 mL each). The aqueous layer was extracted with EtOAc (3 X 25 mL) and the combined organics were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Following concentration *in vacuo,* purification by column chromatography on SiO_2 (0-10% MeOH/DCM) provided 0.36 g (21%) of racemic Compound **107** as a yellow oil (*m/z* 343.1 $(M+H)^+$).

Compound 108

Compound **107** (1.05 mmol) was taken up in THF (5 mL) and treated with freshly prepared 1M LiOH solution (2.1 mmol). The solution was stirred vigorously for 2 h and quenched with 1M HCl (2.1 mmol). The volatiles were removed *in vacuo,* and the resulting oil was azeotroped with toluene until a quantitative yield of racemic Compound **108** was produced as an amorphous white solid that was used without further purification (*m/z* 329.1 $(M+H)^+$).

Scheme 52



I. *p*-$O_2NC_6H_4O(CO)Cl$, NMM, DCM, 0 °C to rt; II. Cmpd. 9, Et_3N, DMAP, THF, 70 °C; III. 1M LiOH, THF

Compound 109

Compound **109** is commercially available from Bachem, and was used as received.

Compound 110

Compound **109** (4.1 mmol) was diluted in DCM (5 mL) and treated with N-methylmorpholine (8.2 mmol). This solution was added slowly to a DCM (5 mL) solution of 4-nitrophenyl chloroformate (4.1 mmol) at 0 °C. The reaction was then allowed to warm to room temperature overnight. The volatiles were removed *in vacuo* and the residue was taken up in EtOAc and sat. Na_2CO_3. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined organics were washed with brine (30 mL) prior to being dried over anhydrous Na_2SO_4. Following concentration *in vacuo*, the residue was purified by column chromatography on SiO_2 (0-25% EtOAc/Hex) to produce 0.75 g (51%) of Compound **110** as an amorphous white solid (*m*/z 354.8 $(M+H)^+$).

Compound 111

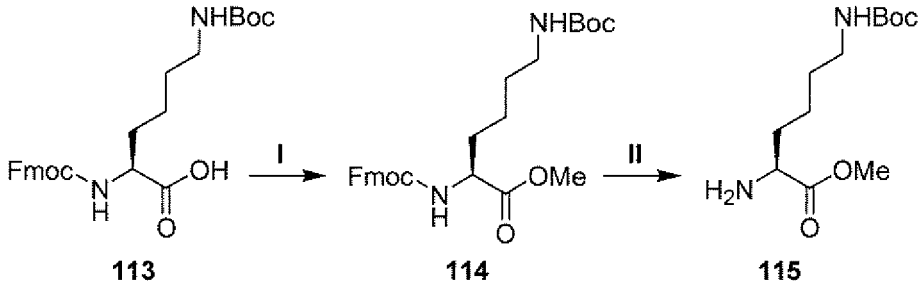
Compound **110** (1.1 mmol) was diluted in THF (3.5 mL). Compound **9** (1.4 mmol) was diluted in THF (3 mL), treated with Et_3N (2.8 mmol) and transferred to the reaction solution. DMAP (0.11 mmol) was added and the reaction was heated to 70 °C for 2 h. After cooling to room temperature, EtOAc (10 mL) and sat. Na_2CO_3 were added. The aqueous phase was extracted with EtOAc (3 X 10 mL) and the combined organics were washed with saturated Na_2CO_3, H_2O, and brine (15 mL each). After drying over anhydrous $MgSO_4$, volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-50% EA/hex) to produce 0.346 g (82%) of Compound **111** (*m*/z 386.0 $(M+H)^+$).

Compound 112

Compound **111** (0.88 mmol) was taken up in THF (4 mL) and treated with freshly prepared 1M LiOH (1.8 mmol). The reaction mixture was stirred vigorously for 1.5 h and quenched with 1M HCl (2.5 mmol). The reaction mixture

was extracted with EtOAc (3 X 10 mL), and the combined organics were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* produced 0.300 g (92%) of Compound **112** as a colorless film that was used without further purification (*m/z* 372.0 $(M+H)^+$).

Scheme 53



113 **114** **115**

I. $TMSCHN_2$, THF/MeOH; II. piperidine, DMF

Compound 113

Compound **113** is commercially available from Chem-Impex, and was used without further purification.

Compound 114

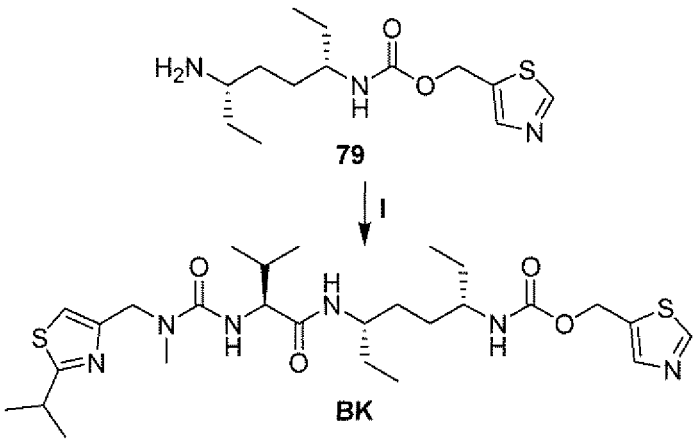
Compound **113** (3.2 mmol) was diluted in THF (15 mL). $TMSCHN_2$ (3.2 mmol) was added slowly, followed by MeOH (5 mL). The solution rapidly became colorless, and heavy evolution of gas was observed. After aging overnight, the volatiles were removed *in vacuo* and the residue purified by column chromatography on SiO_2 (0-50% EtOAc/hex) to produce 0.805 g (52%) of Compound **114** (*m/z* 505.2 $(M+Na)^+$).

Compound 115

Compound **114** (1.7 mmol) was diluted in DMF (4 mL) and piperidine (1 mL) was added. After 30 min, the volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-5% MeOH/DCM) to provide 0.414 (94%) of Compound **115** as an amorphous white solid (*m/z* 261.0 $(M+H)^+$).

Preparation of Example BK

Scheme 54



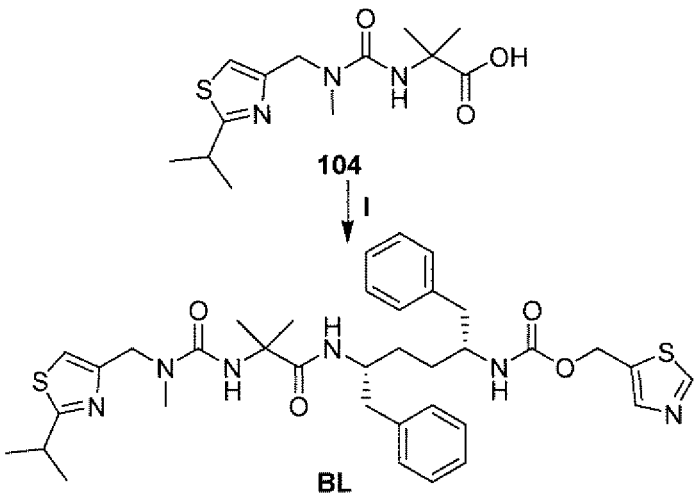
I. Cmpd. 29/EDC/HOBt/DIPEA/THF.

Compound BK

Compound **79** (0.70 mmol) and Compound **29** (0.91 mmol) were combined in THF (7 mL). HOBt (0.91 mmol), DIPEA (1.05 mmol) and EDC (0.91 mmol) were added consecutively at room temperature and the reaction was allowed to age overnight. The volatiles were removed *in vacuo* and the residue taken up in 3/1 $CHCl_3$/IPA and sat. Na_2CO_3 (15 mL each). The aqueous layer was extracted with 3/1 $CHCl_3$/IPA (3 X 10 mL) and the combined organics were washed with sat. Na_2CO_3, water, and brine (15 mL each). Following drying over anhydrous $MgSO_4$, the volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-10% MeOH/DCM) to produce 8.5 mg (2%) of Compound **BK** *m/z* 581.2 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.91 (s, 1H); 7.89 (s, 1H); 7.15 (s, 1H); 6.52-6.0 (br m, 2H); 5.26 (s, 2H); 5.18 (br d, *J* = 8.1 Hz, 1H); 4.55 (s, 2H); 4.06 (br s, 1H); 3.79 (br s, 1H); 3.48 (m, 2H); 3.09 (s, 3H, minor rotamer); 3.01 (s, 3H, major rotamer); 2.34 (m, 1H); 1.60-1.30 (m, 8H); 1.42 (d, *J* = 6.9 Hz, 6H); 0.98 (t, *J* = 7.2 Hz, 6H); 0.86 (m, 6H).

Preparation of Example BL

Scheme 55



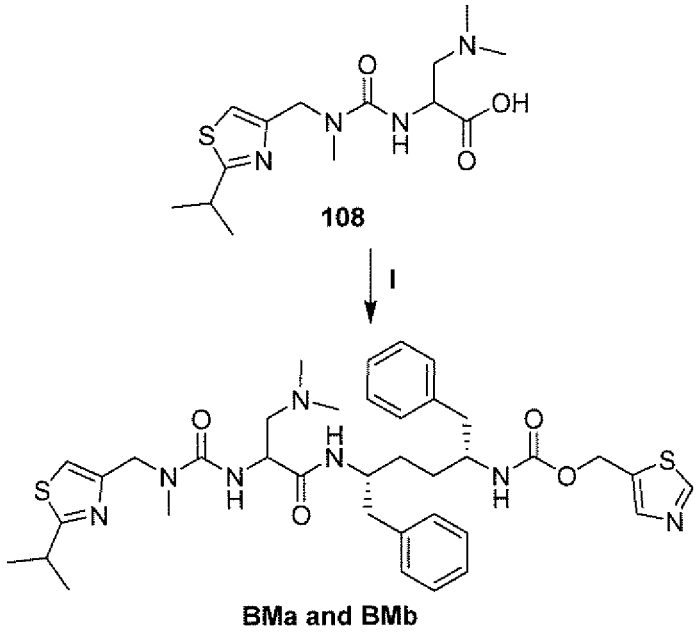
I. Cmpd. 8/EDC/HOBt/DIPEA/THF.

Example BL

Example **BL** was prepared in a similar fashion to Example **BK** using Compound **104** (0.26 mmol) and Compound **8** (0.29 mmol) to produce 0.087 g (64%) of Example **BL** as an amorphous white solid *m/z* 691.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.82 (s, 1H); 7.30-7.10 (m, 11H); 7.06 (s, 1H); 6.54 (d, J = 9.6 Hz, 1H); 5.89 (d, J = 8.4 Hz, 1H); 5.22 (s, 1H); 5.07 (m, 1H); 4.45 (AB d, J = 16.5 Hz, 1H); 4.37 (AB d, J = 15.6 Hz, 1H); 4.07 (m, 1 H); 3.68 (m, 1H); 3.40 (m, 1H); 3.06 (s, 3H, minor rotamer); 2.89 (s, 3H, major rotamer); 2.90-2.54 (m, 4H); 1.60-1.25 (m, 16H).

Preparation of Example BMa and BMb

Scheme 56



i. Cmpd. 8/EDC/HOBt/DIPEA/THF.

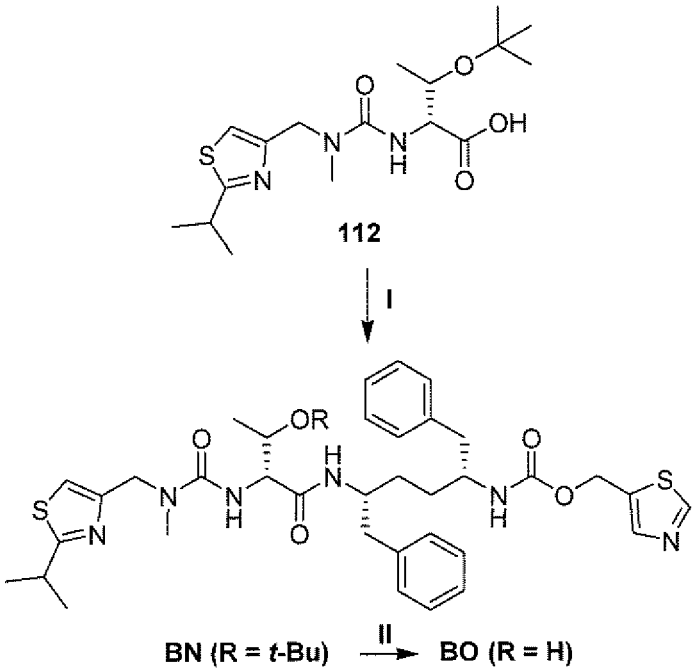
Examples BMa and BMb

Examples **BMa** and **BMb** were prepared in a similar fashion to Compound **BK** using racemic Compound **108** (0.36 mmol) and Compound **8** (0.28 mmol). The enantiomeric products were separated by preparatory HPLC (Chiralcel OD-H (250 X 4.6 mm, 70:30 Heptane/IPA, 30 min) to produce 0.008 g (4%) of enantiomer **BMa** (HPLC R_T = 11.71 min) *m/z* 720.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.73 (s, 1H); 7.78 (s, 1H); 7.41 (br s, 1H); 7.30-7.00 (m, 11H); 6.94 (s, 1H); 5.40 (br s, 1H); 5.18 (br s, 2H); 4.56 (AB d, *J* = 15 Hz, 1H); 4.48 (AB d, *J* = 16 Hz, 1H); 4.39 (br s, 1H); 4.05 (br s, 1H); 3.73 (br s, 1H); 3.25 (s, 3H, minor rotamer); 3.23 (m, 1H); 2.98 (s, 3H, major rotamer); 2.82-2.30 (m, 10H); 1.60-1.20 (m, 6H); 1.32 (d, *J* = 7 Hz, 6H) and 0.010 g (5%) of enantiomer **BMb** (HPLC R_T = 15.41 min). (*m/z* 720.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.78 (s, 1H); 7.83 (s, 1H); 7.38 (br d, *J* = 8 Hz, 1H); 7.30-7.7.05 (m, 11H); 7.02 (s, 1H); 5.52 (d, *J* = 9 Hz, 1H); 5.25 (AB d, *J* = 13 Hz, 1H); 5.21 (AB d, *J* = 13 Hz, 1H); 4.85-4.62 (m, 2H); 4.44 (d, *J* = 16 Hz, 1H); 3.99 (br s, 1H); 3.78

(br s, 1H); 3.37 (br s, 3H, minor rotamer); 3.26 (m, 1H); 3.07 (s, 3H, major rotamer); 2.77 (s, 6H); 2.86-2.60 (m, 4H); 1.6-1.3 (m, 6H); 1.35 (d, J = 7 Hz, 6H).

Preparation of Examples BN and BO

Scheme 57



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Example BN

Example **BN** was prepared in a similar fashion to Example **BK** using Compound **112** (0.78 mmol) and Compound **8** (0.60 mmol) to produce 0.227 g (50%) of Compound **BN** as colorless film. (m/z 763.3 $(M+H)^+$).

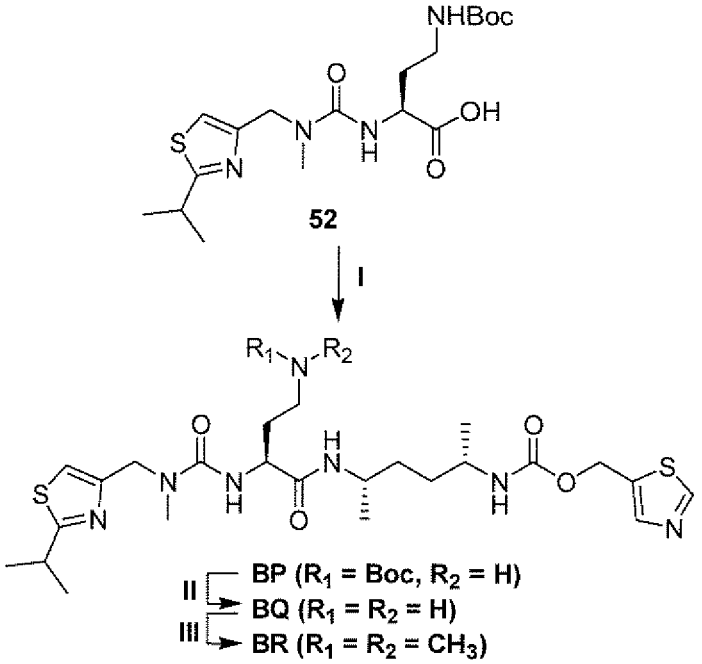
Example BO

Example **BO** was prepared in a similar fashion to Example **AM** using Example **BN** (0.29 mmol) to produce 0.149 g (72%) of Example **BO** as an amorphous white solid. (m/z 707.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.84 (s, 1H); 7.26-7.03 (m, 11H); 6.99 (s, 1H); 6.69 (d, J = 9.6, 1H); 6.42 (br s, 1H); 5.47 (br d, J = 8.7 Hz, 1H); 5.27 (AB d, J = 13 Hz, 1H); 5.22 (AB d, J = 13 Hz, 1H); 4.55 (AB d, J = 16 Hz, 1H); 4.43 (AB d, J = 16 Hz, 1H); 4.18 (m, 1H); 4.00 (m,

2H); 3.72 (br s, 1H); 2.25 (m, 1H); 2.99 (s, 3H); 2.84-2.60 (m, 3H); 2.54-2.42 (m, 1H); 1.64-1.12 (m, 4H); 1.37 (d, J = 7 Hz, 6H); 1.11 (d, J = 6 Hz, 3H).

Preparation of Examples BP-BR

Scheme 58



I. Cmpd. 78/EDC/HOBt/DIPEA/THF; II. 4M HCl/dioxane; III. HCHO, $NaHB(OAc)_3$, MeOH

Example BP

Example **BP** was prepared in a similar fashion to Example **BK** using Compound **52** (0.22 mmol) and Compound **78** (0.20 mmol) to produce 0.091 g (71%) of Example **BP** as colorless film (*m/z* 654.2 $(M+H)^+$).

Example BQ

Example **BP** (0.14 mmol) was treated with 4M HCl in dioxane (2 mL) to produce a white precipitate within 5 min. The solvents were removed, and the solid was taken up in MeOH. Concentration *in vacuo* afforded 0.083 g (99%) of the HCl salt of Example **BQ** as a colorless film (*m/z* 554.1 $(M+H)^+$; ^{1}H-NMR (CD_3OD, 300 MHz): 10.03 (s, 1H); 8.41 (s, 1H); 7.81 (s, 1H); 5.48 (s, 2H, minor rotamer); 5.35 (s, 2H, major rotamer); 4.74 (s, 2H); 4.34 (br s, 1H); 3.90 (br s, 1H); 3.78-3.54 (m,

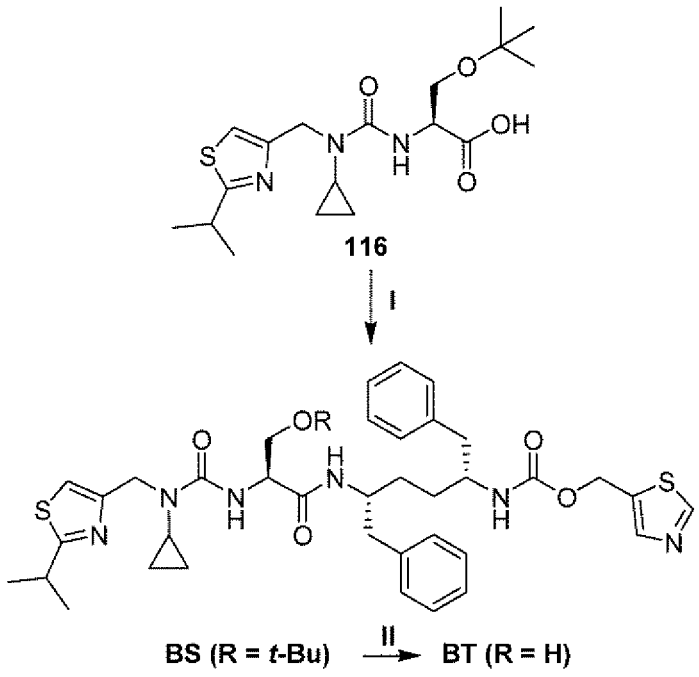
2H); 3.20-2.98 (m, 5H); 2.20 (br s, 1H); 2.07 (br s, 1H); 1.60-1.4 (m, 10H); 1.12 (m, 6H).

Example BR

Example **BQ** (0.11 mmol) was taken up in MeOH (1.5 mL). Formaldehyde (37% in H_2O, 13.4 mmol) was added and aged 10 min. $NaHB(OAc)_3$ (0.324 mmol) was added, and the reaction mixture was allowed to age at room temperature overnight. More formaldehyde (13.4 mmol) and $NaHB(OAc)_3$ (0.324 mmol) were added and allowed to age an additional 6 h at room temperature. The solvents were removed *in vacuo* and the product was isolated by preparatory HPLC to produce 0.058 g (77%) of the TFA salt of Example **BR** as an amorphous solid. *m/z* 582.3 $(M+H)^+$; ^1H-NMR (CD_3OD, 300 MHz): 9.07 (s, 1H); 7.91 (s, 1H); 7.25 (s, 1H); 5.47 (s, 2H, minor rotamer); 5.28 (s, 2H, major rotamer); 4.59 (AB d, J = 16 Hz, 1H); 4.53 (AB d, J = 16 Hz, 1H); 4.31 (dd, J = 9.2, 5 Hz, 1H); 3.88 (m, 1H); 3.59 (m, 1H); 3.32 (m, 1H); 3.20 (m, 2H); 2.98 (s, 3H); 2.89 (br s, 6H); 2.23 (m, 1H); 2.00 (m, 1H); 1.44 (m, 4H); 1.37 (d, J = 7 Hz, 6H); 1.10 (m, 6H).

Preparation of Examples BS and BT

Scheme 59



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Compound 116

Compound **116** was prepared in a similar fashion to Compound **75** using Compound **4** (0.76 mmol) and Compound **47** (0.64 mmol) to produce 0.218 g (90%) of Compound **116** as a foamy white solid (*m/z* 384.1 $(M+H)^+$).

Example BS

Example **BS** was prepared in a similar fashion to Example **BK** using Compound **116** (0.28 mmol) and Compound **8** (0.25 mmol) to produce 0.139 g (72%) of Example **BS** as a colorless film (*m/z* 775.3 $(M+H)^+$).

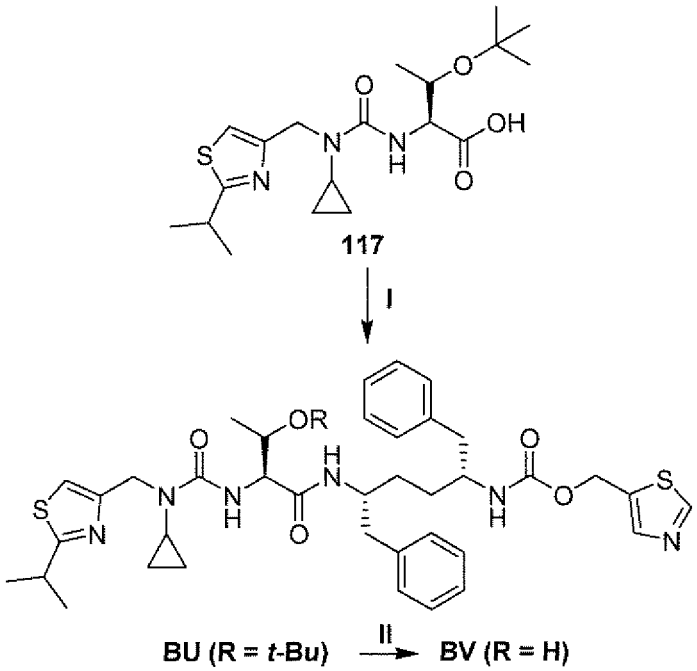
Example BT

Example **BT** was prepared in a similar fashion to Example **AM** using Example **BS** (0.18 mmol) to produce 0.080 g (62%) of Example **BT** as an amorphous white solid. *m/z* 719.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 7.82 (s, 1H); 7.27-7.0 (m, 10H); 6.98-6.82 (m, 1H); 6.85 (s, 1H); 6.44 (br s, 1H); 5.30 (s, 2H, minor rotamer); 5.22 (s, 2H, major rotamer); 5.04 (br s, 1H); 4.62 (AB d,

J = 15 Hz, 1H); 4.54 (AB d, *J* = 15 Hz, 1H); 4.27 (br s, 1H); 4.11 (br s, 1H); 3.97 (br d, *J* = 10 Hz, 1H); 3.82, br s, 1H); 3.57 (br s, 1H); 3.40-3.10 (m, 2H); 2.80-2.60 (m, 4H); 2.55 (m, 1H); 1.54 (m, 2H); 1.46-1.30 (m, 2H); 1.35 (d, *J* = 7 Hz, 6H); 0.94-0.72 (m, 4H).

Preparation of Examples BU and BV

Scheme 60



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Compound 117

Compound **117** was prepared in a similar fashion to Compound **13d** except that Compound **4** (1.5 mmol) and the *L*-enantiomer of Compound **10d** (1.15 mmol) were used to ultimately produce 0.328 g (88%) of Compound **190** as a foamy white solid (*m/z* 398.1 $(M+H)^+$).

Example BU

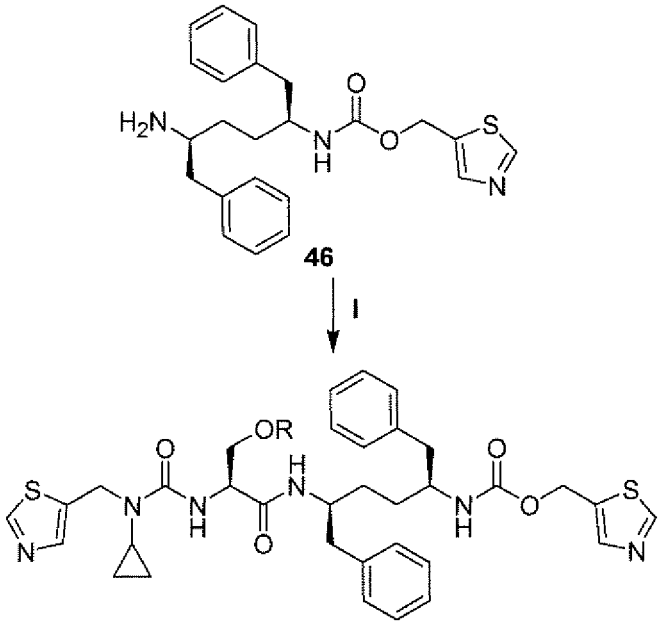
Example **BU** was prepared in a similar fashion to Example **AL** using Compound **117** (0.33 mmol) and Compound **8** (0.30 mmol) to produce 0.196 g (84%) of Example **BU** as an amorphous white solid (*m/z* 789.3 $(M+H)^+$).

Example BV

Example **BV** was prepared in a similar fashion to Example **AM** using Example **BU** (0.29 mmol) to produce 0.140 g (77%) of Example **BV** as an amorphous white solid. *m/z* 733.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.80 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 10H); 6.70-6.10 (m, 1H); 6.86 (s, 1H); 6.20 (br d, *J* = 7 Hz, 1H); 5.24 (s, 2H); 4.81 (br d, *J* = 7 Hz, 1H); 4.82 (s, 2H); 4.34 (br d, *J* = 7 Hz, 1H); 4.16 (br s, 1H); 4.07 (br d, *J* = 6 Hz, 1H); 3.86 (br s, 1H); 3.38 (br s, 1H); 2.69 (m, 6H); 1.62-1.50 (m, 2H); 1.50-1.34 (m, 2H); 1.38 (m, 6H); 1.13 (d, *J* = 6 Hz, 3H); 0.98-0.76 (m, 4H).

Preparation of Examples BW and BX

Scheme 61



I Cmpd. 75/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Example BW

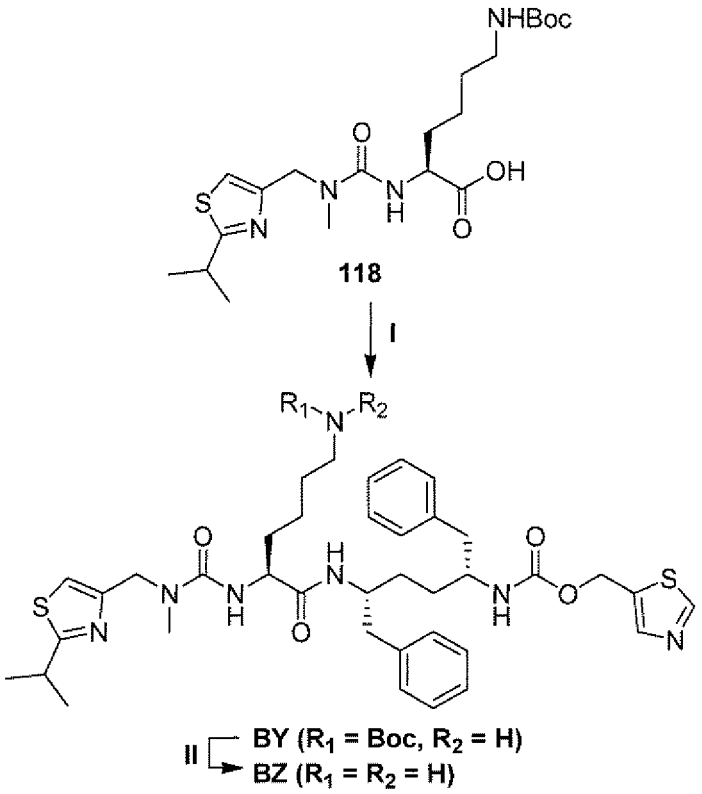
Example **BW** was prepared in a similar fashion to Example **BK** using Compound **75** (0.27 mmol) and Compound **46** (0.24 mmol) to provide 0.154 g (86%) of Example **BW** as an amorphous white solid (*m/z* 733.3 $(M+H)^+$).

Example BX

Example **BX** was prepared in a similar fashion to Example **AM** using Example **BW** (0.21 mmol) to provide 0.091 g (98%) of the TFA salt of Example **BX** as an amorphous white solid. *m/z* 677.5 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.83 (s, 1H); 8.77 (s, 1H); 7.84 (s, 1H); 7.77 (s, 1H); 7.27-7.00 (m, 10H); 6.62 (d, *J* = 9 Hz, 1H); 6.44 (d, *J* = 6 Hz, 1H); 5.35 (d, *J* = 10 Hz, 1H); 5.24 (s, 2H); 4.69 (AB d, *J* = 15 Hz, 1H); 4.62 (AB d, *J* = 16 Hz, 1H); 4.14 (br m, 2H); 3.96-3.78 (m, 2H); 3.51 (dd, *J* = 11, 4.5 Hz, 1H); 3.38 (br s, 1H); 2.82-2.58 (m, 4H); 2.41 (m, 1H); 1.70-1.24 (m, 4H); 1.20-0.88 (m, 2H); 0.88-0.54 (m, 2H).

Preparation of Examples BY and BZ

Scheme 62



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. 4M HCl/dioxane.

Compound 118

Compound **118** was prepared in a similar fashion to Compound **104** except that Compound **115** (0.40 mmol) was used instead of Compound **102**, which was

reacted with Compound **9** (0.48 mmol) to ultimately provide 0.075 g (89%) of Compound **118** as a foamy white solid (*m/z* 443.4 $(M+H)^+$).

Example BY

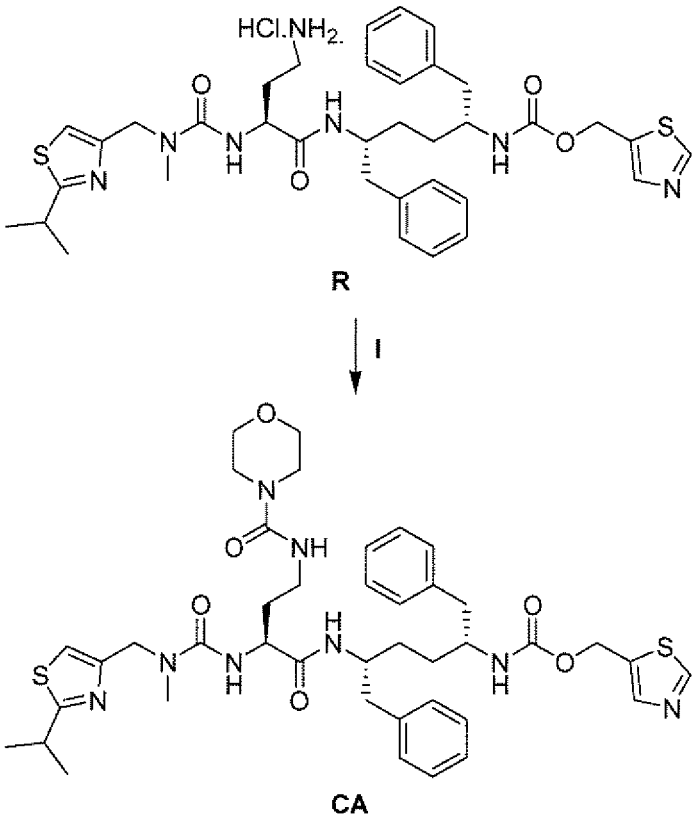
Example **BY** was prepared in a similar fashion to Example **BM** using Compound **118** (0.17 mmol) and Compound **8** (0.15 mmol) to produce 0.079 g (62%) of Example **BY** as an amorphous white solid (*m/z* 834.3 $(M+H)^+$).

Example BZ

Example **BZ** was prepared in a similar fashion to Example **BQ** using Example **BY** (0.095 mmol) to provide 0.082 g (99%) of the HCl salt of Example **BZ** as an amorphous white solid *m/z* 734.2 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.08 (s, 1H); 7.86 (br m, 3H); 7.58 (d, *J* = 9 Hz, 1H); 7.25-7.00 (m, 11H); 6.32 (br s, 1H); 5.16 (s, 2H); 4.99 (br m, 4H); 4.48 (AB d, *J* = 15 Hz, 1H); 4.43 (AB d, *J* = 15 Hz, 1H); 4.02 (m, 1H); 3.89 (m, 1H); 3.63 (m, 1H); 3.22 (hep, *J* = 7 Hz, 1H); 2.87 (s, 3H); 2.76-2.56 (m, 4H); 1.58-1.15 (m, 10H); 1.29 (d, *J* = 7 Hz, 6H).

Preparation of Example CA

Scheme 63



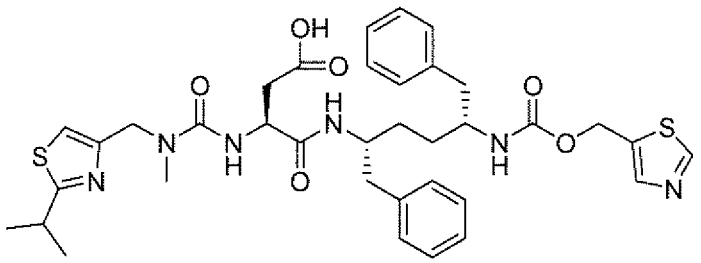
I. 4-morpholinecarbonyl chloride, DIPEA, DCM.

Example CA

Example **R** (0.11 mmol) was diluted in DCM (1 mL) and treated with 4-morpholinecarbonyl chloride (0.13 mmol) and DIPEA (0.16 mmol). After 2 h, volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-20% MeOH/DCM) to afford 0.068 g (76%) of Example **CA** as an amorphous white solid *m/z* 819.1 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.85 (s, 1H); 7.27-7.07 (m, 12H); 6.94 (s, 1H); 6.26 (br s, 1H); 5.73 (d, *J* = 8 Hz, 1H); 5.28 (AB d, *J* = 13 Hz, 1H); 5.22 (AB d, *J* = 13 Hz, 1H); 4.50 (AB d, *J* = 16 Hz, 1H); 4.44 (AB d, *J* = 16 Hz, 1H); 4.17 (m, 1H); 3.98 (br s, 1H) 3.76 (br s, 1H); 3.68 (br s, 1H); 3.60 (m, 4H); 3.40 (m, 2H), 3.32 (m, 4H); 2.97 (s, 3H); 2.87 (dd, *J* = 13, 5 Hz, 2H); 2.73, (m, 2H); 2.57 (m, 2H); 1.79 (m, 2H); 1.60-1.20 (m, 6H); 1.37 (d, *J* = 7 Hz, 6H).

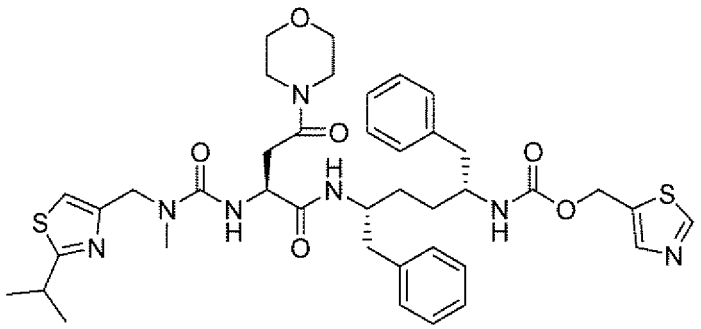
Preparation of Compound CB

Scheme 64



AF

I



CB

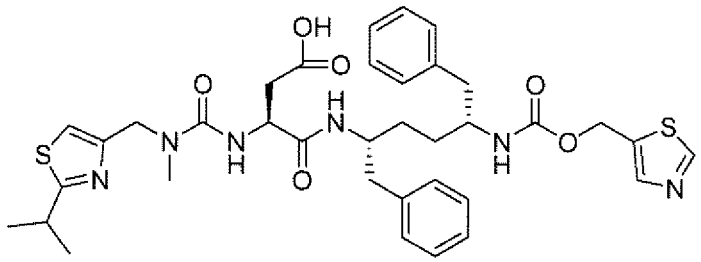
I. morpholine, EDC, HOBt, THF.

Example CB

Example **AF** (0.15 mmol) was diluted in THF (1 mL) and treated with morpholine (0.61 mmol), HOBt (0.18 mmol) and finally EDC (0.18 mmol). The reaction mixture was allowed to age overnight. The reaction mixture was then diluted in EtOAc and sat. Na_2CO_3. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified via preparatory HPLC to provide 0.024 g (20%) of Example **CB** as an amorphous white solid. *m/z* 790.4 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.81 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 10H); 6.96 (s, 1H); 6.78 (d, *J* = 8 Hz, 1H); 6.67 (s, 1H); 5.36 (d, *J* = 9 Hz, 1H); 5.27 (AB d, *J* = 13 Hz, 1H); 5.20 (AB d, *J* = 13 Hz, 1H); 4.59 (s, 1H); 4.51 (s, 2H); 4.02 (m, 1H); 3.80-3.30 (m, 10H); 2.98 (s, 3H); 2.90-2.45 (m, 6H); 1.52 (m, 2H); 1.39 (d, *J* = 7 Hz, 6H); 1.32 (m, 2H).

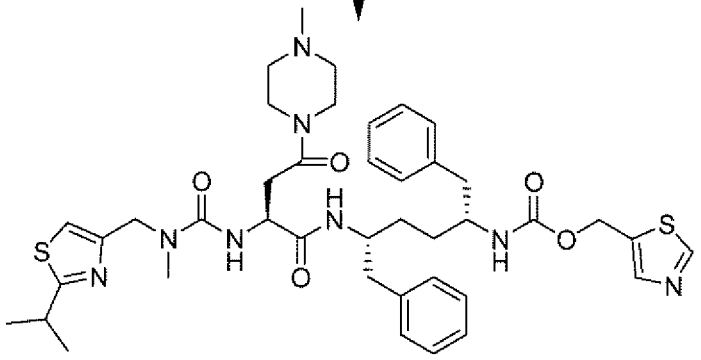
Preparation of Compound CC

Scheme 65



AF

I



CC

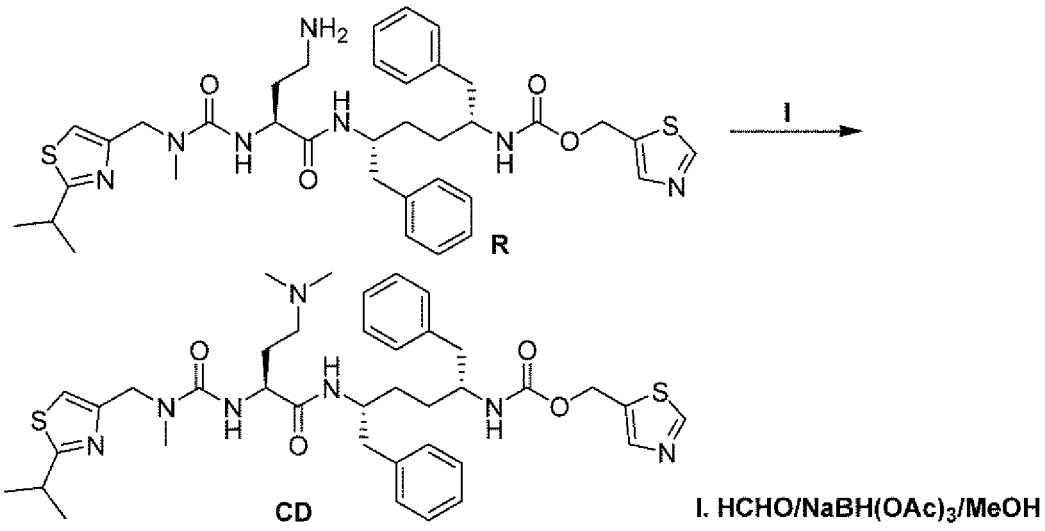
I. N-methylpiperazine, EDC, HOBt, DIPEA,THF.

Example CC

Example **CC** was prepared in a similar fashion to Example **CB** except that N-methylpiperazine (0.16 mmol) was reacted with Compound **AF** (0.10 mmol) instead of morpholine and DIPEA (0.19 mmol) was added to produce 0.009 g (11%) of Example **CC** as an amorphous white solid *m/z* 803.4 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.80 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 11H); 6.91 (s, 1H); 6.78 (m, 2H); 5.27 (AB d, *J* = 13 Hz, 1H); 5.21 (AB d, *J* = 13 Hz, 1H); 4.59 (m, 1H); 4.49 (AB d, *J* = 16 Hz, 4.44 (AB d, *J* = 16 Hz, 1H); 4.01 (m, 1H); 3.90-3.40 (m, 4H); 3.27 (hep, *J* = 7 Hz, 1H); 3.10-2.90 (m, 1H); 2.97 (s, 3H); 2.90-2.30 (m, 11H); 1.60-1.25 (m, 6H); 1.37 (d, *J* = 7 Hz, 6H).

Preparation of Example CD

Scheme 66

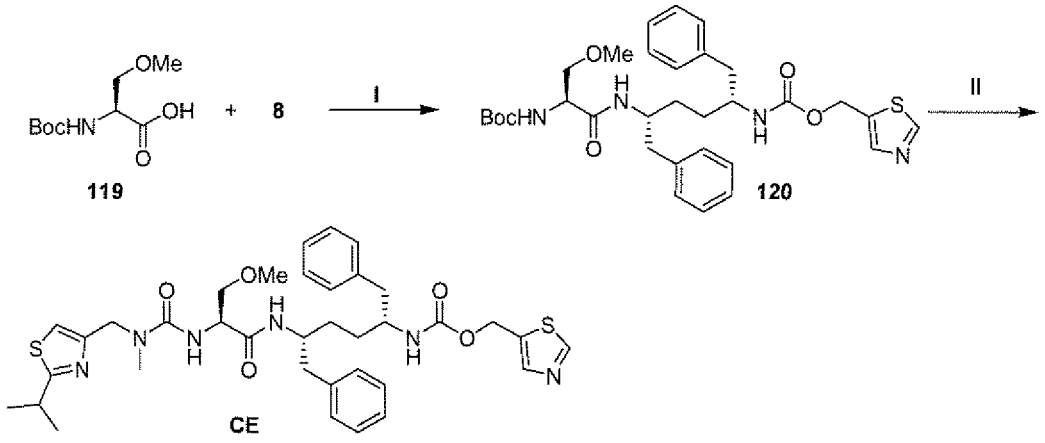


Example CD

To a solution of Example **R** (30.5 mg, 0.043 mmol) in methanol (1.5 mL) was added formaldehyde (1 mL, 37% in H_2O). After stirring for 10 minutes, $NaBH(OAc)_3$ (49 mg, 0.23 mmol) was added and the resulting mixture was stirred for 10 h. The reaction was monitored with LC/MS. When LC/MS indicated the absence of starting material Example **R**, the reaction mixture was evaporated to dryness, and filtered through a cotton plug. The crude product was then purified through CombiFlash (10% MeOH/CH_2Cl_2) to give 29.7 mg of Example **CD** ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.78 (s, 1H); 7.83 (s, 1H); 7.12-7.22 (m, 10H); 6.85 (s, 1H); 5.83 (d, 1H, J = 8.5 Hz), 5.23 (d_{AB}, 2H, J = 13.1 Hz); 4.49 (d_{AB}, 2H, J = 16.5 Hz); 4.29 (m, 1H); 4.15 (m, 1H); 3.75 (m, 1H); 3.30 (m, 1H); 2.93 (s, 3H); 2.87 (dd, 1H, J1= 5.5 Hz, J2 = 13.5 Hz); 2.72 (m, 2H); 2.66 (dd, J1= 7.3 Hz, J2 = 13.3 Hz), 2.47 (br s, 1H), 2.36 (br s, 1H), 2.23 (s, 6H), 1.91 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H), 1.40 (d, 6H, J = 6.8 Hz). *m/z* 734 $(M+H)^+$; 756 $(M+Na)^+$;

Preparation of Example CE

Scheme 67



I.EDC, HOBt, iPr_2NEt, THF II. a. HCl;/dioxane; b. CDI, iPr_2NEt, Compound 9, CH_2Cl_2

Compound 119

Compound **119** is commercially available from Aldrich, and was used as received.

Compound 120

A mixture of Compound **119** (200 mg, 0.91 mmol), Compound **8** (373.7 mg, 0.91 mmol), EDC (212 mg, 1.37 mmol), HOBt (160.3 mg, 1.19 mmol) and iPr_2NEt (794.7 μL, 4.56 mmol) in THF was stirred for 10 h at room temperature. The mixture was then evaporated to a small volume and purified by CombiFlash (eluted with 1 to 10 % MeOH/CH_2Cl_2). The fractions containing the target Compounds were collected and re-purified by CombiFlash (40-100% EtOAc/hexanes) to give 449 mg of Compound **120** as oil. (*m/z* 611.0 $(M+H)^+$).

Example CE

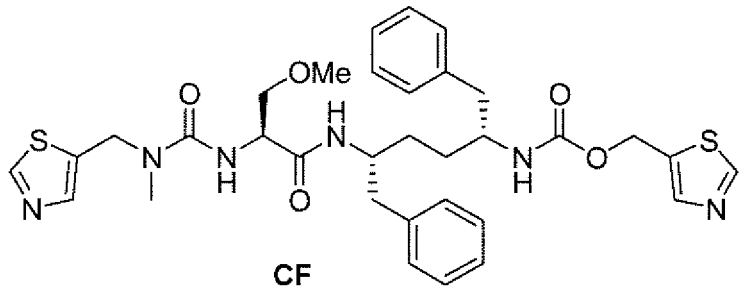
Compound **120** (449 mg, 0.74 mmol) was treated with HCl/dioxane (3 mL). The resulting mixture was evaporated to dryness and lyophilized to provide 373.6 mg of a white solid.

To a solution of the above white compound (52.5 mg, 0.096 mmol) in CH_2Cl_2 (10 mL) was added Compound **9** (19.8 mg, 0.096 mmol), CDI (15.6 mg,

0.096 mmol) followed by iPr_2NEt (33.4 μL, 0.192 mmol). The mixture was stirred for 20 h before it was evaporated to dryness. The mixture was added CH_2Cl_2, then filtered through a cotton plug. The filtrate was evaporated to dryness and purified with CombiFlash. The fractions with Example **CE** was collected and re-purified on the TLC to give 15.1 mg of Example **CE.** ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 7.82 (s, 1H); 7.09-7.27 (m, 10H), 6.94 (s, 1H); 6.25 (d, 2H, J = 8.7 Hz); 5.23 (s, 2H); 5.17 (br s, 1H); 4.43 (d_{AB}, 2H, J = 16.5 Hz); 4.29 (m, 1H); 4.13 (m, 1H), 3.76 (m, 2H); 3.48 (m, 1H); 3.29 (s, 3H); 3.25 (m, 1H), 2.94 (s, 3H), 2.65-2.82 (m, 4H), 1.75 (m, 2H), 1.54 (m, 2H), 1.39 (d, 5H, J = 6.9 Hz). *m/z* 707 $(M+H)^+$; 729 $(M+Na)^+$.

Preparation of Example CF

Scheme 68



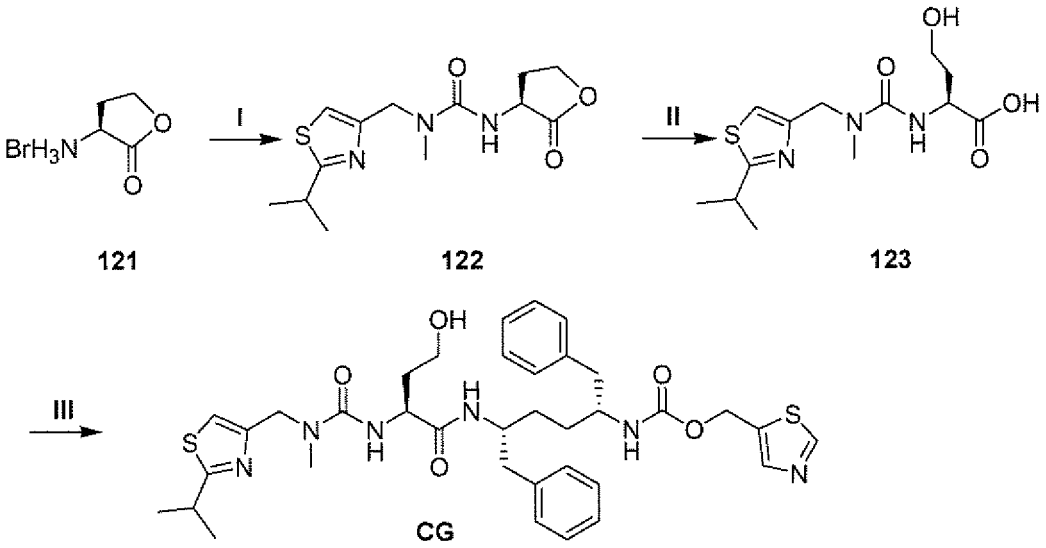
CF

Example CF

Example **CF** was prepared using the same method as Example **CE**, except that Compound **9** was replaced with Compound **68.** ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 8.74 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H); 7.12-7.27 (m, 10H); 6.15 (d, 1H, J = 8.7 Hz), 5.39 (d, 1H, J = 6.8 Hz); 5.21 (s, 2H), 5.06 (d, J = 9.1 Hz, 1H); 4.64 (d_{AB}, 2H, J = 15.5 Hz); 4.28 (m, 1H); 4.134 (m, 1H), 3.79 (m, 1H), 3.70 (m, 1H); 3.34 (m, 1H); 3.28 (s, 3H); 2.87 (s, 3H); 2.72 (m, 4H); 1.57 (m, 2H); 1.50 (m, 2H). (*m/z* 665.2 $(M+H)^+$; 687.3 $(M+Na)^+$.

Preparation of Compound CG

Scheme 69



I. a. CDI, DIPEA, MeCN; b. compound 9, MeCN. II. 1M LiOH, THF.
III. EDCI, HOBt, iPr2NEt, compound 8

Compound 121

Compound **121** is commercially available from Aldrich, and was used as received.

Compound 122

To a suspension of Compound **121** (2.05 g, 11.3 mmol) in CH_2Cl_2 (40 mL) was added. iPr_2NEt (5.87 mL, 33.9 mmol) followed by CDI (1.86 g, 11.3 mmol). The resulting mixture was stirred at room temperature for 6 h, then Compound **9** (2.33g, 11.3 mmol) was added. The resulting mixture was stirred for another 10 h before it was evaporated to dryness. The mixture was re-dissolved in CH_2Cl_2 and the solid was removed by filtration. The filtrate was evaporated to dryness and purified by CombiFlash (eluted with 20-80% EtOAc/hexanes) to give 3.2 g of Compound **207** as a pale yellow oil. *m/z* 298.0 $(M+H)^+$.

Compound 123

To a solution of Compound **122** (3.2g, 10.8 mmol) in THF (100 mL) was added freshly prepared 1M LiOH (10.8 mmol). The biphasic reaction was stirred

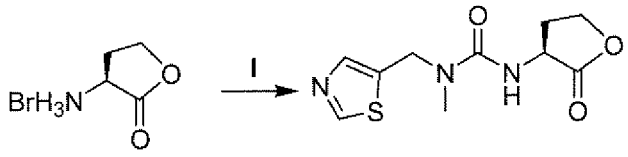
vigorously at room temperature for 16 h before being quenched with 1M HCl. The pH of the mixture was adjusted to 2.5-3, and then evaporated to a small volume. The mixture was partitioned between CH_2Cl_2 and brine (50 mL), the aqueous layer was separated and extracted with CH_2Cl_2 twice. The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and concentrated to give 3.37 g of Compound **123** a pale yellow oil that is used with further purification. *m/z* 316.0 $(M+H)^+$, 338 $(M+Na)^+$;

Example CG

Example **CG** was prepared following the same procedure for Example **C** instead that Compound **123** was used instead of Compound **7**. ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.80 (s, 1H); 7.83 (s, 1H), 7.11-7.26 (m, 10H), 6.96 (s, 1H); 7.12-7.27 (m, 10H); 6.52 (br s, 1H), 6.40 (br s, 1H), 5.23 (s, 2H), 5.20 (m, 1H), 4.44 (d_{AB}, 2H, J = 15.5 Hz), 4.39 (m, 1H), 4.11 (m, 1H), 3.80 (m, 1H), 3.61 (m, 2H), 3.28 (sep, 1H, J = 7.0 Hz); 2.94 (s, 3H), 2.79 (dd, 1H, J1 = 6.1 Hz, J2= 13.4 Hz); 2.71 (m, 3H), 1.93 (m, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 1.38 (d, 6H, J = 7.0 Hz) 1.37 (m, 1H). (: $)^+$; *m/z* 707.3 $(M+H)^+$), 729.2 $(M+Na)^+$.

Preparation of Compound 100

Scheme 70



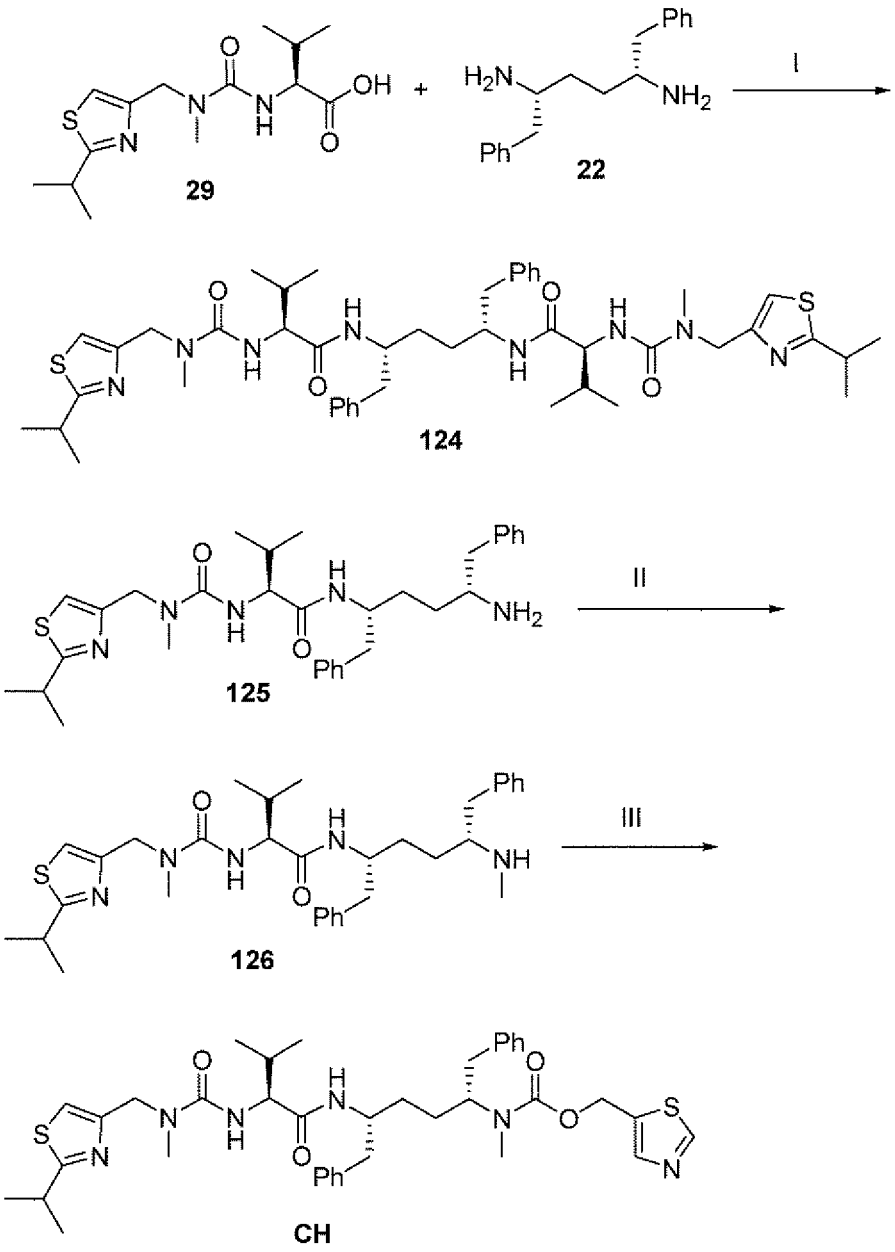
121 **100**

I. a. CDI, DIPEA, MeCN;

Compound **100** was prepared using the same method used to prepare Compound **122**, except that Compound **9** was replaced with Compound **68.**

Preparation of Example CH

Scheme 71



I. EDCI/HOBt/iPr_2NEt/THF; II. HCHO/$NaBH(OAc)_3$/HOAc/CH_3CN;
III. Cmpd. 16/iPr_2NEt/CH_3CN

Compounds 124 and 125

To a solution of Compound **29** (135 mg, 0.43 mmol) and Compound **22** (116 mg, 0.43 mmol) in THF (5 mL) were added HOBt (70 mg, 0.52 mmol), EDC (94 μL, 0.52 mmol), and diisopropylethylamine (150 μL, 0.83 mmol). The mixture was

stirred for 12 hours and concentrated. Purification by reverse HPLC gave Compound **124** (70 mg) and Compound **125** (120 mg). Compound **124**: ^{1}H-NMR ($CDCl_3$) δ 7.2-7.1 (10 H, m), 7.0 (2 H, s), 6.45 (2 H, m), 6.15(2 H, m), 4.45 (4 H, s), 4.1 (2 H, m), 3.96 (2 H, m), 3.3 (2 H, m), 2.98 (6 H, s), 2.7 (4 H, m), 2.1 (2 H, m), 1.6-1.3 (16 H, m), 0.90 (12 H, m). m/z 859.3 $(M+H)^+$; Compound **125**: m/z 564.3 $(M+H)^+$

Compound 126

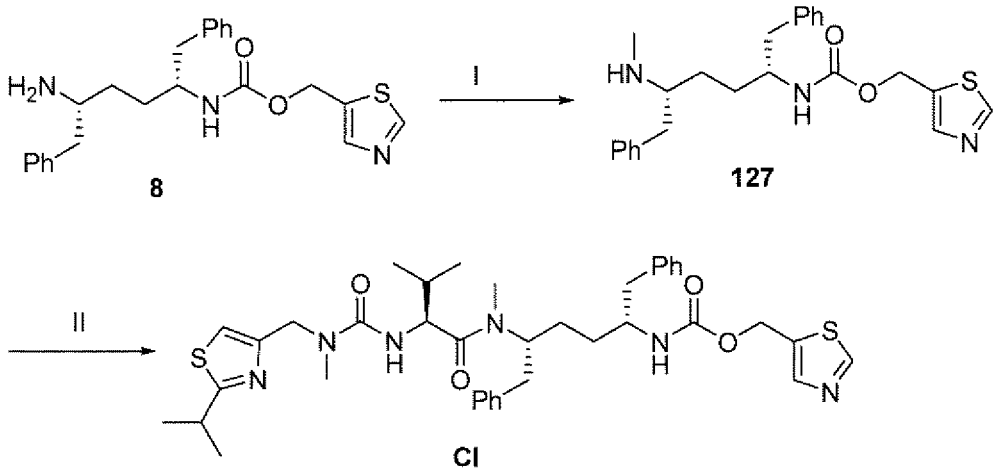
To a solution of Compound **125** (120 mg, 0.21 mmol) in CH_3CN (1 mL) was added 37% formaldehyde solution (17 μL, 0.23 mmol), followed by HOAc (24 μl, 0.42 mmol). The mixture was stirred for 2 hours, and $NaBH(OAc)_3$ (140 mg, 0.63 mmol) was added. The mixture was stirred for 2 additional hours and diluted with EtOAc. The organic phase was washed with saturated Na_2CO_3 solution, water, and brine, and dried over Na_2SO_4. Concentration gave Compound **126**, which was used in the next step without further purification. m/z 578.3 $(M+H)^+$

Example CH

Example **CH** (26 mg) was prepared following the procedure used to prepare Example **L**, except that Compound **126** was used instead of Compound **22**. ^{1}H-NMR (CDCl3) δ 8.91 (1 H, m), 7.82 (1 H, m), 7.2-7.0 (11 H, m), 6.4 (1 H, m), 6.2 (1 H, m), 5.23-5.05 (2 H, m), 4.44 (2 H, s), 4.44 (1 H, m), 4.2 (1 H, m), 3.95 (1 H, m), 3.32 (1 H, m), 2.98 (3 H, s), 2.8-2.5 (7 H, m), 2.15 (1 H, m), 1.7-1.2 (10 H, m), 0.88 (6 H, m). m/z 719.3 $(M+H)^+$

Preparation of Example CI

Scheme 72



I. HCHO/$NaBH(OAc)_3$/HOAc/CH_3CN; II. Cmpd. 29/EDCI/HOBt/iPr_2NEt/THF

Compound 127

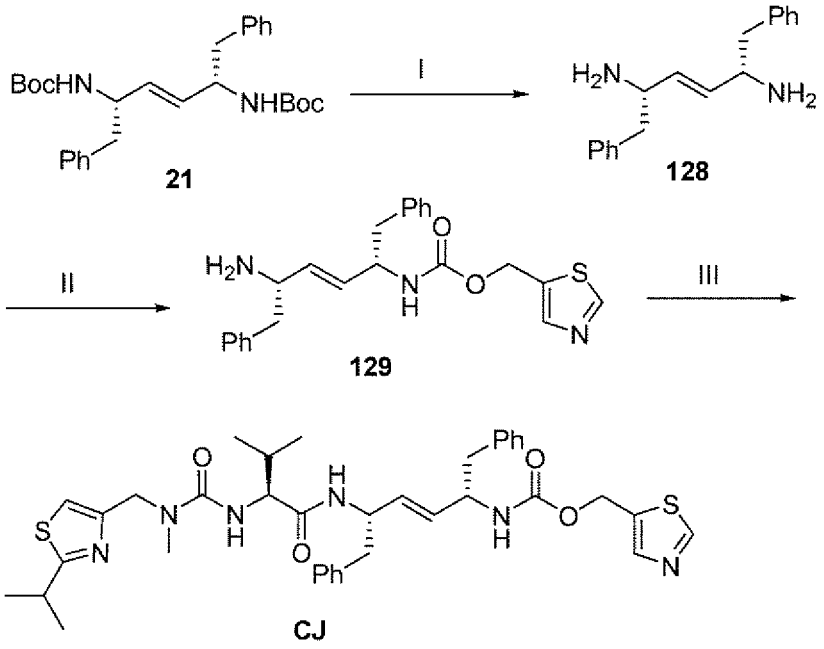
Compound **127** (110 mg) was prepared following the procedure used to prepare Compound **126**, except that Compound **8** was used instead of Compound **125**. m/z 424.4 $(M+H)^+$

Example CI

Example **CI** (7 mg) was prepared following the procedure used to prepare Example **C**, except that Compounds **127** and **29** were used instead of Compounds **8** and **7**. ^{1}H-NMR (CDCl3) δ 9.0 (1 H, s), 8.92 (1 H, s), 7.4-7.0 (11 H, m), 5.25 (2 H, m), 4.6-4.0 (5 H, m), 3.4 (1 H, m), 3.1-2.6 (10 H, m), 1.9 (1 H, m), 1.8 (10 H, m), 0.9 (6 H, m); m/z 719.2 $(M+H)^+$

Preparation of Compound CJ

Scheme 73



I. a. TFA/CH_2Cl_2; b. Na_2CO_3; II. Cmpd. 16/iPr_2NEt/CH_3CN;
III. Cmpd. 29/EDCI/HOBt/iPr_2NEt/THF

Compound 128

To a solution of Compound **21** (100 mg) in dichloromethane (5 mL) was added TFA (1 mL). The mixture was stirred for 3 hours, and excess reagents were evaporated. The oil was diluted with EtOAc, and then was washed with saturated Na_2CO_3 solution (2x), water (2x), and brine, and dried over Na_2SO_4. Concentration gave Compound **128** (46 mg). m/z 267.1 $(M+H)^+$

Compound 129

Compound **129** (44 mg) was prepared following the procedure for Compound **8**, except that Compound **128** was used instead of Compound **22**. m/z 408.10 $(M+H)^+$

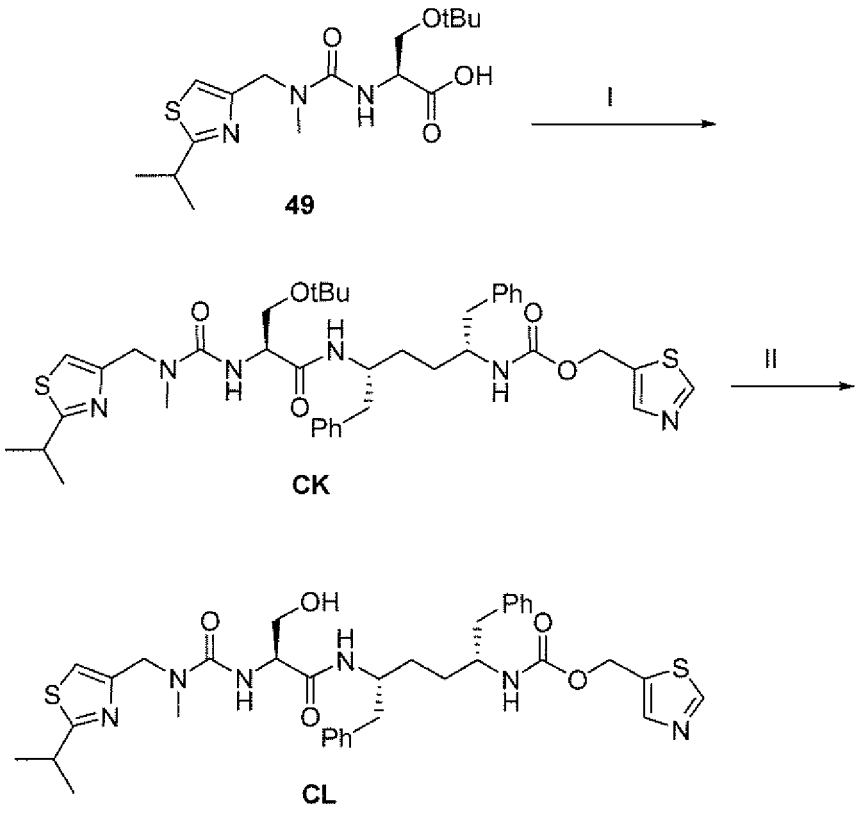
Example CJ

Example **CJ** (55 mg) was prepared following the procedure for Example **C**, except that Compounds **129** and **29** were used instead of Compounds **8** and **7**. ^1H-

NMR (CDCl3) δ 8.81 (1 H, s), 7.85 (1 H, s), 7.2-7.0 (11 H, m), 6.4 (1 H, m), 6.12 (1 H, m), 5.44 (2 H, m), 5.26 (2 H, s), 4.85 (1 H, m), 4.70 (1 H, m), 4.4 (3 H, m), 4.06 (1 H, m), 3.25 (1 H, m), 2.98 (3 H, s), 2.78 (4 H, m), 2.21 (1 H, m), 1.38 (6 H, m), 0.88 (6 H, m); m/z 703.2 $(M+H)^+$

Preparation of Compounds CK and CL

Scheme 74



I. Cmpd 8/EDC/HOBt; II. a. TFA; b. NaOH/THF

Example CK

Example **CK** (88 mg) was prepared following the procedure used to prepare Example **C**, except that Compound **49** was used instead of Compound **7**. m/z 749.2 $(M+H)^+$

Example CL

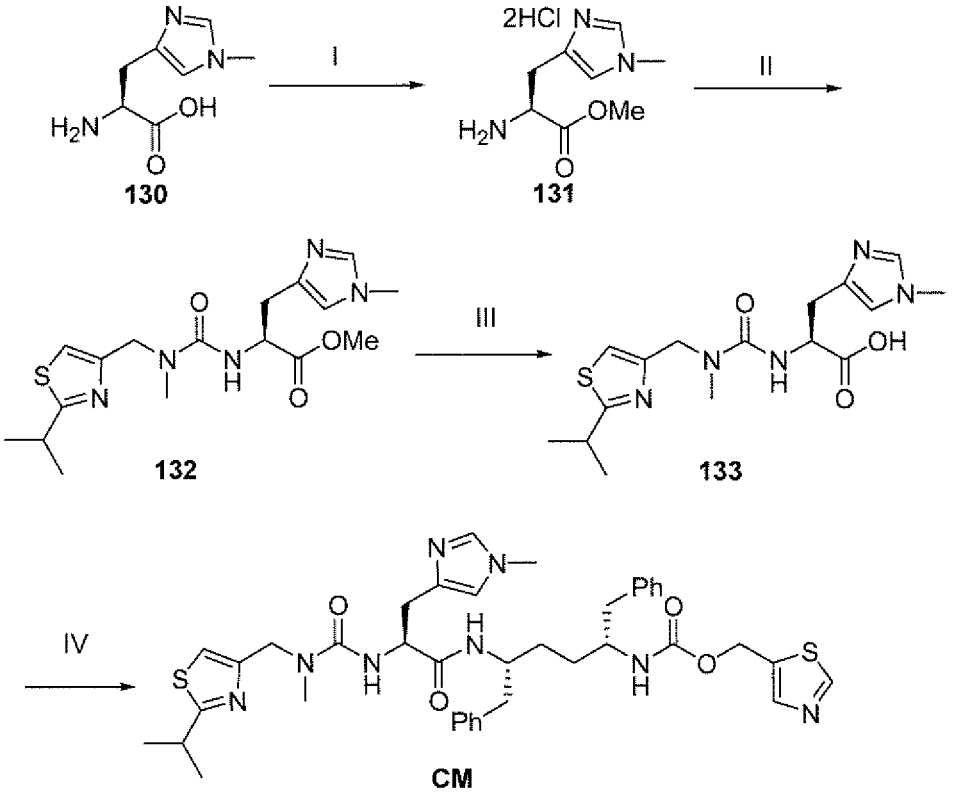
A mixture of Example **CK** (85 mg) and TFA (5 mL) was stirred for 3 hours. Excess TFA was evaporated and the mixture was dried under high vacuum. The

mixture was dissolved in THF (5 mL), and 1.0 N sodium hydroxide solution was added until the pH was 11. The solution was stirred for 10 minutes, and extracted with EtOAc. The organic phase was washed with water, brine, and dried over Na_2SO_4.

Concentration and purification by flash column chromatography (EtOAc) gave Example **CL** (66 mg). ^{1}H-NMR (CDCl3) δ 8.81 (1 H, s), 7.84 (1 H, s), 7.30-6.96 (11 H, m), 5.22 (2 H, s), 4.90 (1 H, m), 4.45 (1 H, m), 4.35-4.0 (4 H, m), 3.8 (1 H, m), 3.6 (1 H, m), 3.21 (1 H, m), 2.95 (3 H, s), 2.8-2.6 (4 H, m), 2.0-1.4 (4 H, m), 1.25 (6H, m). m/z 693.2 $(M+H)^+$.

Preparation of Example CM

Scheme 75



I. $SOCl_2$/MeOH; II. a. CDI/iPr_2NEt; b. Cmpd. 9; III.a. NaOH/THF/H_2O; b. HCl; IV. Cmpd. 8/EDC/HOBt;

Compound 130

Compound **130** is commercially available from (TCI), and was used as received.

Compound 131

To the solution of Compound **130** (510 mg, 3 mmol) in methanol (12 mL) at 0 ºC was added thionyl chloride (0.5 mL, 6.6 mmol), dropwise. The mixture was stirred at 0 ºC for 30 minutes and brought to reflux for 3 hours. Concentration gave Compound **131** as a white solid.

Compound 132

To a stirred solution of Compound **131** (3 mmol) and diisopropylethylamine (2 mL, 12 mmol) in dichloromethane (35 mL) was added CDI (486 mg, 3 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (CH_2Cl_2/iPrOH = 10/1) gave Compound **132** (414 mg). m/z 380.0 $(M+H)^+$

Compound 133

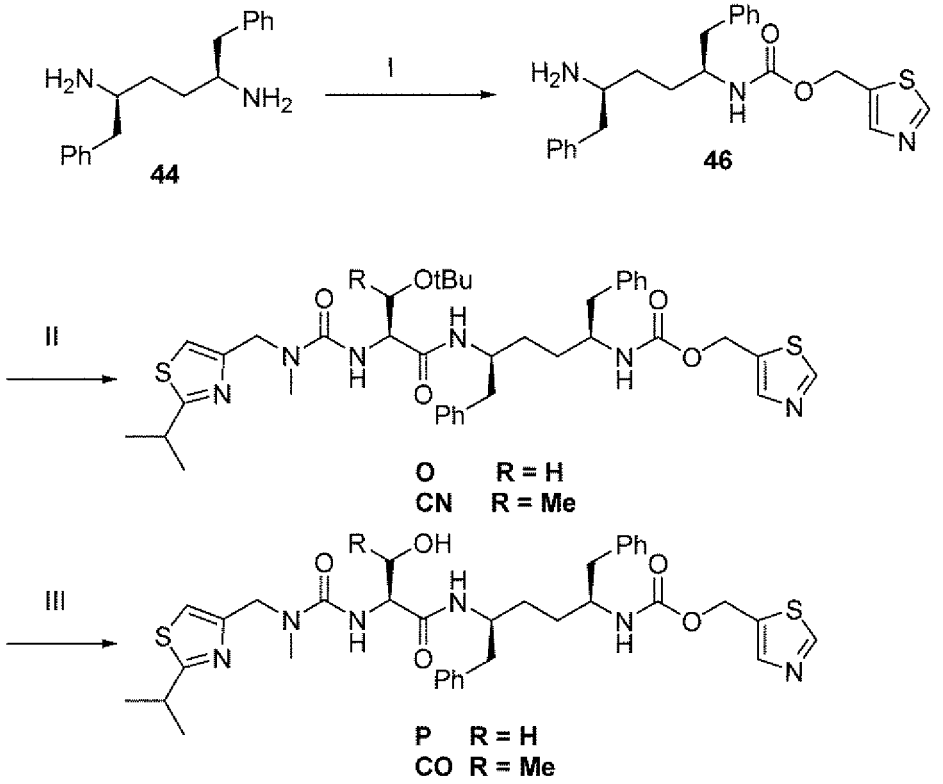
Compound **133** was prepared following the procedure for Compound **67**, except that Compound **132** was used instead of Compound **66**. m/z 364.0$(M-H)^-$

Example CM

Example **CM** (600 mg) was prepared following the procedure for Example **C**, except Compound **133** was used instead of Compound **7**. ^{1}H-NMR (CDCl3) δ 9.18 (1 H, s), 8.35 (1 H, s), 7.95 (1 H, s), 7.6 (1 H, m), 7.3-7.0 (11 H, m), 5.22 (2 H, m), 4.70 (1 H, m), 4.50 (2 H, m), 4.05 (1 H, m), 3.86 (3 H, s), 3.80 (2 H, m), 3.55 (1 H, m), 3.10 (1 H, m), 2.90 (3 H, s), 2.70 (4 H, m), 1.45 (10 H, m); m/z 757.3 $(M+H)^+$

Preparation of Examples O, P, CN, and CO

Scheme 76



I. Cmpd. 16/iPr2NEt; II. Cmpd. 13d or Cmpd. 49/EDC/HOBt; III. a. TFA; b. NaOH/THF

Example O

Example **O** (17 mg) was prepared following the procedure for Example **C**, except Compounds **46** and **49** were used instead of Compounds **8** and **7**. m/z 749.3 $(M+H)^+$

Example CN

Example **CN** (22 mg) was prepared following the procedure used to prepare Example **C**, except Compounds **46** and **13e** were used instead of Compounds **8** and **7**. m/z 763.2 $(M+H)^+$

Example P

Example **P** (12 mg) was prepared following the procedure used to prepare Example **CL**, except Example **O** was used instead of Example **CK**. ^{1}H-NMR ($CDCl_3$) δ 8.76 (1 H, s), 7.79 (1 H, s), 7.25-6.9 (11 H, m), 6.51 (1 H, broad), 5.42 (1 H,

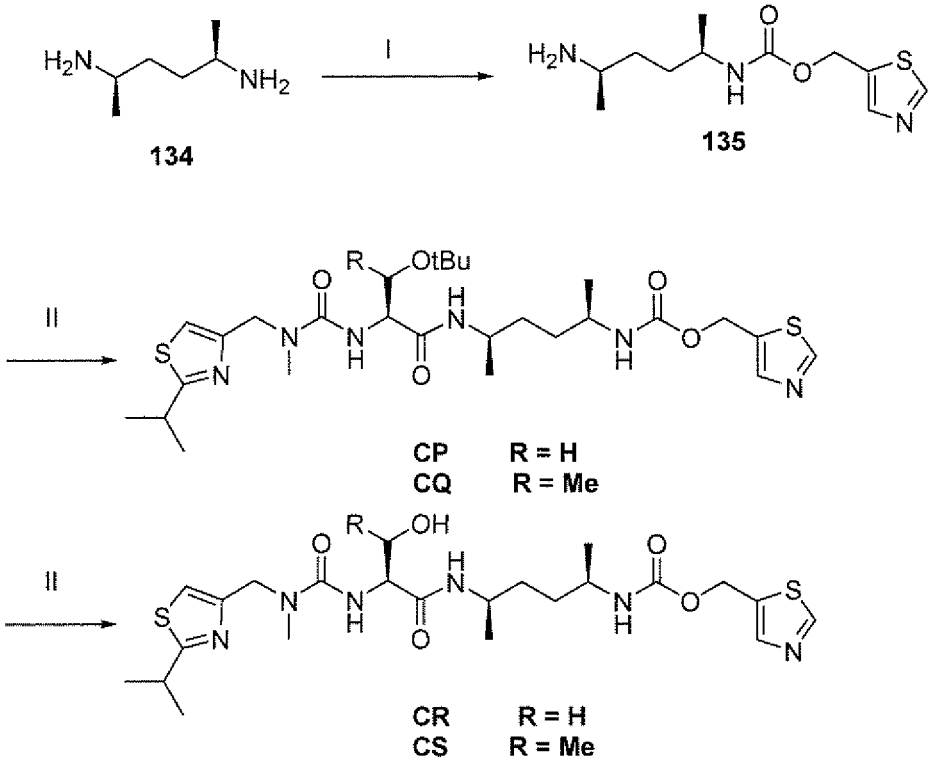
m), 5.18 (2 H, m), 4.42 (2 H, m), 4.22 (1 H, m), 4.10 (1 H, m), 3.95 (1 H, m), 3.79 (1 H, m), 3.58 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.9-2.5 (4 H, m), 1.6-1.2 (10 H, m); m/z: 693.2 $(M+H)^+$.

Compound CO

Example **CO** (13 mg) was prepared following the procedure used to prepare Example **CL**, except Example **CN** was used instead of Compound **CK**. ^{1}H-NMR ($CDCl_3$) δ 8.85 (1H, m), 7.88 (1 H, m), 7.3-7.0 (11 H, m), 6.55 (1 H, m), 6.24 (1 H, m), 5.45 (1 H, m), 5.23 (2 H, m), 4.6 (2 H, m), 4.2 (1 H, m), 4.0 (2 H, m), 3.7 (1 H, m), 3.5 (1 H, m), 3.02 (3 H, s), 2.70 (4 H, m), 1.6-1.0 (13 H, m); m/z: 707.3 $(M+H)^+$.

Preparation of Examples CP-CS

Scheme 77



I. Cmpd. 16/iPr_2NEt; II. Cmpd. 13d or 49/EDC/HOBt; III. a. TFA; b. NaOH/THF

Compound 134

Compound **134** was prepared using procedure described for Compound **76**, except that CBZ-D-alaninol was used instead of CBZ-L-alaninol.

Compound 135

Compound **135** was prepared following the procedure used to prepare Compound **8**, except Compound **134** was used instead of Compound **22**.

Example CP

Example **CP** (12 mg) was prepared following the procedure used to prepare Example **C**, except Compounds **135** and **49** were used instead of Compounds **8** and **7**. m/z 597.2 $(M+H)^+$.

Example CQ

Example **CQ** (11 mg) was prepared following the procedure used to prepare Example **C**, except Compounds **135** and **13d** were used instead of Compounds **8** and **7**. m/z 611.2 $(M+H)^+$.

Example CR

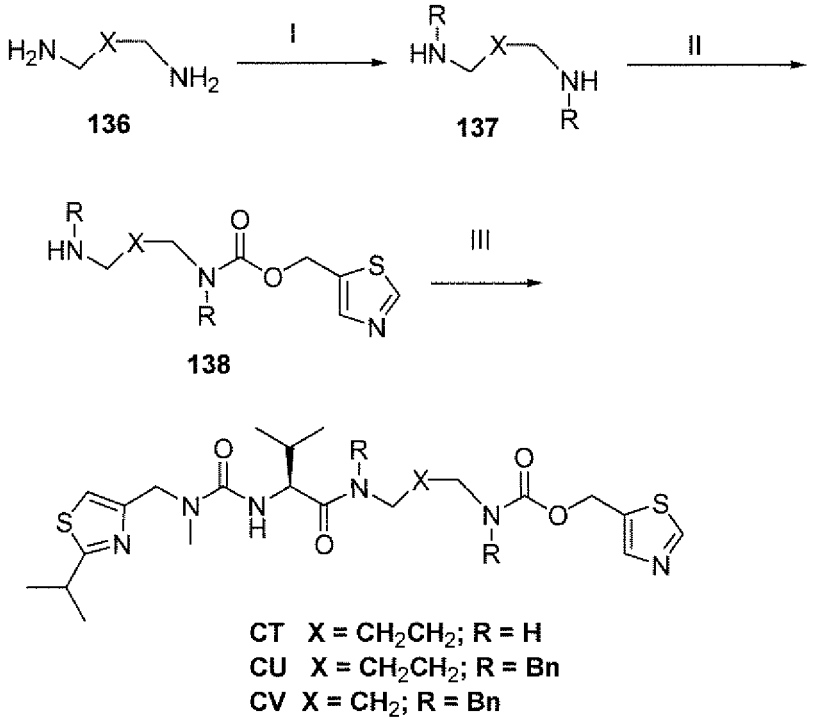
Example **CR** (7 mg) was prepared following the procedure used to prepare Example **P**, except that Example **CP** was used instead of Example **O** . ^{1}H-NMR ($CDCl_3$) δ 8.82 (1 H, s), 7.88 (1 H, s), 7.02 (1 H, s), 6.92 (1 H, m), 5.28 (2 H, s), 5.10 (1 H, m), 4.5 (2 H, m), 4.15 (2 H, m), 3.88 (1 H, m), 3.8-3.5 (2 H, m), 3.35 (1 H, m), 3.0 (3 H, s), 1.5-1.0 (16 H, m); m/z: 541.1 $(M+H)^+$.

Example CS

Example **CS** (8 mg) was prepared following the procedure used to prepare Example **CO**, except that Example **CQ** was used instead of Example **CN**. ^{1}H-NMR ($CDCl_3$) δ 8.83 (1 H, s), 7.88 (1 H, s), 6.98 (1 H, s), 6.81 (1 H, m), 6.58 (1 H, m), 5.28 (2 H, s), 5.18 (1 H, m), 4.4-4.3 (2 H, m), 4.03 (1 H, m), 3.85 (1 H, m), 3.58 (2 H, m), 3.3 (1 H, m), 2.99 (3 H, s), 1.5-0.98 (19 H, m); m/z: 555.2 $(M+H)^+$.

Preparation of Examples CT-CV

Scheme 78



I. PhCHO/$NaBH_4$; II. Cmpd 16/iPr_2NEt; II. Cmpd 13d/EDC/HOBt;

Compound 136

Compounds **136a-c** are commercially available (Sigma-Aldrich).

Compound 137

To a solution of Compound **136** (20 mmol) in methanol (25 mL) was added benzaldehyde (40 mmol) dropwise. The mixture was stirred for 2 hours and was cooled to 0 ºC. Sodium borohydride (44 mmol) was added in portions. The mixture was warmed to 25 ºC and stirred for 2 hours. Acetic acid (10 mL) was added and the mixture was stirred for 10 minutes. Methanol was removed and the mixture was partitioned between EtOAc and 3 N NaOH solution. The organic layer was separated and water phase was extracted with EtOAc (2x). The combined organic layers was washed with water, brine, and dried over Na_2SO_4. Concentration gave Compound **137**.

Compound 138

Compound **138** was prepared following the procedure used to prepare Compound **8**, except that Compound **137** was used instead of Compound **22**.

Example CT

Example **CT** (70 mg) was prepared following the procedure used to prepare Example **C**, except that Compounds **29** and **138a** was used instead of Compounds **7** and **8**. .^{1}H-NMR ($CDCl_3$) δ 8.79 (1 H, s), 7.86 (1 H, s), 6.97 (1 H, s), 6.49 (1 H, m), 6.15 (1 H, m), 5.28 (2 H, s), 5.20 (1 H, m), 4.44 (2 H, m), 4.05 (1 H, m), 3.25 (5 H, m), 3.0 (3 H, s), 2.24 (1 H, m), 1.8-1.45 (4 H, m), 1.38 (6 H, m), 0.97 (6 H, m); m/z: 525.2 $(M+H)^+$.

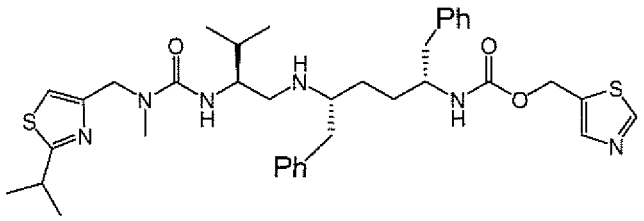
Example CU

Example **CU** (140 mg) was prepared following the procedure used to prepare Example **C**, except that Compounds **29** and **138b** was used instead of Compounds **7** and **8**. ^{1}H-NMR ($CDCl_3$) δ 8.78 (1 H, s), 7.85 (1 H, m), 7.4-7.05 (10 H, m), 6.93 (1 H, s), 5.90 (1 H, m), 5.35 (2 H, s), 4.9-4.6 (2 H, m), 4.6-4.4 (4 H, m), 4.2 (1 H, m), 3.4-3.05 (5 H, m), 3.0 (3 H, s), 2.0 (1 H, m), 1.8-1.3 (10 H, m), 0.90 (6 H, m); m/z: 705.2 $(M+H)^+$.

Examle CV

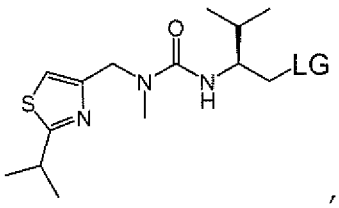
Example **CV** (145 mg) was prepared following the procedure used to prepare Example **C**, except that Compounds **29** and **138c** was used instead of Compounds **7** and **8**. ^{1}H-NMR ($CDCl_3$) δ 8.76 (1 H, m), 7.86 (1 H, m), 7.4-7.02 (10 H, m), 6.97 (1 H, m), 5.75 (1 H, m), 5.38 (2 H, m), 4.95-4.3 (6 H, m), 4.15 (1 H, m), 3.4-3.0 (5 H, m), , 3.0 (3 H, s), 2.2-1.6 (3 H, m), 1.4 (6 H, m), 0.88 (6 H, m); m/z: 691.2$(M+H)^+$.

Preparation of Example CW



CW

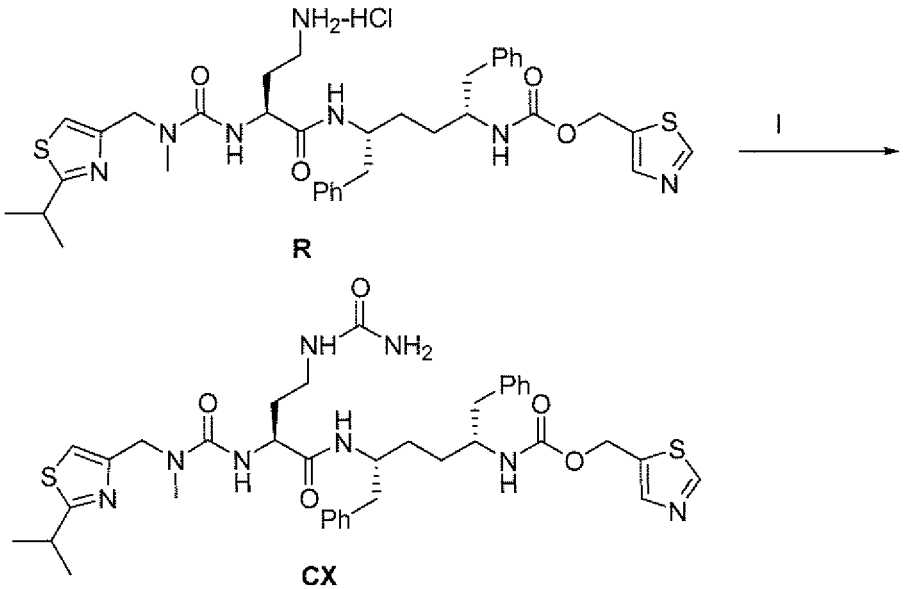
Example **CW** could be prepared, e.g. by reacting Compound **8** with a compound having the following structure:



where "LG" is a leaving group such as a halogen. Such compounds could be prepared by one-carbon degradation of the corresponding carboxylic acid or ester (e.g., Compounds **28** or **29**) by known methods such as the Hunsdieker reaction or the Kochi reaction or similar methods.

Preparation of Example CX

Scheme 79



R

CX

I. a.TMSNCO/iPr_2NEt/THF; b. MeOH

Example R

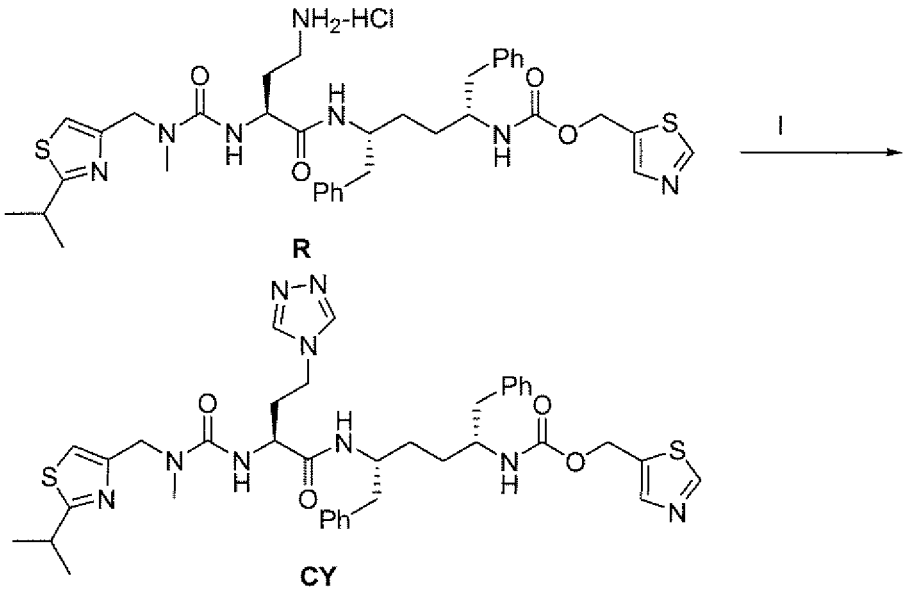
Example **R** (hydrochloride salt) was synthesized following the procedure described in WO 2008/010921 A2 (herein incorporated by reference in its entirety for all purposes) or as described above.

Example CX

To a suspension of Example **R** (hydrochloride salt) (150 mg, 0.2 mmol) in THF (2 mL) was added diisopropylethylamine (70 •l, 0.4 mmol). The mixture was stirred until a clear solution was obtained. To this solution was added trimethylsilyl isocyanate (30 •l, 0.22 mmol) dropwise, and the mixture was stirred for 12 hours. The solvent was removed and the mixture was coevaporated twice with 5 mL of MeOH. Purification with preparative thin layer chromatography (preparative TLC) gave Example **CX** (86 mg). m/z: 749.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.99 (s, 1H); 7.83 (s, 1H); 7.72 (m, 1H); 7.30-7.00 (m, 11H); 5.22 (s, 2H); 4.54 (s, 2H); 4.19 (s, 1H); 4.07 (m, 1H); 3.75 (m, 1H); 3.28 (m, 1H); 3.30-2.90 (m, 2H); 2.97 (s, 3H); 2.71 (m, 4H); 1.79 (m, 2H); 1.50 (m, 4H); 1.38 (d, 6H, *J*=7 Hz).

Preparation of Example CY

Scheme 80



I. diformylhydrazine/ pyridine/Et_3N/TMSCl/100 C

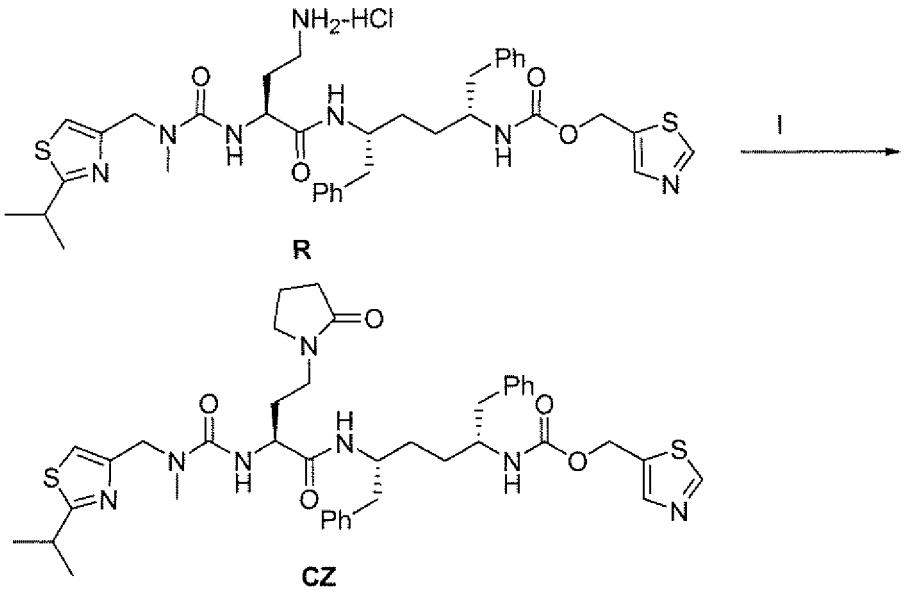
Example CY

To a solution of Example **R** (hydrochloride salt) (269 mg, 0.36 mmol) in pyridine (3 mL) was added diformylhydrazine (95 mg, 1.1 mmol), followed by

chlorotrimethylsilane (2.7 mL) and triethylamine (0.34 mL). The mixture was heated at 100 °C for 14 hours, and solvents were removed. The mixture was quenched with water, and extracted three times with EtOAc. The organic layer was dried over Na_2SO_4 and concentrated to give a white solid. Purification by HPLC and preparative TLC (5% MeOH in dichloromethane) gave Example **CY** (5 mg). m/z: 758.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.98 (s, 1H); 8.50 (s, 2H); 7.83 (s, 1H); 7.30-7.00 (m, 11H); 5.21 (s, 2H); 4.54 (m, 2H); 4.11 (m, 4H); 3.76 (m, 1H); 3.28 (m, 1H); 2.95 (s, 3H); 2.69 (m, 4H); 2.04 (m, 2H); 1.70-1.20 (m, 10H).

Preparation of Example CZ

Scheme 81



I. Methyl 4-bromobutyrate/$NaHCO_3$/DMF/60 C

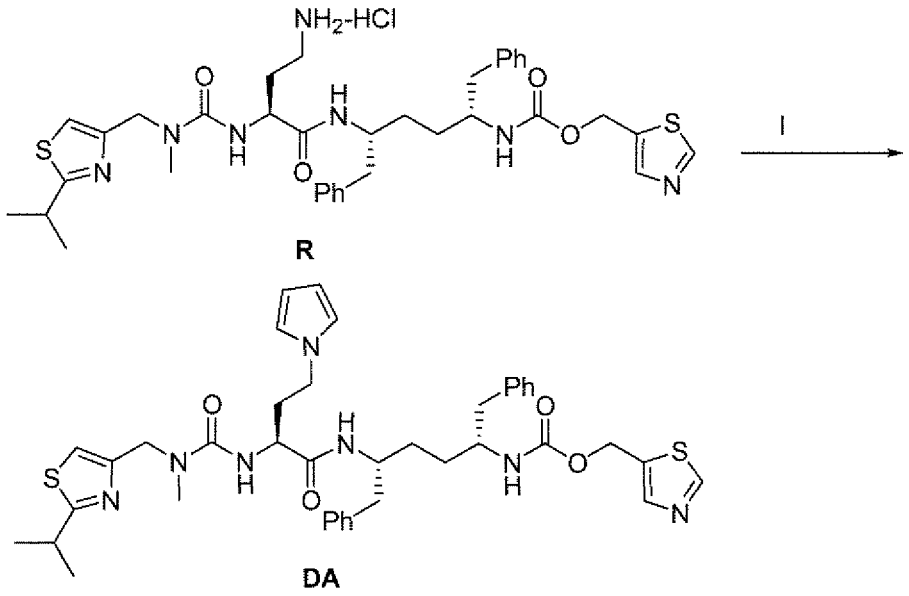
Example CZ

To a suspension of Example **R** (hydrochloride salt) (200 mg, 0.27 mmol) and sodium bicarbonate (92 mg, 1.1 mmol) in DMF (2 mL) was added a solution of methyl 4-bromobutyrate (74 •l, 0.54 mmol) in DMF (1 mL). The mixture was heated at 65 °C for 20 hours and the solvent was removed under reduced pressure. The mixture was quenched with water, and extracted with EtOAc. The organic layer was washed three times with water, twice with sodium carbonate solution, and once with brine, and dried over Na_2SO_4. Concentration followed by

purification using HPLC gave Example **CZ** as a white solid (23 mg). m/z: 774.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.99 (s, 1H); 7.84 (s, 1H); 7.30-7.00 (m, 11H); 5.22 (s, 2H); 4.55 (m, 2H); 4.09 (m, 2H); 3.90-3.60 (m, 1H); 3.55-3.10 (m, 5H); 2.98 (s, 3H); 2.71 (m, 4H); 2.37 (m, 2H); 2.04 (m, 2H); 1.81 (m, 2H); 1.70-1.20 (m, 10H).

Preparation of Example DA

Scheme 82



I. 2,5-dimethoxyTHF/NaOAc/HOAc/125 C

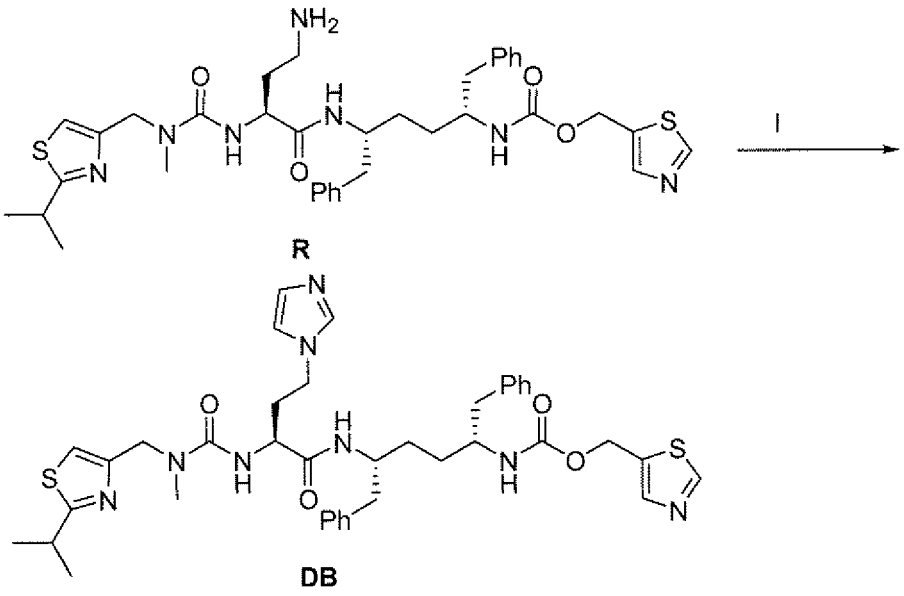
Example DA

To a suspension of Example **R** (hydrochloride salt) (250 mg, 0.34 mmol) in acetic acid (0.73 mL) was added sodium acetate (153 mg, 1.9 mmol), followed by 2,5-dimethoxyTHF (44 •l, 0.34 mmol). The mixture was heated at 125 °C for 90 minutes, and the solvent was removed under reduced pressure. The residue was quenched with saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was washed sequentially with saturated $NaHCO_3$ solution, water, and brine, and dried over Na_2SO_4. Concentration and purification by HPLC gave a white solid, which was further purified by preparative TLC to give Example **DA** (25 mg). m/z: 756.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.96 (s, 1H); 7.82 (s, 1H); 7.30-7.00 (m, 11H); 6.62 (s, 2H); 6.02 (s, 2H); 5.20 (s, 2H); 4.51 (s, 2H); 4.20-3.95

(m, 2H); 3.88 (m, 2H); 3.75 (m, 1H); 3.26 (m, 1H); 2.93 (s, 3H); 2.70 (m, 4H); 2.01 (m, 2H); 1.70-1.20 (m, 10H).

Preparation of Example DB

Scheme 83



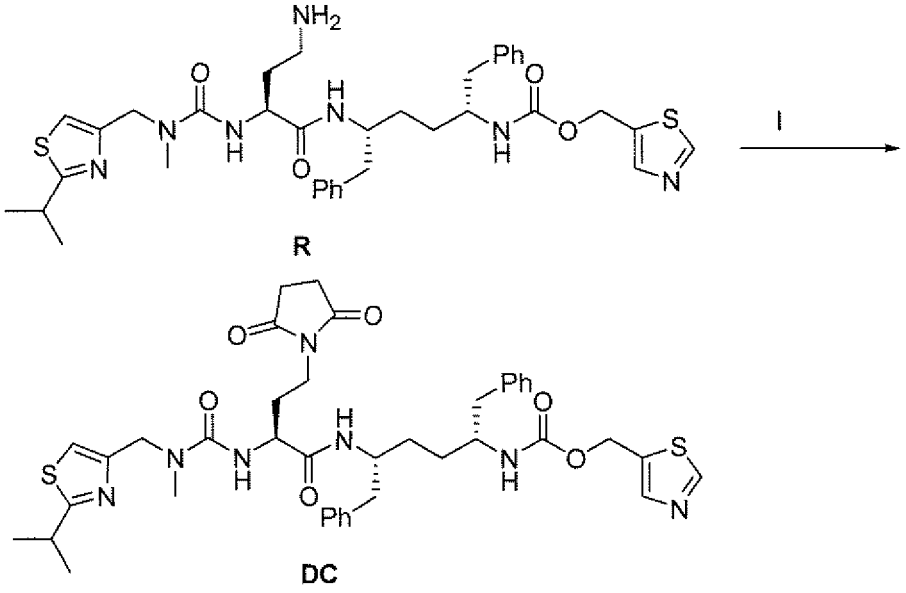
I. NH_3-H_2O/formaldehyde/glyoxal/n-PrOH/80 C

Example DB

To Example **R** (220 mg, 0.34 mmol) in propanol (1.9 mL) was added aqueous ammonia (39 mg, 0.34 mmol, 28-30%). The mixture was stirred for 5 minutes. To the above mixture was added a solution of glyoxal (53 mg, 0.37 mmol, 40%wt) and formaldehyde (30 mg, 0.37 mmol, 37%wt) in propanol (3.7 mL) dropwise. The mixture was heated at 80 °C for 5 hours. The solvent was removed under reduced pressure, and the residue was diluted with EtOAc. The organic layer was washed with water and brine, and dried over Na_2SO_4. Concentration of the organic layer and purification by HPLC gave Example **DB** as a white powder (101 mg). m/z: 757.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (s, 1H); 7.82 (s, 1H); 7.60 (s, 1H); 7.30-7.00 (m, 12H); 6.96 (s, 1H); 5.20 (s, 2H); 4.53 (m, 2H); 4.20-3.90 (m, 4H); 3.76 (m, 1H); 3.28 (m, 1H); 2.95 (s, 3H); 2.70 (m, 4H); 2.02 (m, 2H); 1.70-1.20 (m, 10H).

Preparation of Example DC

Scheme 84



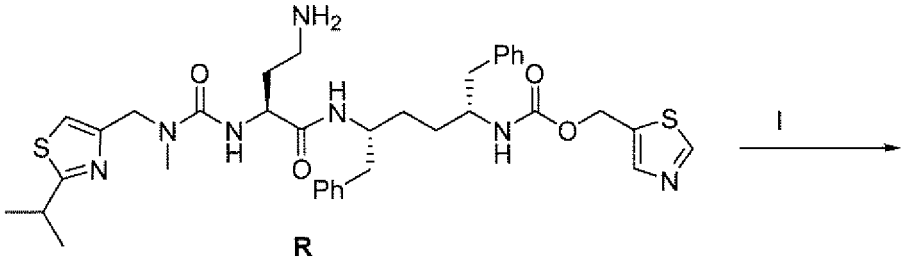
I. a. succinic anhydride/CH_2Cl_2; b. Ac_2O/NaOAc

Example DC

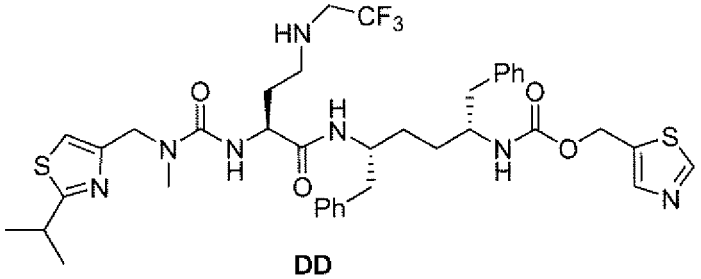
To a solution of Example **R** (220 mg, 0.34 mmol) in dichloromethane (1.5 mL) was added succinic anhydride (41 mg, 0.41 mmol). The mixture was heated at 45 °C for 12 hours. The solvent was removed and a white solid was dried under high vacuum. To this solid was added sodium acetate (10 mg, 0.12 mmol), followed by acetic anhydride (1.5 mL). The mixture was heated at 85 °C for 1 hour, and the solvent was removed under reduced pressure. The residue was diluted with EtOAc, and was washed sequentially with water, saturated $NaHCO_3$, water, and brine, and dried over Na_2SO_4. Concentration gave Example **DC** (190 mg). m/z: 788.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.99 (s, 1H); 7.84 (s, 1H); 7.30-7.00 (m, 11H); 5.22 (s, 2H); 4.70-4.40 (m, 2H); 4.20-3.90 (m, 2H); 3.75 (m, 1H); 3.54 (m, 1H); 3.42 (m, 1H); 3.28 (m, 1H); 2.98 (s, 3H); 2.67 (m, 8H); 2.00 (m, 1H); 1.81 (m, 1H); 1.70-1.20 (m, 10H).

Preparation of Example DD

Scheme 85



R



DD

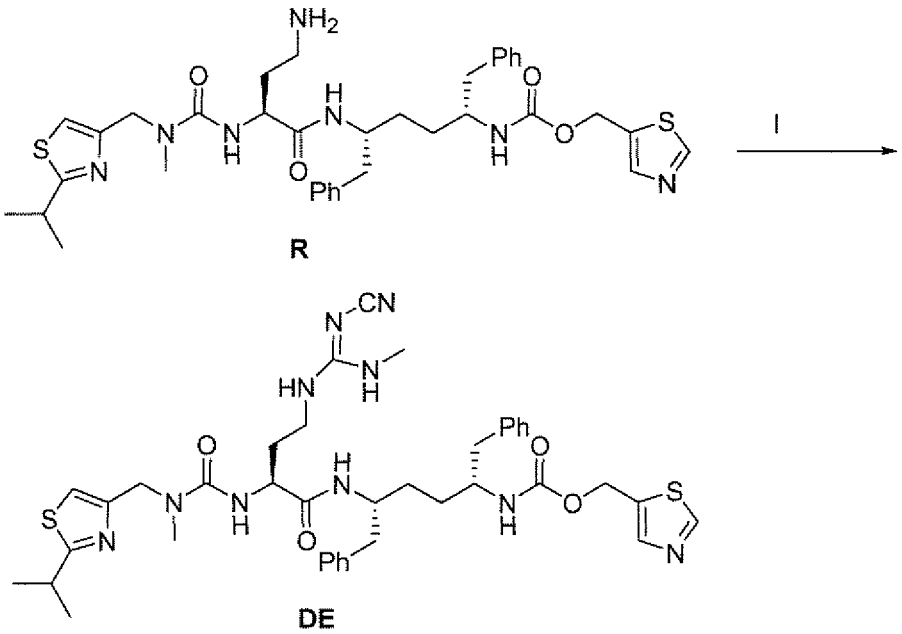
I. $CF_3CH_2OSO_2CCl_3/NaHCO_3/DMF$

Example DD

To a solution of Example **R** (220 mg, 0.34 mmol) in DMF (3 mL) was added sodium carbonate (100 mg), followed by 2,2,2-trifluoroethyl trichloromethanesulfonate (112 •l, 0.68 mmol). The mixture was stirred for 3 days and the solvent was removed under reduced pressure. The residue was diluted with EtOAc. The organic layer was sequentially washed twice with saturated sodium carbonate solution, once with water, and once with brine, and dried over Na_2SO_4. Concentration and purification by flash column chromatography (9% MeOH in dichloromethane) gave Example **DD** (109 mg). m/z: 788.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.98 (s, 1H); 7.82 (s, 1H); 7.62 (d, 1H, *J*=9 Hz); 7.30-7.00 (m, 11H); 6.85 (d, 1H, *J*=9 Hz); 5.20 (m, 2H); 4.54 (s, 2H); 4.23 (m, 1H); 4.11 (m, 1H); 3.77 (m, 1H); 3.31 (m, 2H); 3.12 (q, 2H, *J*=10 Hz); 2.95 (m, 3H); 3.80-2.50 (m, 6H); 1.77 (m, 2H); 1.70-1.20 (m, 10H). ^{19}F NMR (CD_3OD) • -73.28 (t, 1H, *J*=10 Hz).

Preparation of Example DE

Scheme 86



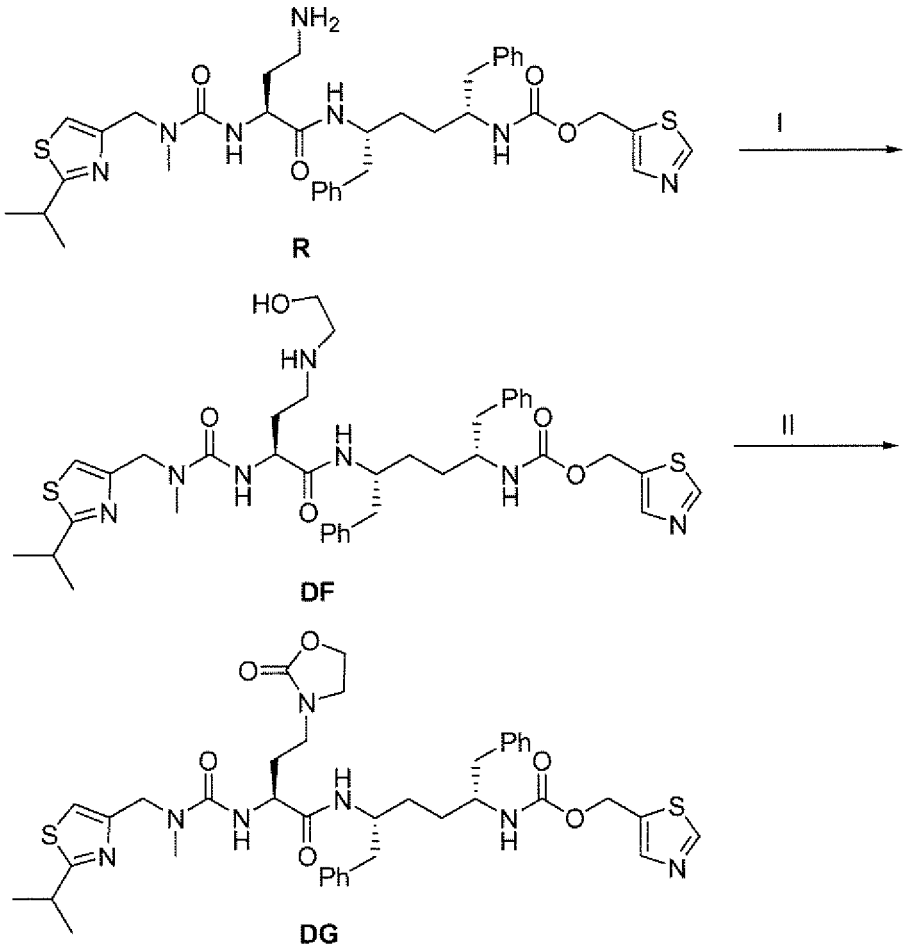
I. a. $(MeS)_2C=NCN$/EtOH; b. $MeNH_2$/EtOH

Example DE

To a clear solution of dimethyl N-cyanodithioiminocarbonate (50 mg, 0.34 mmol) in ethanol (0.5 mL) was added slowly a solution of Example **R** (220 mg, 0.34 mmol) in ethanol (2.5 mL). The mixture was stirred for 12 hours. To the above mixture was added a solution of methylamine in EtOH (1.6 mL, 33%wt). The mixture was stirred for 6 hours, and solvents were removed under reduced pressure. Purification by HPLC gave Example **DE** (92 mg). m/z: 787.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.98 (s, 1H); 7.83 (s, 1H); 7.30-7.00 (m, 11H); 5.21 (s, 2H); 4.51 (s, 2H); 4.18 (m, 1H); 4.09 (m, 1H); 3.77 (m, 1H); 3.28 (m, 2H); 3.16 (m, 1H); 2.97 (s, 3H); 2.80 (s, 3H); 2.715 (m, 4H); 1.84 (m, 1H); 1.70 (m, 1H); 1.65-1.20 (m, 10H).

Preparation of Examples DF-DG

Scheme 87



I. $BrCH_2CH_2OH/Na_2CO_3/DMF/70$ C; II. CDI/DMAP/THF/70 C

Example DF

To a solution of Example **R** (220 mg, 0.34 mmol) in DMF (1 mL) was added sodium carbonate (72 mg, 0.68 mmol), followed by a solution of 2-bromoethanol (24 •l, 0.34 mmol) in DMF (0.4 mL). The mixture was heated at 70 °C for 12 hours. Concentration under high vacuum gave Example **DF**. m/z: 750.2

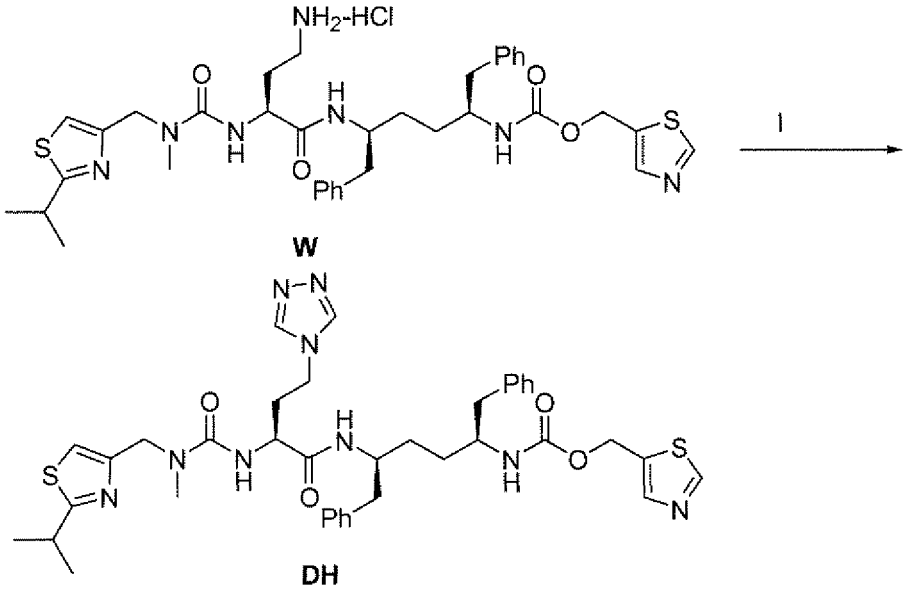
Example DG

To a suspension of Example **DF** (0.34 mmol) in THF (3.4 mL) was added carbonyldiimidazole (CDI) (83 mg, 0.51 mmol), followed by DMAP (4 mg). The mixture was heated at 70 °C for 3 hours, and the solvent was removed. The residue was diluted with EtOAc, and was washed with water and brine, and

dried over Na_2SO_4. Concentration and purification with preparative TLC gave Example **DG** (83 mg). m/z: 776.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.98 (s, 1H); 7.83 (s, 1H); 7.67 (m, 1H); 7.30-7.00 (m, 11H); 6.87 (m, 1H); 6.49 (m, 1H); 5.21 (s, 2H); 4.70-4.40 (m, 2H); 4.34 (t, 2H, *J*=8 Hz); 4.18 (m, 1H); 4.06 (m, 1H); 3.76 (m, 1H); 3.60 (t, 2H, *J*=8 Hz); 3.24 (m, 3H); 2.97 (s, 3H); 2.71 (m, 4H); 1.86 (m, 2H); 1.70-1.20 (m, 10H).

Preparation of Example DH

Scheme 88



I. diformylhydrazine/ pyridine/Et_3N/TMSCl/100 C

Example W

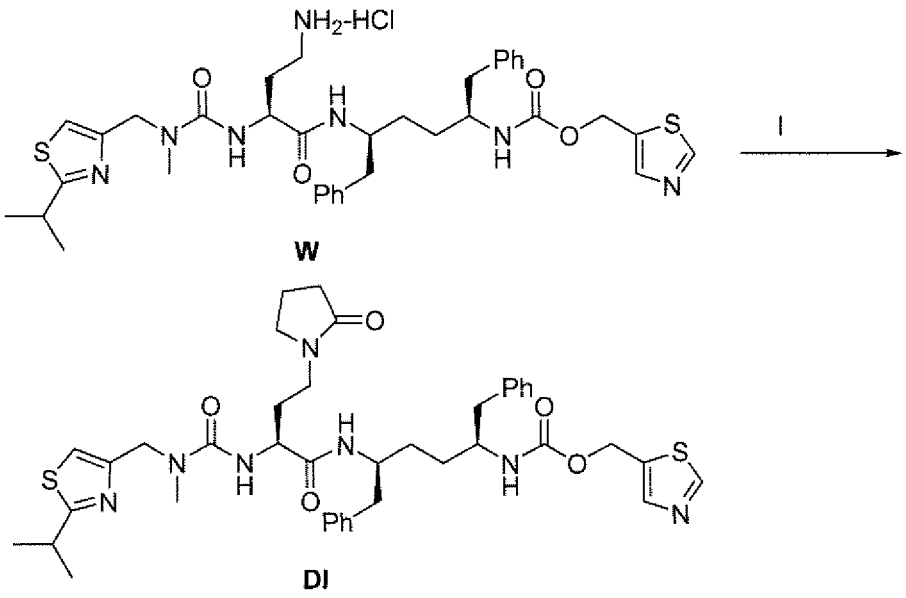
Example **W** was synthesized following the procedure described in WO2008/010921 A2, and as described above in Scheme **25**.

Example DH

Example **DH** (100 mg) was prepared following the procedure used to prepare example **CY**, except that Example **W** was used instead of Example **R**. ^1H NMR (CD_3OD): δ 8.97 (s, 1H), 8.40 (s, 2H), 7.81 (s, 1H), 7.15 (m, 10H), 5.20 (s, 2H), 4.54 (m, 2H), 4.20 (m, 1H), 4.07 (m, 1H), 3.87 (m, 3H), 3.24 (m, 1H), 2.95 (s, 3H), 2.85 (m, 1H), 2.60 (m, 3H), 1.81 (m, 2H), 1.60-1.43 (m, 4H), 1.33 (d, J=7.2 Hz, 6H). Mass Spectrum (*m/e*): $(M+H)^+$ 758.2, $(M-H)^-$ 755.9.

Preparation of Example DI

Scheme 89



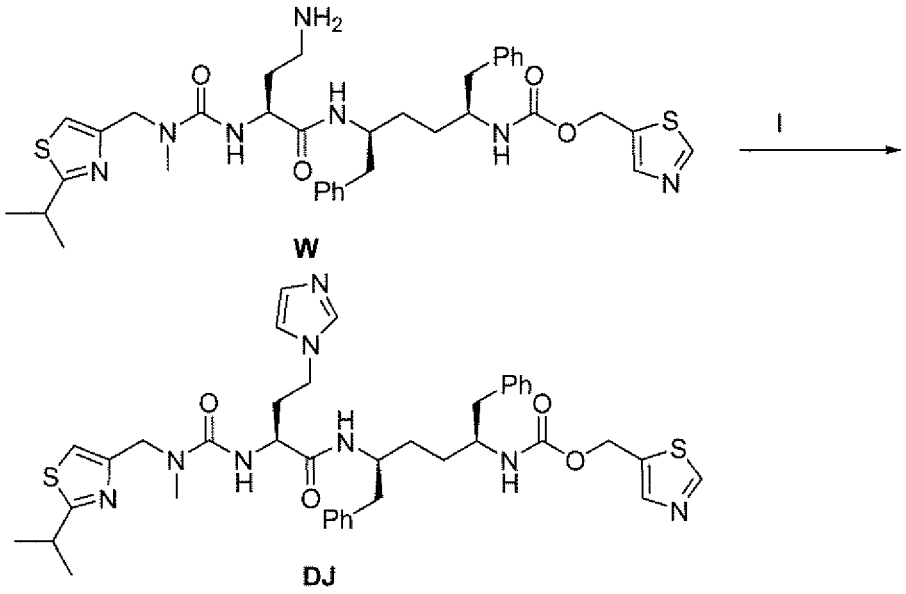
I. Methyl 4-bromobutyrate/$NaHCO_3$/DMF/60 C

Example DI

Example **DI** (28 mg) was prepared following the procedure used to prepare Example **CZ**, except that compound **W** (160 mg) was used instead of Example **R**. m/z: 774.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (1 H, s), 7.81 (1 H, s), 7.24-7.02 (11 H, m), 5.20 (2 H, s), 4.54 (2 H, m), 4.18 (1 H, m), 4.0 (1 H, m), 3.75 (1 H, m), 3.20 (4 H, m), 3.01 (1 H, m), 2.99 (3 H, s), 2.8-2.5 (4 H, m), 2.38 (2 H, m), 2.04 (2 H, m), 1.62-1.40 (6 H, m), 1.31 (6 H, m).

Preparation of Example DJ

Scheme 90



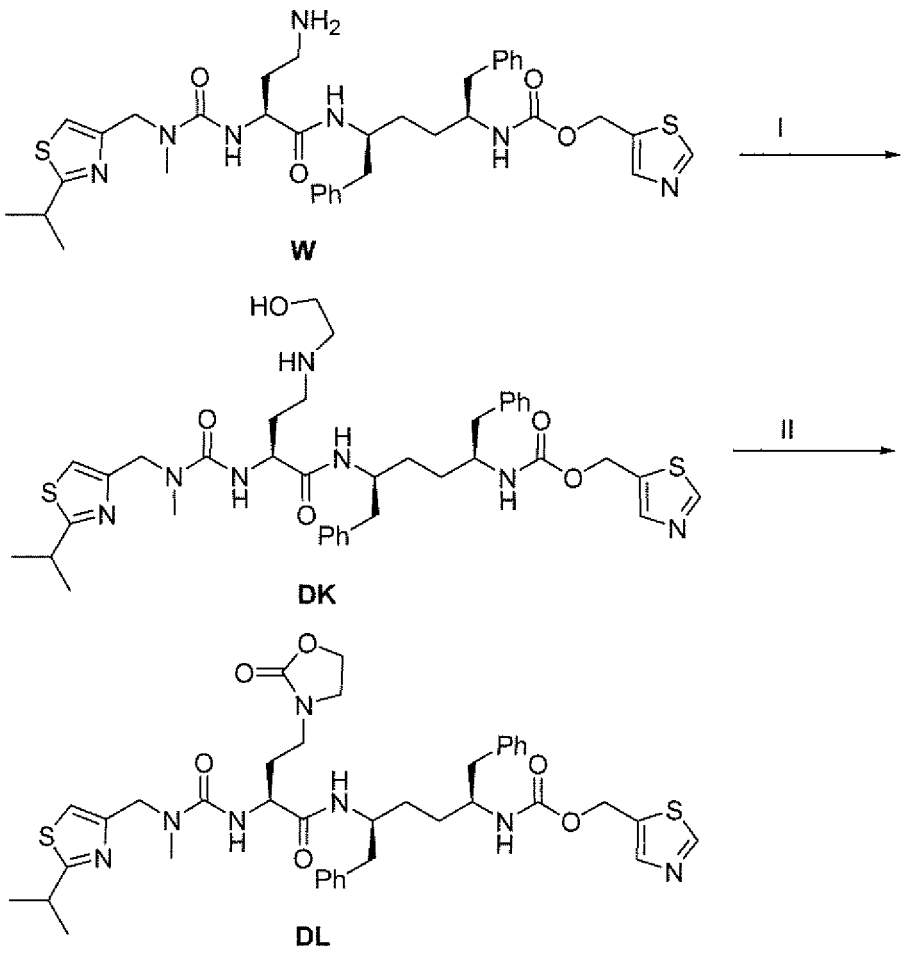
I. NH_3-H_2O/formaldehyde/glyoxal/n-PrOH/80 C

Example DJ

Example **DJ** (44 mg) was prepared following the procedure used to prepare Example **DB**, except that Example **W** (160 mg) was used instead of Example **R**. m/z: 757.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (1 H, s), 7.83 (1 H, s), 7.50 (1 H, s), 7.25-7.04 (11 H, m), 6.99-6.96 (2 H, m), 5.20 (2 H, s), 4.52 (2 H, m), 4.20 (1 H, m), 4.03 (1 H, m), 3.78 (3 H, m), 3.22 (1 H, m), 2.95 (3 H, s), 2.9-2.4 (4 H, m), 1.8 (2 H, m), 1.7-1.4 (4 H, m), 1.31 (6 H, m).

Preparation of Examples DK-DL

Scheme 91



I. $BrCH_2CH_2OH/Na_2CO_3/DMF/70$ C; II. CDI/DMAP/THF/70 C

Example DK

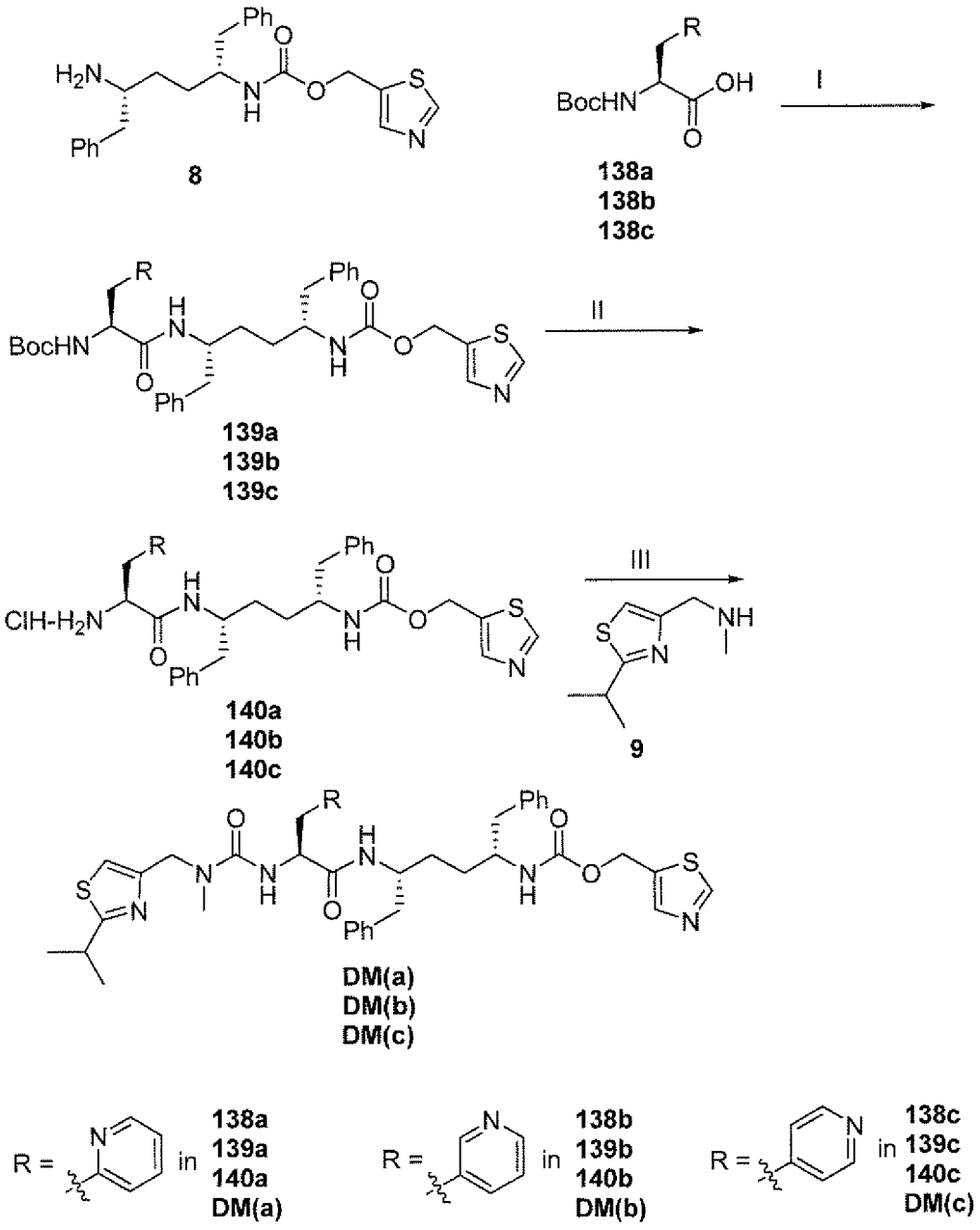
Example **DK** was prepared following the procedure used to prepare Example **DF**, except that Example **W** (160 mg) was used instead of Example **R**.

Example DL

Example **DL** (28 mg) was prepared following the procedure used to prepare Example **DG**, except that Example **DK** was used instead of Example **DF**. m/z: 776.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (1 H, s), 7.81 (1 H, s), 7.25-7.05 (11 H, m), 5.20 (2 H, s), 4.55 (2 H, m), 4.31 (2 H, m), 4.2-4.0 (2 H, m), 3.75 (1 H, m), 3.44 (2 H, m), 3.3-3.0 (3 H, m), 2.98 (3 H, s), 2.8-2.4 (4 H, m), 1.7-1.4 (6 H, m), 1.32 (6 H, m).

Preparation of Examples DM(a-c)

Scheme 92



I. EDC/HOBt/DIPEA/THF; II. HCl/dioxane; III. a. CDI/DIPEA; b. cmpd **9**/DIPEA

Compound 8

Compound **8** was synthesized following the procedure described in WO2008/010921 A2, and as described above.

Compounds 138a/138b/138c

Compounds **138a**, **138b**, and **138c** were obtained from Aldrich.

Compound 139a

To a solution of acid **138a** (266 mg, 1.0 mmol) and amine **8** (409 mg, 1.0 mmol) in THF (10 mL) were added HOBt (203 mg, 1.5 mmol), EDC (294 •l, 2.0 mmol), and diisopropylethylamine (0.835 mL, 4.0 mmol). The mixture was stirred for 12 hours and the solvents were removed. The residue was diluted with EtOAc. The organic phase was washed three times with saturated Na_2CO_3 solution, twice with water, and once with brine, and dried over Na_2SO_4. Concentration and purification by flash column chromatography (0%-10% MeOH in dichloromethane) gave Compound **139a** (509 mg). m/z: 658.1 $(M+H)^+$.

Compound 139b

Compound 139b (543 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **138b** was used instead of Compound **138a**. m/z: 658.1 $(M+H)^+$.

Compound 139c

Compound **139c** (587 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **138c** was used instead of Compound **138a**. m/z: 658.2 $(M+H)^+$.

Compound 140a

To Compound **139a** (500 mg) was added 10 mL of HCl/dioxane solution (4N, 40 mmol). The mixture was stirred for 1 hour, and the solvents were removed. The residue was diluted with diethyl ether, and stirred for 1 hour. The diethyl ether layer was decanted. The solid was washed with diethyl ether (2x) and dried under vacuum. The resulting Compound **140a** was a brown powder (520 mg). m/z: 558.3 $(M+H)^+$.

Compound 140b

Compound **140b** (476 mg) was prepared following the procedure used to prepare Compound **140a**, except that Compound **139b** was used instead of Compound **139a**. m/z: 558.2 $(M+H)^+$.

Compound 140c

Compound **140c** (536 mg) was prepared following the procedure used to prepare Compound **140a**, except that Compound **139c** was used instead of Compound **139a**. m/z: 558.3 $(M+H)^+$.

Compound 9

Compound **9** was synthesized following the procedure described in WO2008/010921 A2.

Example DM(a)

To the stirred solution of Compound **140a** (520 mg, 0.75 mmol) and diisopropylethylamine (0.52 mL, 3.0 mmol) in dichloromethane (6 mL) was added CDI (122 mg, 0.75 mmol). The mixture was stirred for 12 hours. To this mixture was added a solution of Compound **9** (128 mg, 0.75 mmol) in dichloromethane (2 mL), and the mixture was stirred for 5 additional hours. The solvents were removed, and the residue was diluted with EtOAc. The organic layer was washed twice with water and once with brine, and dried over Na_2SO_4. Concentration and purification by HPLC gave Example **DM(a)** (270 mg). m/z: 754.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (s, 1H); 8.41 (m, 1H); 7.82 (s, 1H); 7.70 (m, 2H); 7.30-7.00 (m, 11H); 6.99 (s, 1H); 5.21 (s, 2H); 4.56 (m, 1H); 4.48 (s, 2H); 4.02 (m, 1H); 3.72 (m, 1H); 3.28 (m, 1H); 3.15-2.90 (m, 2H); 2.93 (s, 3H); 2.68 (m, 4H); 1.60-1.30 (m, 10H).

Example DM(b)

Example **DM(b)** (36 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **140b** was used instead of Compound **140a**. m/z: 754.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (s, 1H); 8.38 (m, 2H); 7.83 (s, 1H); 7.68 (m, 1H); 7.33 (m, 1H); 7.30-7.00 (m, 10H); 6.96 (s, 1H); 5.21 (s, 2H); 4.45 (m, 3H); 4.01 (m, 1H); 3.72 (m, 1H); 3.28 (m, 1H); 3.15-2.90 (m, 2H); 2.90 (s, 3H); 2.68 (m, 4H); 1.60-1.30 (m, 10H).

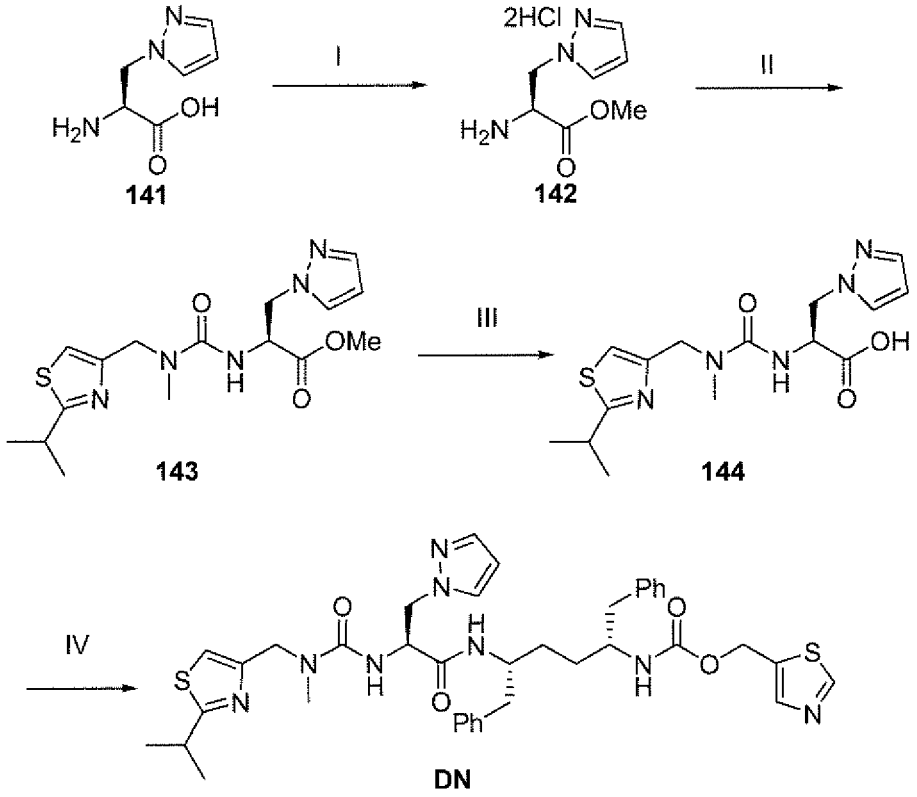
Example DM(c)

Example **DM(c)** (283 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **140c** was used instead of Compound **140a**. m/z: 754.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (s, 1H); 8.39 (d, 2H,

J=6 Hz); 7.82 (s, 1H); 7.27 (d, 2H, *J*=6 Hz); 7.30-7.00 (m, 10H); 6.94 (s, 1H); 5.21 (s, 2H); 4.53 (m, 1H); 4.45 (s, 2H); 4.03 (m, 1H); 3.74 (m, 1H); 3.32 (m, 1H); 3.10-2.90 (m, 2H); 2.90 (s, 3H); 2.72 (m, 4H); 1.60-1.30 (m, 10H).

Preparation of Example DN

Scheme 93



I. $SOCl_2$/MeOH; II. a. CDI/iPr_2NEt; b. cmpd **9**; III.a. NaOH/THF/H_2O; b. HCl; IV. cmpd **8**/EDC/HOBt;

Compound 141

Compound **141** was obtained from TCI.

Compound 142

To a solution of Compound **141** (1.0 g, 6.4 mmol) in methanol (20 mL) at 0 °C was added thionyl chloride (1.0 mL, 14.2 mmol) dropwise. The mixture was stirred at 0 °C for 30 minutes and brought to reflux for 3 hours. Concentration gave Compound **142** as a white solid.

Compound 143

Compound **143** (1.68 g) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **142** was used instead of Compound **140a**. m/z: 366.0 $(M+H)^+$.

Compound 144

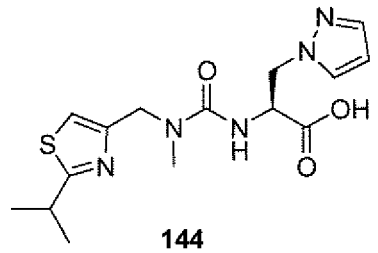
To a solution of Compound **143** (1.68 g, 4.8 mmol) in MeOH/H_2O (20 mL/20 mL) at 0 °C was added sodium hydroxide (229 mg, 5.74 mmol). The mixture was stirred for 1 hour and the solvents were removed under reduced pressure. Hydrochloric acid in dioxane (1.5 mL, 4 N, 6 mmol) was added, and the mixture was evaporated and dried under high vacuum. Compound **144** was obtained as a white solid (1.8 g).

Example DN

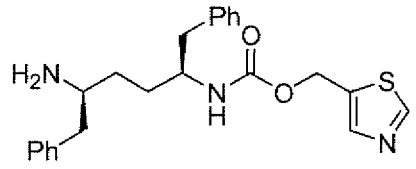
Example **DN** (260 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **144** was used instead of Compound **138a**. m/z: 743.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (1 H, s), 7.81 (1 H, s), 7.44 (1 H, s), 7.39 (1 H, s), 7.3-7.0 (10 H, m), 6.95 (2 H, m), 6.7 (1 H, br), 6.2 (1 H, m), 5.3 (1 H, m), 5.2 (2 H, m), 4.5-4.2 (5 H, m), 4.1 (1 H, m), 3.70 (1 H, m), 3.22 (1 H, m), 2.96 (3 H, s), 2.8-2.5 (4 H, m), 1.5-1.2 (10 H, m).

Preparation of Example DO

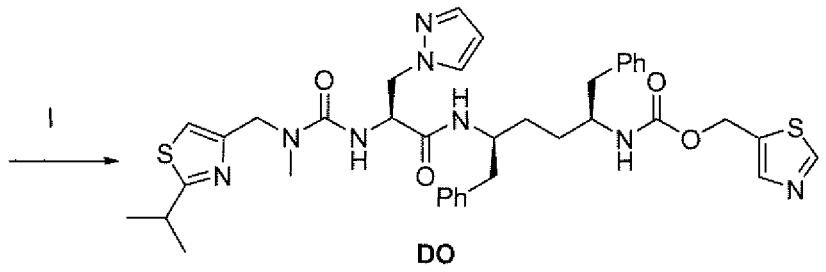
Scheme 94



144



46



DO

I. EDC/HOBt;

Compound 46

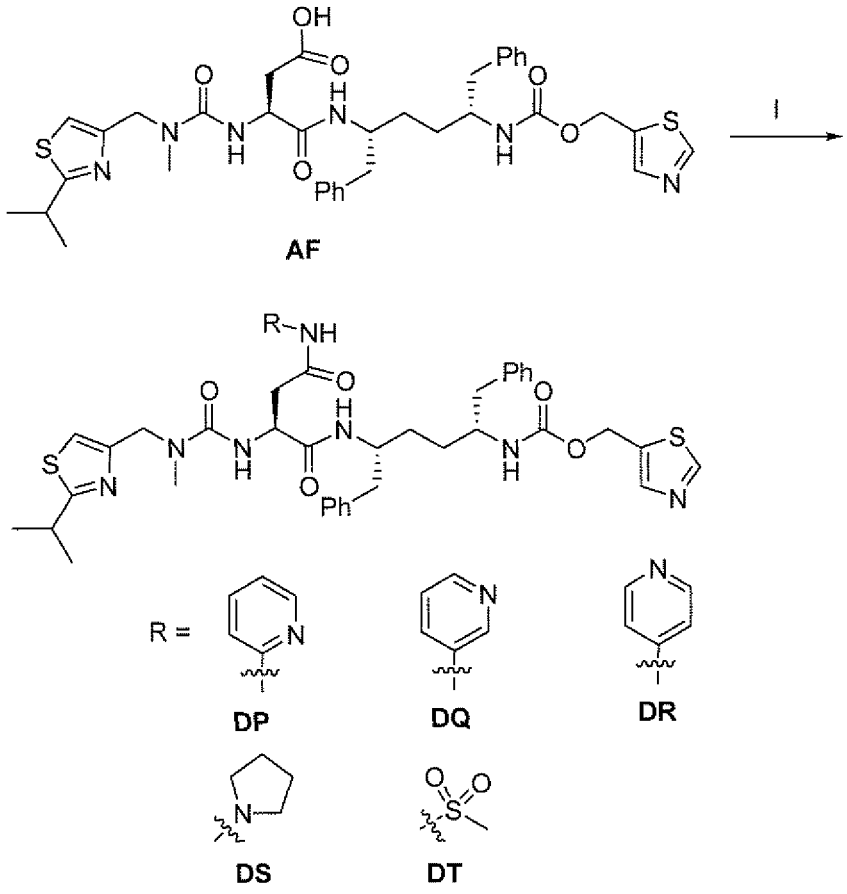
Compound **46** was synthesized following the procedure described in WO2008/010921 A2.

Example DO

Example **DO** (215 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compounds **144** and **46** were used instead of Compounds **8** and **138a**. m/z: 743.2 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (s, 1H); 7.82 (s, 1H); 7.45 (s, 1H); 7.30-7.00 (m, 13H); 6.19 (s, 1H); 5.20 (s, 2H); 4.60-4.40 (m, 2H); 4.21 (m, 2H); 4.09 (m, 1H); 3.25 (m, 1H); 2.93 (s, 3H); 2.90-2.50 (m, 5H); 1.70-1.20 (m, 10H).

Preparation of Examples DP-DT

Scheme 95



I. RNH_2/EDC/HOBt;

Example AF

Example **AF** was synthesized following the procedure described in WO2008/010921 A2, and as described above in **Scheme 27**.

Example DP

Example **DP** (23 mg) was prepared following the procedure used to prepare Compound **139a**, except that Example **AF** and 2-aminopyridine were used instead of Compounds **8** and **138a**. m/z: 797.2 $(M+H)^+$. ^1H NMR (DMSO-d_6) δ 10.45 (1H, s), 9.06 (1 H, s), 8.31 (1 H, m), 8.04 (1 H, m), 7.85 (1 H, m), 7.75 (1 H, m), 7.55 (1 H, m); 7.2-7.0 (13 H, m), 6.54 (1 H, m), 5.12 (2 H, s), 4.52 (1 H, m), 4.43 (2 H, s), 3.93 (1 H, m), 3.58 (1 H, m), 3.17 (1 H, m), 2.85 (3 H, s), 2.8-2.4 (6 H, m), 1.36 (4 H, m), 1.25 (6 H, m).

Example DQ

Example **DQ** (32 mg) was prepared following the procedure used to prepare Compound **139a**, except that Example **AF** and 3-aminopyridine were used instead of Compounds **8** and **138a**. m/z: 797.2 $(M+H)^+$. ^1H NMR (DMSO-d6) δ 10.39 (1H, s), 9.06 (1 H, s), 8.88 (1 H, s), 8.36 (1 H, m), 8.18 (1 H, m), 7.85 (1 H, s), 7.54 (2 H, m), 7.2-7.0 (12 H, m), 6.60 (1 H, m), 5.14 (2 H, s), 4.55 (1 H, m), 4.45 (2 H, s), 4.0-3.5 (2 H, m), 3.19 (1 H, m), 2.86 (3 H, s), 2.8-2.4 (6 H, m), 1.37 (4 H, m), 1.26 (6 H, m).

Example DR

Example **DR** (30 mg) was prepared following the procedure used to prepare Compound **139a**, except that Example **AF** and 4-aminopyridine were used instead of Compounds **8** and **138a**. m/z: 797.3 $(M+H)^+$. ^1H NMR (DMSO-d6) δ 11.24 (1 H, s), 9.05 (1 H, s), 8.61 (2 H, d, J = 6.3 Hz), 7.96 (2 H, d, J = 6.3 Hz), 7.84 (1 H, s), 7.58 (1 H, m), 7.2-7.0 (12 H, m), 6.65 (1 H, m), 5.14 (2 H, s), 4.6 (1 H, m), 4.46 (2 H, s), 3.9 (1 H, m), 3.4 (1 H, m), 3.20 (1 H, m), 2.87 (3 H, s), 2.7-2.4 (6 H, m), 1.37 (4 H, m), 1.25 (6 H, m).

Example DS

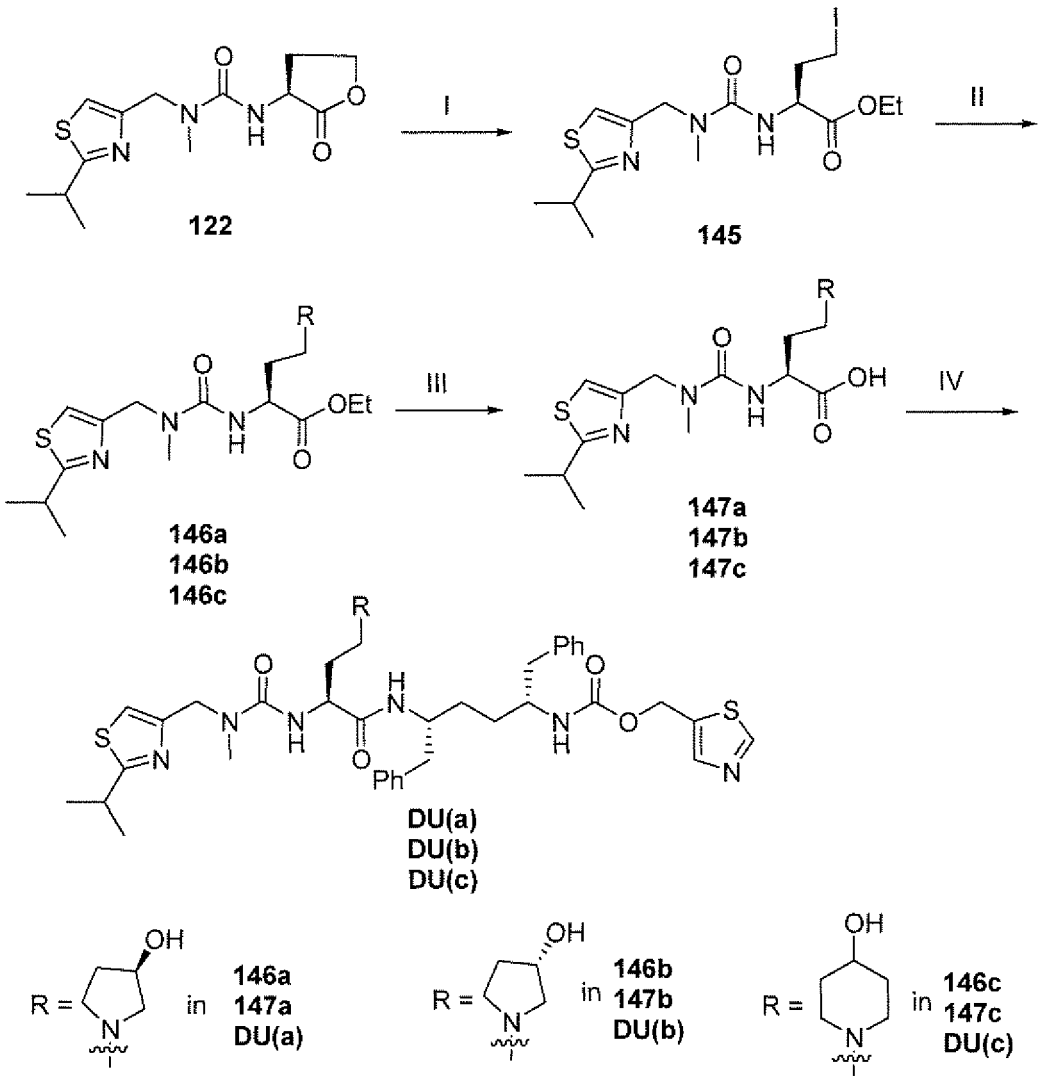
Example **DS** (50 mg) was prepared following the procedure used to prepare Compound **139a**, except that Example **AF** and 1-aminopyrrolidine were used instead of Compounds **8** and **138a**. m/z: 789.2 $(M+H)^+$. ^1H NMR (DMSO-d6) δ 9.06 (1 H, s), 8.63 (1 H, s), 8.26 (1 H, s), 7.85 (1 H, s), 7.55 (1 H, m), 7.35 (1 H, m), 7.2-7.0 (10 H, m); 6.40 (1 H, m), 5.15 (2 H, s), 4.55-4.30 (3 H, m), 3.85 (1 H, m), 3.63 (1 H, m), 3.4-3.1 (5 H, m), 2.86 (3 H, s), 2.8-2.4 (6 H, m), 1.66 (4 H, m), 1.4-1.2 (10 H, m).

Example DT

Example **DT** (50 mg) was prepared following the procedure used to prepare Compound **139a**, except that Example **AF** and methanesulfonamide were used instead of Compounds **8** and **138a**. m/z: 798.2 $(M+H)^+$. ^1H NMR (DMSO-d6) δ 11.65 (1 H, s), 9.10 (1 H, s), 7.88 (1 H, s), 7.50 (1 H, m), 7.2-7.0 (12 H, m), 6.6 (1 H, m), 5.15 (2 H, s), 4.5-4.4 (3 H, m), 4.0-3.4 (2 H, m), 3.20 (1 H, m), 3.15 (3 H, s), 2.85 (3 H, s), 2.7-2.4 (6 H, m), 1.4-1.2 (10 H, m).

Preparation of Examples DU(a-c)

Scheme 96



I. TMSI/EtOH/DCM; II. amino alcohol/DCM; III. a. NaOH/THF/H_2O; b. HCl;
IV. cmpd **8**/EDC/HOBt/DIPEA/DMF

Compound 122

Compound **122** was synthesized following the procedure described in WO2008/010921 A2, and as described above in **Scheme 69**.

Compound 145

To a solution of Compound **122** (1.0 g, 4 mmol) in dichloromethane (5 mL) was added ethyl alcohol (1.5 mL, 25.6 mmol), followed by iodotrimethylsilane (2 mL, 14.3 mmol). The mixture was stirred for 6 hours and the mixture was used directly for the next step. m/z: 453.9 $(M+H)^+$.

Compound 146a

To a solution of Compound **145** (1 mmol) in dichloromethane (2 mL) was added a solution of (R)-3-hydroxypyrrolidine (435 mg, 5 mmol) in dichloromethane (1 mL). The mixture was stirred for 12 hours and the solvents were removed under reduced pressure. Purification by flash column chromatography (0-20% MeOH in dichloromethane) gave Compound **146a** (230 mg). m/z: 413.1 $(M+H)^+$.

Compound 146b

Compound **146b** (200 mg) was prepared following the procedure used to prepare Compound **146a**, except that compound (S)-3-hydroxypyrrolidine was used instead of compound (R)-3-hydroxypyrrolidine. m/z: 413.1 $(M+H)^+$.

Compound 146c

Compound **146c** (380 mg) was prepared following the procedure used to prepare Compound **146a**, except that compound 4-hydroxypiperidine was used instead of compound (R)-3-hydroxypyrrolidine. m/z: 427.1 $(M+H)^+$.

Compound 147a

Compound **147a** (250 mg) was prepared following the procedure used to prepare Compound **144**, except that Compound **146a** was used instead of Compound **143**.

Compound 147b

Compound **147b** (210 mg) was prepared following the procedure used to prepare Compound **144**, except that Compound **146b** was used instead of Compound **143**.

Compound 147c

Compound **147c** (400 mg) was prepared following the procedure used to prepare Compound **144**, except that Compound **146c** was used instead of Compound **143**.

Example DU(a)

Example **DU(a)** (250 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **147a** was used instead of

Compound **138a**. m/z: 776.3 $(M+H)^+$. ^1H NMR (CD_3OD) δ 8.97 (1 H, s), 7.81 (1 H, s), 7.25-7.05 (11 H, m), 5.19 (2 H, m), 4.54 (2 H, m), 4.25 (1 H, m), 4.2-4.1 (2 H, m), 3.75 (1 H, m), 3.22 (1 H, m), 2.94 (3 H, s), 2.8-2.7 (6 H, m), 2.5-2.3 (4 H, m), 2.1-1.8 (2 H, m), 1.7-1.4 (6 H, m), 1.37 (6 H, m).

Example DU(b)

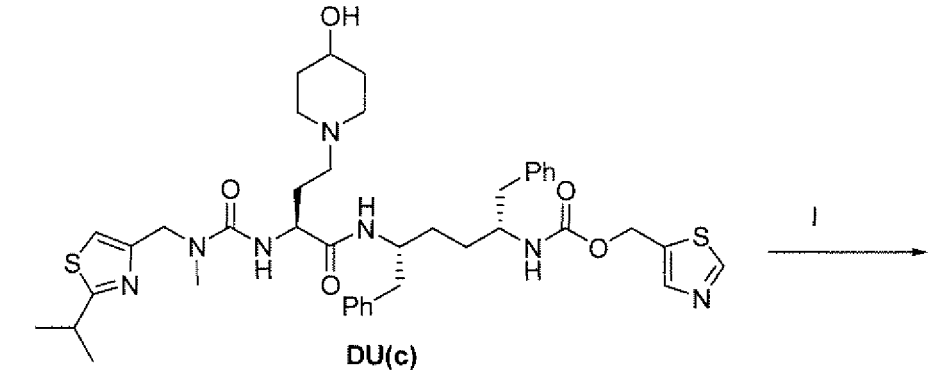
Example **DU(b)** (253 mg) was prepared following the procedure used to prepare Compound **139a**, except that compound **147b** was used instead of Compound **138a**. m/z: 776.3 $(M+H)^+$. ^1H NMR (CD3OD) δ 8.97 (1 H, s), 7.81 (1 H, s), 7.22-7.05 (11 H, m), 5.18 (2 H, m), 4.5 (2 H, m), 4.25 (1 H, m), 4.2-4.1 (2 H, m), 3.78 (1 H, m), 3.25 (1 H, m), 2.95 (3 H, s), 2.8-2.6 (6 H, m), 2.6-2.3 (4 H, m), 2.1-1.8 (2 H, m), 1.8-1.4 (6 H, m), 1.37 (6 H, m).

Example DU(c)

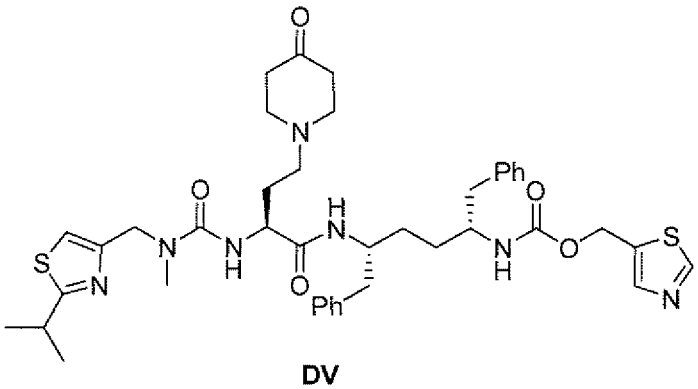
Example **DU(c)** (450 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **147c** was used instead of Compound **138a**. m/z: 790.3 $(M+H)^+$. ^1H NMR (CD3OD) δ 8.97 (1 H, s), 7.81 (1 H, s), 7.25-7.05 (11 H, m), 5.20 (2 H, m), 4.54 (2 H, m), 4.2-4.0 (2 H, m), 3.75 (1 H, m), 3.58 (1 H, m), 3.25 (1 H, m), 2.97 (3 H, s), 2.8-2.6 (6 H, m), 2.25 (2 H, m), 2.08 (2 H, m), 1.9-1.6 (4 H, m), 1.6-1.4 (6 H, m), 1.38 (6 H, m).

Preparation of Example DV

Scheme 97



DU(c)



DV

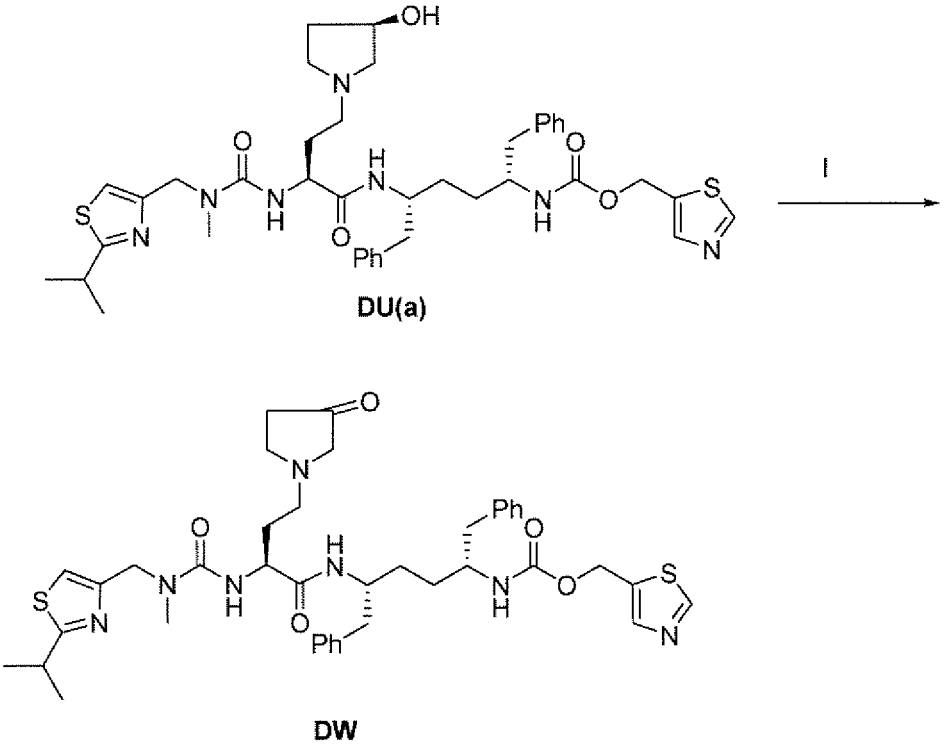
I. SO_3-pyridine/Et_3N/DMSO

Example DV

A mixture of Example **DU(c)** (230 mg, 0.29 mmol) and triethylamine (0.14 mL) in DMSO (1 mL) was stirred at 25 °C for 30 minutes, and then was cooled to 5-10 °C. Sulfur trioxide pyridine complex (0.17 g) was added to above reaction mixture and the mixture was stirred for 1 hour at 5-10 °C. The mixture was poured into ice water, and stirred for 20 minutes, and was extracted with EtOAc. The organic phase was washed twice with water, twice with saturated $NaHCO_3$ solution, twice with water, and once with brine, and dried over Na_2SO_4. Concentration and purification by flash column chromatography (0-20% MeOH in dichloromethane) gave Example **DV** (67 mg). m/z: 788.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (1 H, s), 7.81 (1 H, s), 7.3-7.1 (10 H, m), 6.90 (1 H, s), 6.5 (1 H, br), 5.35 (1 H, m), 5.22 (2 H, s), 4.4-4.0 (4 H, m), 3.78 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.8-2.5 (8 H, m), 2.4-2.2 (6 H, m), 2.0-1.4 (6 H, m), 1.32 (6 H, m).

Preparation of Example DW

Scheme 98



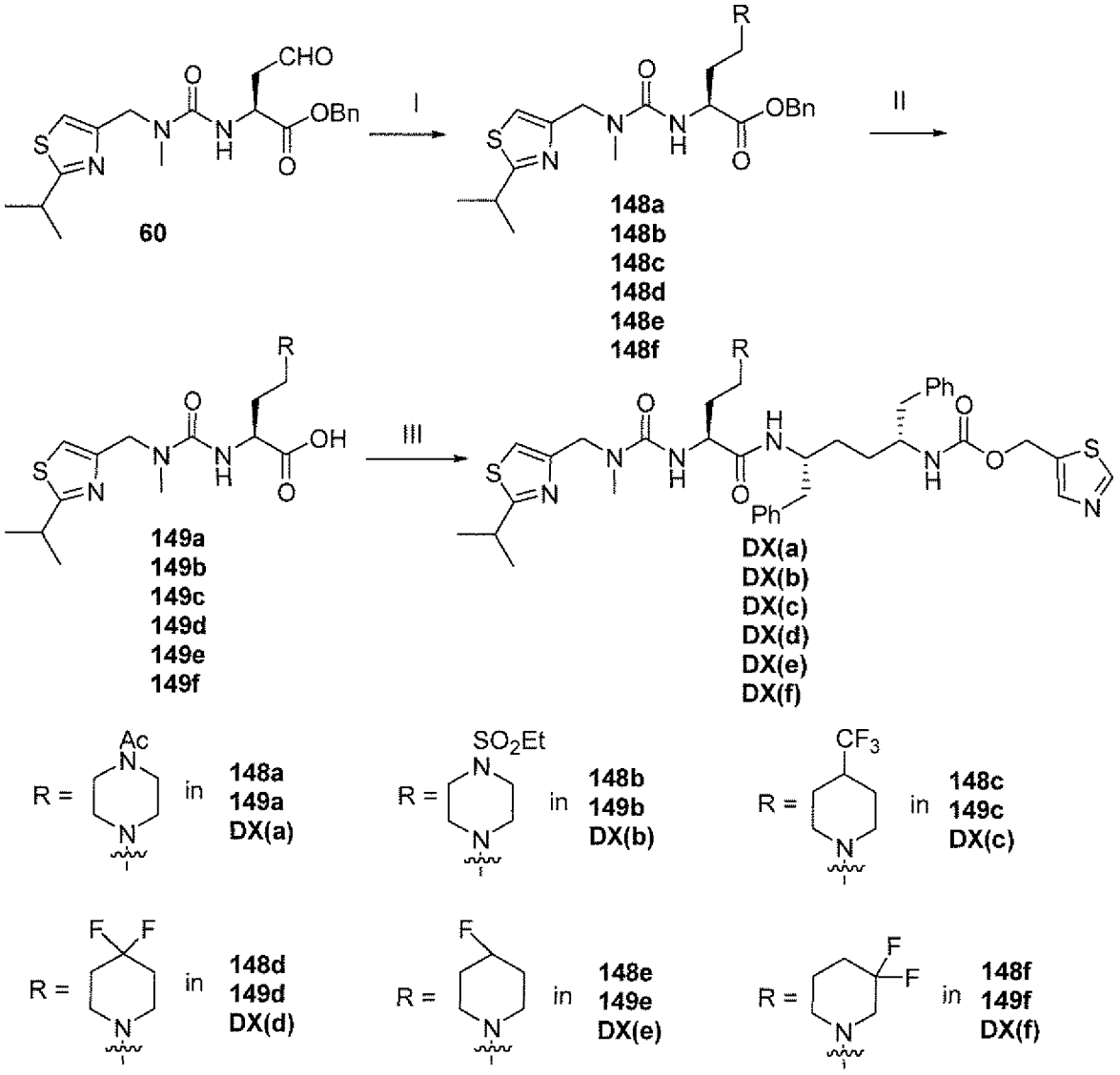
I. SO_3-pyridine/Et_3N/DMSO

Example DW

Example **DW** (78 mg) was prepared following the procedure used to prepare Example **DV**, except that Example **DU(a)** was used instead of Example **DU(c)**. m/z: 774.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (1 H, s), 7.82 (1 H, s), 7.3-7.0 (10 H, m), 6.89 (1 H, s), 6.55 (1 H, br), 5.40 (1 H, m), 5.21 (2 H, s), 4.5-4.2 (3 H, m), 4.15 (1 H, m), 3.78 (1 H, m), 3.23 (1 H, m), 3.1-2.9 (4 H, m), 2.9 (3 H, s), 2.8-2.5 (6 H, m), 2.40 (2 H, m), 1.90 (2 H, m), 1.55 (2 H, m), 1.38 (8 H, m).

Preparation of Examples DX(a-f)

Scheme 99



I. amine/$NaBH(OAc)_3$/AcOH/CH_3CN; II. a. NaOH/EtOH/H_2O; b. HCl;
III.compound **8**/EDC/HOBt/DIPEA

Compound 60

Compound **60** was synthesized following the procedure described in WO2008/010921 A2, and as described above in **Scheme 23**.

Compound 148a

To a solution of Compound **60** (800 mg, 2 mmol) in CH_3CN (8 mL) was added a solution of 1-acetylpiperazine (512 mg, 4 mmol) in CH_3CN (1 mL),

followed by HOAc (240 ul, 4 mmol) and $NaBH(OAc)_3$ (1.33 g, 6 mmol). The mixture was stirred for 12 hours and was diluted with EtOAc. The organic phase was washed with saturated Na_2CO_3 solution, water, and brine, and dried over Na_2SO_4. Concentration and purification by flash column chromatography (0-12% iPrOH in dichloromethane) gave Compound **148a** (250 mg). m/z: 516.1 $(M+H)^+$.

Compound 148b

Compound **148b** (530 mg) was prepared following the procedure used to prepare Compound **148a**, except that 1-ethylsulfonylpiperazine was used instead of 1-acetylpiperazine. m/z: 566.1 $(M+H)^+$.

Compound 148c

Compound **148c** (384 mg) was prepared following the procedure used to prepare Compound **148a**, except that 4-trifluoromethylpiperidine was used instead of 1-acetylpiperazine. m/z: 541.2 $(M+H)^+$.

Compound 148d

Compound **148d** (342 mg) was prepared following the procedure used to prepare Compound **148a**, except that 4, 4-difluoropiperidine was used instead of 1-acetylpiperazine. m/z: 509.1 $(M+H)^+$.

Compound 148e

Compound **148e** (320 mg) was prepared following the procedure used to prepare Compound **148a**, except that 4-fluoropiperidine was used instead of 1-acetylpiperazine. m/z: 491.1 $(M+H)^+$.

Compound 148f

Compound **148f** (389 mg) was prepared following the procedure used to prepare Compound **148a**, except that 3,3-difluoropiperidine was used instead of 1-acetylpiperazine. m/z: 509.1 $(M+H)^+$.

Example 149a

To a solution of Compound **148a** (250 mg, 0.48 mmol) in ethyl alcohol (3 mL) was added 1.0 N sodium hydroxide solution (0.53 mL, 0.53 mmol). The mixture was stirred for 1 hour and the solvents were removed under reduced pressure. 4.0 N Hydrochloric acid in dioxane (0.13 mL, 0.52 mmol) was added,

and the mixture was evaporated. Coevaporation with DMF (2x100 mL) gave Compound **149a**, which was used without further purification in the next step.

Example 149b

Compound **149b** was prepared following the procedure used to prepare Compound **149a**, except that Compound **148b** was used instead of Compound **148a**.

Example 149c

Compound **149c** was prepared following the procedure used to prepare Compound **149a**, except that Compound **148c** was used instead of Compound **148a**.

Example 149d

Compound **149d** was prepared following the procedure used to prepare Compound **149a**, except that Compound **148d** was used instead of Compound **148a**.

Example 149e

Compound **149e** was prepared following the procedure used to prepare Compound **149a**, except that Compound **148e** was used instead of Compound **148a**.

Example 149f

Compound **149f** was prepared following the procedure used to prepare Compound **149a**, except that Compound **148f** was used instead of Compound **148a**.

Example DX(a)

Example **DX(a)** (90 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149a** was used instead of Compound **138a**. m/z: 817.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.78 (1 H, s), 7.81 (1 H, s), 7.3-7.0 (10 H, m), 6.90 (1 H, s), 6.40 (1 H, m), 5.40 (1 H, m), 5.22 (2 H, s), 4.6-4.3 (2 H, m), 4.3-4.1 (2 H, m), 3.78 (1 H, m), 3.5-3.2 (5 H, m), 2.92 (3 H, s), 2.9-2.6 (4 H, m), 2.4-2.2 (6 H, m), 2.07 (3 H, s), 1.9 (2 H, m), 1.6-1.3 (10 H, m).

Example DX(b)

Example **DX(b)** (150 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149b** was used instead of Compound **138a**. m/z: 867.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.78 (1 H, s), 7.81 (1 H, s), 7.3-7.0 (10 H, m), 6.92 (1 H, s), 6.4 (1 H, br), 5.35 (1 H, br), 5.2 (2 H, s), 4.6-4.0 (4 H, m), 3.78 (1 H, m), 3.3-3.1 (5 H, m), 2.92 (5 H, m), 2.8-2.6 (4 H, m), 2.5-2.2 (6 H, m), 1.90 (2 H, m), 1.6-1.3 (13 H, m).

Example DX(c)

Example **DX(c)** (427 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149c** was used instead of Compound **138a**. m/z: 842.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.77 (1 H, s), 7.80 (1 H, s), 7.3-7.0 (10 H, m), 6.88 (1 H, s), 6.40 (1 H, br), 5.50 (1 H, br), 5.20 (2 H, m), 4.7-4.3 (2 H, m), 4.18 (2 H, m), 3.75 (1 H, m), 3.23 (1 H, m), 3.05-2.8 (4 H, m), 2.8-2.6 (4 H, m), 2.25 (2 H, m), 2.0-1.65 (6 H, m), 1.6-1.2 (14 H, m).

Example DX(d)

Example **DX(d)** (390 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149d** was used instead of Compound **138a**. m/z: 810.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.78 (1 H, s), 7.81 (1 H, s), 7.4-7.0 (10 H, m), 6.89 (1 H, s), 6.40 (1 H, br), 5.40 (1 H, br), 5.22 (2 H, m), 4.6-4.3 (2 H, m), 4.22 (2 H, m), 3.78 (1 H, m), 3.24 (1 H, m), 3.0-2.6 (7 H, m), 2.5 -2.2 (6 H, m), 2.0-1.7 (6 H, m), 1.6-1.2 (10 H, m).

Example DX(e)

Example **DX(e)** (160 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149e** was used instead of Compound **138a**. m/z: 792.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.77 (1 H, s), 7.81 (1 H, s), 7.3-7.0 (10 H, m), 6.87 (1 H, s), 6.45 (1 H, br), 5.55 (1 H, br), 5.20 (2 H, m), 4.9-4.3 (3 H, m), 4.3-4.1 (2 H, m), 3.75 (1 H, m), 3.25 (1 H, m), 3.1-2.8 (5 H, m), 2.8-2.6 (4 H, m), 2.6-2.1 (6 H, m), 2.0-1.4 (8 H, m), 1.37 (6 H, m).

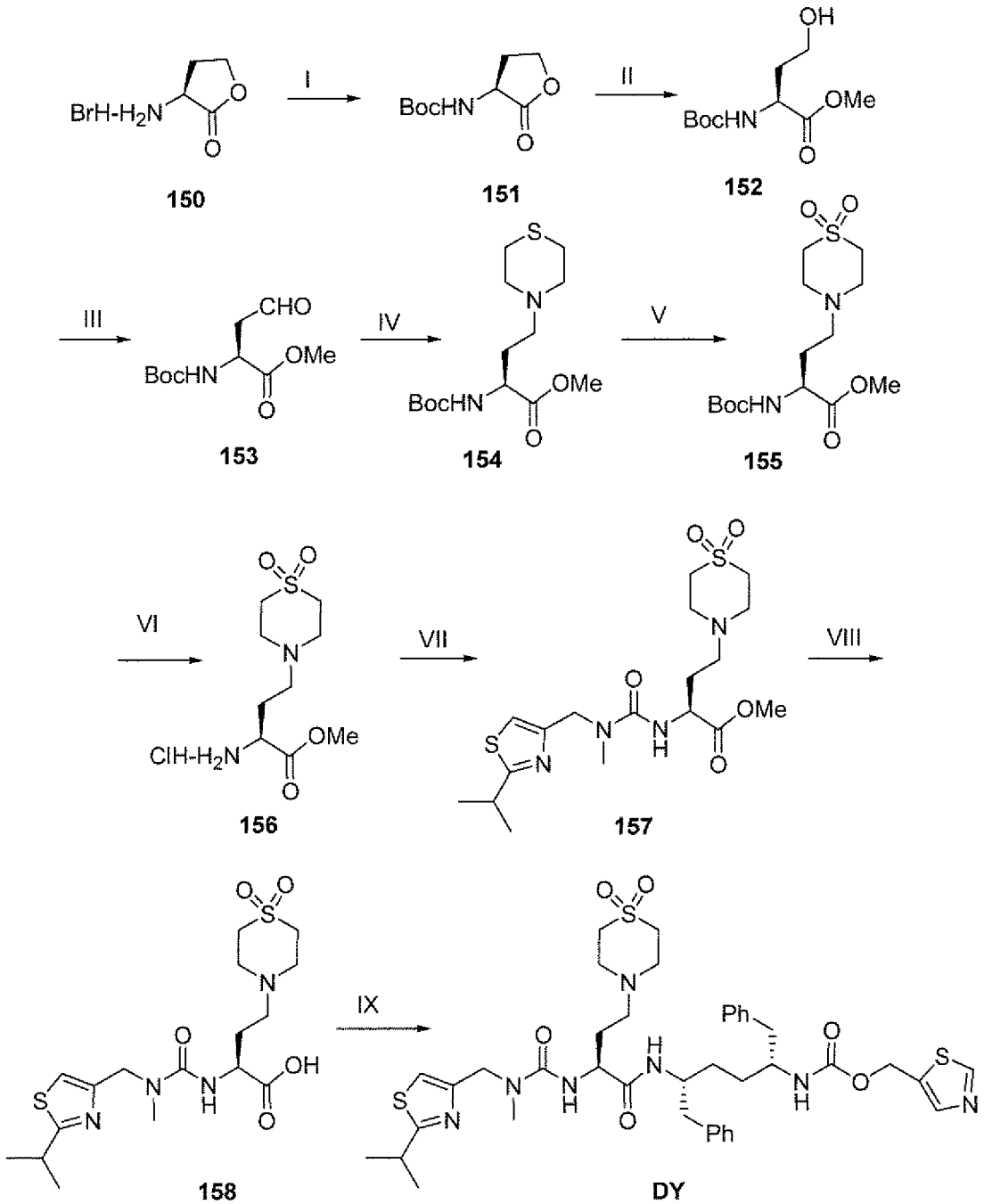
Example DX(f)

Example **DX(f)** (480 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **149f** was used instead of

Compound **138a**. m/z: 810.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.77 (1 H, s), 7.80 (1 H, s), 7.3-7.0 (10 H, m), 6.93 (1 H, br), 6.84 (1 H, s), 6.40 (1 H, br), 5.50 (1 H, br), 5.20 (2 H, m), 4.5-4.3 (2 H, m), 4.3-4.1 (2 H, m), 3.75 (1 H, m), 3.24 (1 H, m), 3.05-2.8 (5 H, m), 2.8-2.6 (4 H, m), 2.5-2.2 (6 H, m), 2.0-1.75 (4 H, m), 1.7-1.37 (10 H, m).

Preparation of Example DY

Scheme 100



1. Boc_2O/THF; II.NaOMe/MeOH; III. SO_3-pyridine/DMSO/Et_3N;
IV. thiomorpholine/$NaBH(OAc)_3$/HOAc; V. 4-methylmorpholine N-oxide/OsO_4;
VI. HCl; VII. a. CDI; b. cmpd **9**; VIII. a. NaOH; b. HCl;
IX. EDC/HOBt/cmpd **8**

Compound 150

Compound **150** was obtained from Aldrich.

Compound 151

To a suspension of Compound **150** (25 g, 137 mmol) in THF (400 mL) was added triethylamine (21 mL, 151 mmol), followed by Boc_2O (31.5 g, 144 mmol). The mixture was stirred for 48 hours, and the solvents were removed. The residue was diluted with EtOAc, and washed twice with saturated sodium carbonate solution, once with water, and once with brine, and dried over Na_2SO_4. Concentration gave Compound **151** (25 g).

Compound 152

To a solution of Compound **151** (2.0 g, 10 mmol) in MeOH (20 mL) at 0 °C was added 4.4 N sodium methoxide solution in methanol (0.46 mL, 2 mmol). The mixture was stirred for 45 minutes, and quenched with saturated NH_4Cl solution. The solvent was evaporated, and the residue was diluted with EtOAc. The organic phase was washed with saturated NH_4Cl solution, water, and brine, and dried over Na_2SO_4. Concentration gave Compound **152** (2.6 g).

Compound 153

Compound **153** (1.9 g) was prepared following the procedure used to prepare Example **DV**, except that Compound **152** was used instead of Example **DU(c)**.

Compound 154

Compound **154** (1.65 g) was prepared following the procedure used to prepare Compound **148a**, except that Compound **153** and 4-thiomorpholine were used instead of Compound **60** and1-acetylpiperazine.

Compound 155

To a solution of Compound **154** (1.55 g, 4.86 mmol) in acetone/water (270 mL/70 mL) was added 4-methylmorpholine N-oxide (1.25 g, 10 mmol), followed by OsO_4/tBuOH solution (6.8 mL, 2.5%). The mixture was stirred for 12 hours and the solvents were removed under reduced pressure. Purification by flash column chromatography (60-100% EtAOc in hexanes) gave Compound **155** (1.44 g).

Compound 156

Compound **156** was prepared following the procedure used to prepare Compound **140a**, except that Compound **155** was used instead of Compound **139a**.

Compound 157

Compound **157** (660 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **156** was used instead of Compound **140a**. m/z: 447.0 $(M+H)^+$.

Compound 158

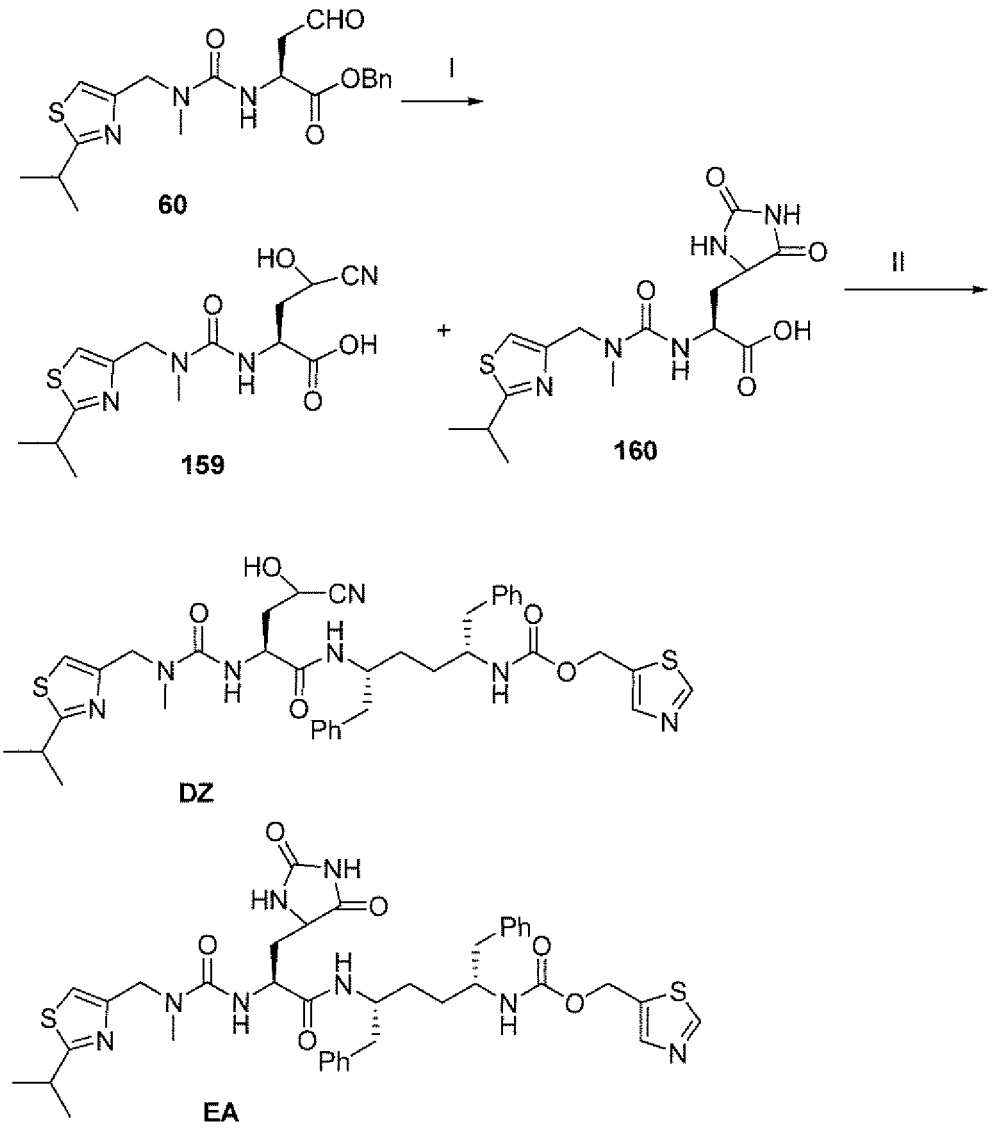
Compound **158** was prepared following the procedure used to prepare Compound **144**, except that Compound **157** was used instead of Compound **143**. m/z: 433.1 $(M+H)^+$.

Example DY

Example **DY** (350 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **158** was used instead of Compound **138a**. m/z: 824.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.80 (1 H, s), 7.82 (1 H, s), 7.2-7.0 (10 H, m), 6.96 (1 H, s), 6.71 (1 H, br), 6.4 (1 H, br), 5.21 (2 H, m), 5.15 (1 H, br), 4.5-4.1 (4 H, m), 3.80 (1 H, m), 3.22 (1 H, m), 3.0-2.8 (11 H, m), 2.8-.2.6 (4 H, m), 2.47 (2 H, m), 2.0-1.7 (2 H, m), 1.6-1.3 (10 H, m).

Preparation of Examples DZ-EA

Scheme 101



I. $NaCN/(NH_4)_2CO_3/EtOH/H_2O$/90 C; II. EDC/HOBt/cmpd **8**

Compounds 159/160

To a solution of Compound **60** (1.6 mmol) in $EtOH/H_2O$ (1.6 mL/1.6 mL) was added ammonium carbonate (600 mg, 6.4 mmol), followed by sodium cyanide (158 mg). The mixture was heated at 90 °C for 16 hours and cooled to 25 °C. 1 N hydrochloric acid was added until pH = 3-4. The residue was diluted with EtOAc, and washed with water and brine. The organic phase was dried over

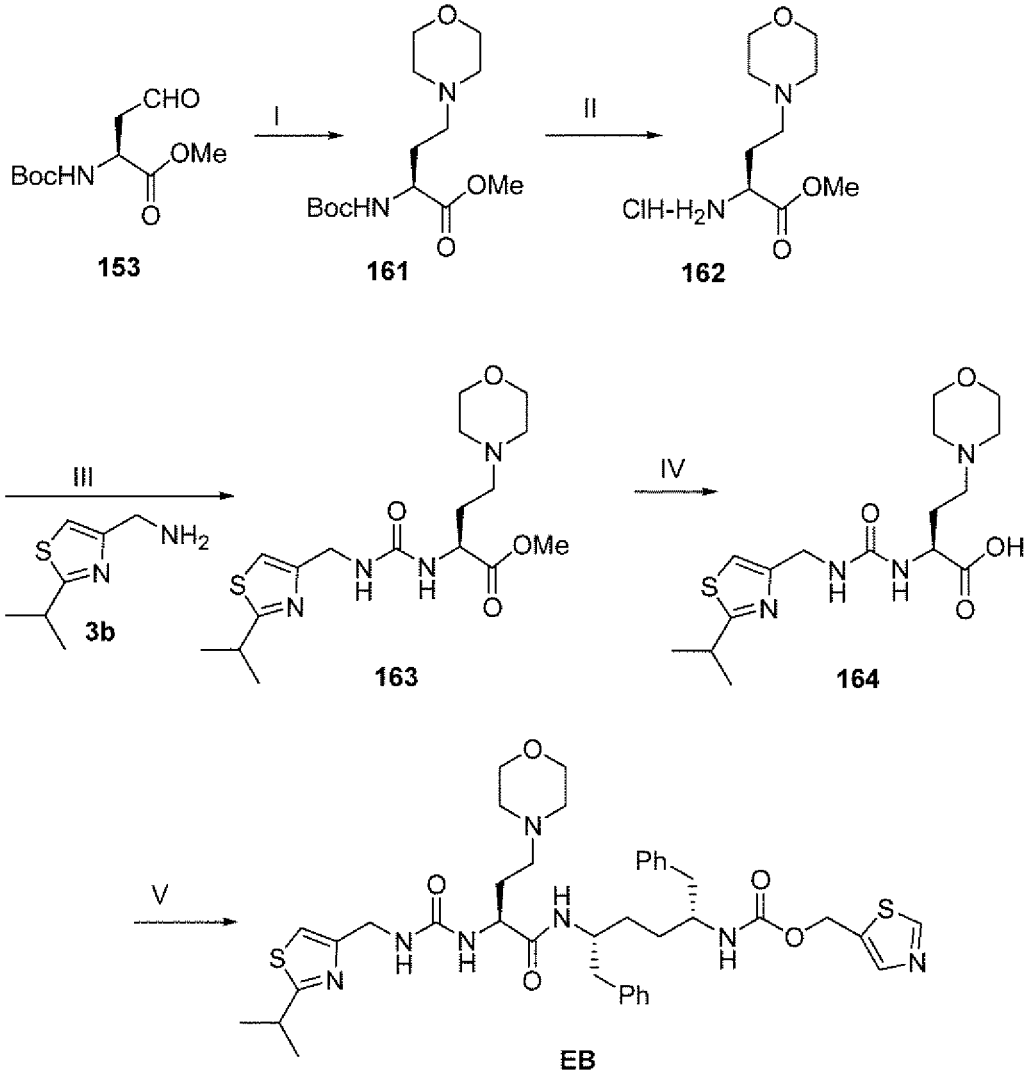
Na_2SO_4 and concentrated to give Compounds **159** and **160**, which were used without further purification in the next step.

Examples DZ/EA

Examples **DZ** (80 mg) and **EA** (60 mg) were prepared following the procedure used to prepare Compound **139a**, except that Compounds **159** and **160** were used instead of Compound **138a**. Example **DZ**: m/z: 732.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.75 (1 H, m), 7.80 (1 H, m), 7.3-7.0 (10 H, m), 6.95 (1 H, m), 6.8 (1 H, br), 6.40 (1 H, br), 5.8 (1 H, br), 5.20 (2 H, m), 4.40 (2 H, m), 4.2-3.8 (3 H, m), 3.78 (1 H, m), 3.23 (1 H, m), 2.95 (3 H, m), 2.8-2.3 (6 H, m), 1.6-1.3 (10 H, m). Example **EA**: m/z: 775.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.81 (1 H, s), 8.02 (1 H, br), 7.9 (1 H, s), 7.85 (1 H, br), 7.3-7.0 (11 H, m), 6.3 (1 H, br), 5.4-5.1 (3 H, m), 4.6-4.3 (2 H, m), 4.2-3.8 (2 H, m), 3.8-3.4 (1 H, m), 3.3 (1 H, m), 3.1-2.9 (3 H, m), 2.8-2.4 (4 H, m), 2.15 (2 H, m), 1.7-1.2 (10 H, m).

Preparation of Example EB

Scheme 102



I. morpholine/$NaBH(OAc)_3$/HOAc; II. HCl; III. a. CDI; b. cmpd **3b**; IV. a. NaOH; b. HCl; V. EDC/HOBt/cmpd **8**

Compound 161

Compound **161** (11 g) was prepared following the procedure used to prepare Compound **148a**, except that Compounds **153** and morpholine were used instead of Compounds **60** and 1-acetylpiperazine. m/z: 303.0 $(M+H)^+$.

Compound 162

Compound **162** (10.4 g) was prepared following the procedure used to prepare Compound **140a**, except that Compound **161** was used instead of Compound **139a**. m/z: 203.1 $(M+H)^+$.

Example 3b

Compound **3b** was synthesized following the procedure described in WO2008/010921 A2, and as described above in **Scheme 10**.

Example 163

Compound **163** (540 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compounds **162** and **36** were used instead of Compounds **140a** and **9**. m/z: 385.1 $(M+H)^+$.

Example 164

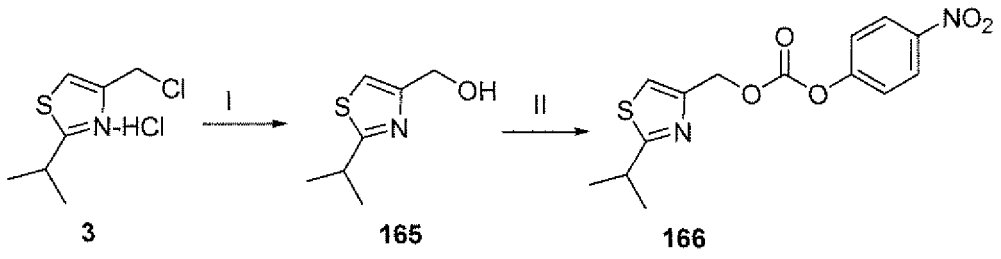
Compound **164** (780 mg) was prepared following the procedure used to prepare Compound **144**, except that Compound **163** was used instead of Compound **143**. m/z: 371.0 $(M+H)^+$.

Example EB

Example **EB** (210 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **164** was used instead of Compound **138a**. m/z: 762.2 $(M+H)^+$. ^1H NMR (DMSO-d6) • 9.06 (1 H, s), 7.85 (1 H, s), 7.7 (1 H, br), 7.2-7.0 (12 H, m), 6.55 (1 H, br), 6.20 (1 H, br), 5.18 (2 H, s), 4.23 (2 H, m), 4.15 -3.8 (2 H, m), 3.65 (1 H, m), 3.55 (4 H, m), 3.2 (1 H, m), 2.7-2.4 (6 H, m), 2.3-2.0 (6 H, m), 1.5-1.2 (10 H, m).

Preparation of Compound 166

Scheme 103



I. $NaOH/H_2O$; II. bis(4-nitrophenyl) carbonate/Et_3N

Compound 3

Compound **3** was synthesized following the procedure described in WO2008/010921 A2.

Compound **165**

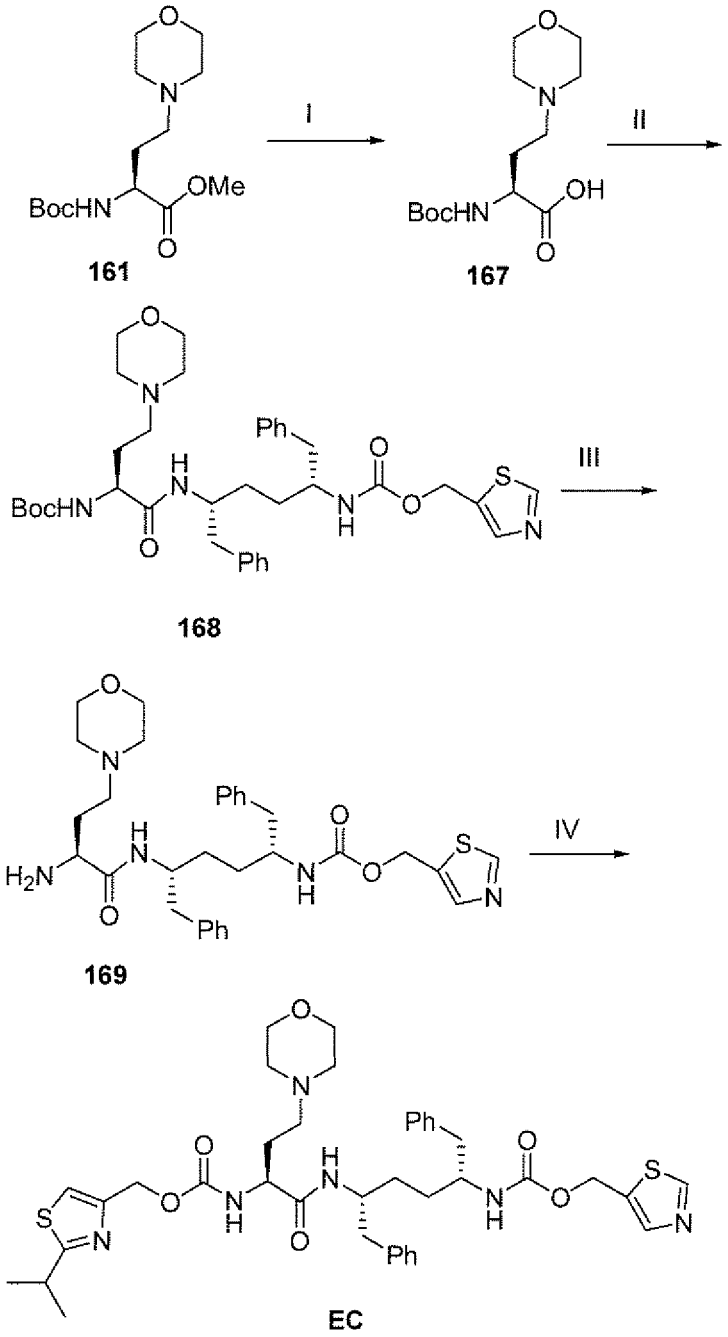
To a suspension of Compound **3** (2.65 g, 12.5 mmol) in water (10 mL) was added sodium hydroxide (1.5 g, 38 mmol). The mixture was heated at 90 °C for 12 hours and cooled to 25 °C. The mixture was extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Purification by flash column chromatography (50% EtOAc in hexanes) gave Compound **165** (810 mg).

Compound 166

To a solution of Compound **165** (810 mg, 5.2 mmol) in DCM (12 mL) was added bis(4-nitrophenyl) carbonate (1.73 g, 5.7 mmol), followed by triethylamine (1.1 mL, 7.8 mmol). The mixture was stirred for 14 hours, and the solvents were removed. The residue was diluted with EtOAc, and washed twice with saturated sodium carbonate, followed by water, and then brine, and was dried over Na_2SO_4. Concentration and purification by flash column chromatography (20% EtOAc in hexanes) gave Compound **166** (1.4 g).

Preparation of Example EC

Scheme 104



161 **167** **168** **169** **EC**

I. a. NaOH; b. HCl; V. EDC/HOBt/cmpd **8**; III. a. HCl; b. NaOH;
IV. cmpd **166**/iPr_2NEt

Compound 167

Compound **167** was prepared following the procedure used to prepare Compound **144**, except that Compound **161** was used instead of Compound **143**.

Compound 168

Compound **168** (1.2 g) was prepared following the procedure used to prepare Compound **139a**, except that Compound **167** was used instead of Compound **138a**. m/z: 680.3 $(M+H)^+$.

Compound 169

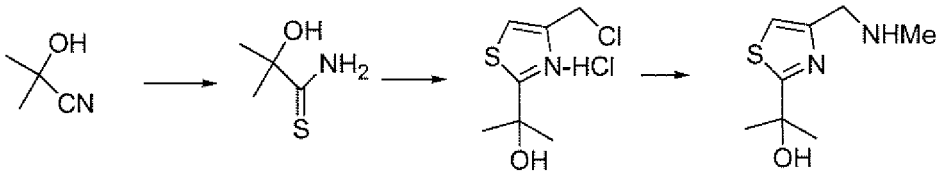
To a solution of Compound **168** (1.2 g, 1.8 mmol) in MeOH (10 mL) was added 4 N hydrochloric acid (4.4 mL, 17.6 mmol). The mixture was stirred for 6 hours, and the solvents were removed. The residue was basified with 2 N sodium hydroxide solution (pH = 11), and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Concentration gave Compound **169** (1.0 g)

Example EC

To a solution of Compound **169** (116 mg, 0.2 mmol) in CH_3CN (2 mL) was added Compound **166** (71 mg, 0.22 mmol), followed by triethylamine (71 •L, 0.4 mmol). The mixture was stirred for 48 hours, and was diluted with EtOAc. The organic layer was washed with saturated sodium carbonate solution, water, and brine, was dried over Na_2SO_4. Purification by flash column chromatography (0-15% iPrOH in DCM) gave compound 1073 (130 mg). m/z: 763.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.75 (1 H, s), 7.78 (1 H, s), 7.67 (1 H, br), 7.3-7.0 (11 H, m), 6.22 (1 H, m), 5.24 (2 H, s), 5.16 (2 H, s), 5.10 (1 H, br), 4.28-4.10 (2 H, m), 3.8 (1 H, m), 3.6 (4 H, m), 3.32 (1 H, m), 2.9-2.6 (4 H, m), 2.4-2.1 (6 H, m), 1.8 (2 H, m), 1.6 (2 H, m), 1.4 (8 H, m).

Preparation of Compound 173

Scheme 105



170 **171** **172** **173**

Compound 170

Compound **170** was obtained from Aldrich.

Compound 171

Hydrogen sulfide gas was passed through a solution of Compound **170** (1.8 mL, 20 mmol) in pyridine (100 mL) and triethylamine (4.4 mL) for 5 hours. The solution was purged with nitrogen for 10 minutes, and the solvents were removed. The residue was coevaporated three times with 10 mL of ethyl alcohol. Purification by flash column chromatography (10% iPrOH in DCM) gave Compound **171** (2.0 g).

Compound 172

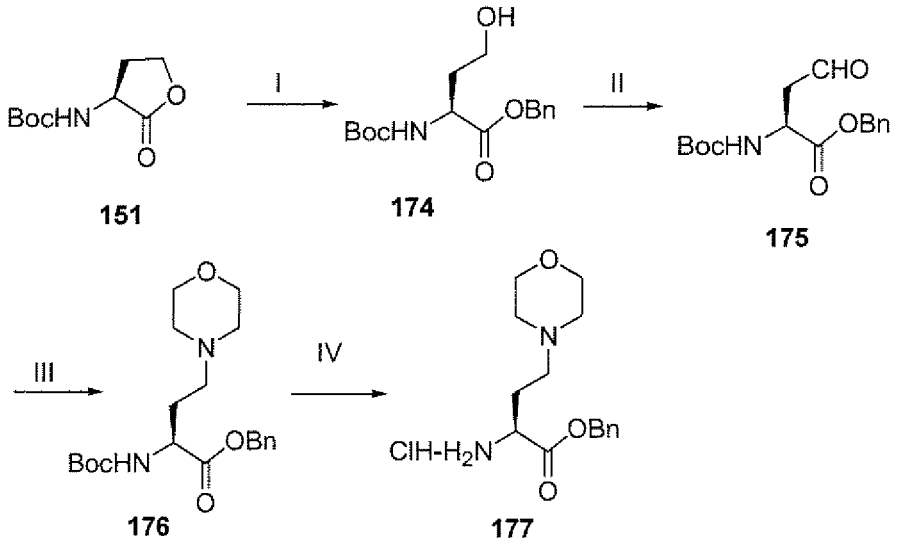
To a solution of Compound **171** (2 g, 17 mmol) in acetone (30 mL) was added 1,3-dichloroacetone (2.1 g, 17 mmol), followed by $MgSO_4$ (2.0 g, 17 mmol). The mixture was refluxed for 12 hours and cooled to 25 °C. The mixture was filtered. Concentration gave Compound **172**. m/z: 191.9 $(M+H)^+$.

Compound 173

To a solution of 40% methylamine in water (36 mL) was added a solution of Compound **172** (17 mmol) in water (10 mL). The mixture was stirred for 1 hour, and concentrated under reduced pressure. Purification by flash column chromatography (10% MeOH in DCM) gave Compound **173**. m/z: 187.0 $(M+H)^+$.

Preparation of Compound 177

Scheme 106



151 **174** **175** **176** **177**

I. a. NaOH/EtOH/H_2O; b. BnBr/DMF; II. SO_3-pyridine;
III. morpholine/$NaBH(Oac)_3$/HOAc; IV. HCl

Compound 174

To a solution of Compound **151** (10.5 g, 50 mmol) in ethyl alcohol (160 mL) was added sodium hydroxide solution (2.1 g, 52.5 mmol, 30 mL). The mixture was stirred for 1 hour, and the solvent was removed under reduced pressure. The residue was coevaporated three times with 200 mL of ethyl alcohol. The white solid was dried at 60 °C for 2 hours under high vacuum. To this solid was added DMF (80 mL), followed by benzyl bromide (7.3 mL, 61 mmol). The mixture was stirred for 12 hours in darkness and diluted with EtOAc. The organic phase was washed five times with water followed once with brine, and was then dried over Na_2SO_4. Concentration gave Compound **174** (15 g).

Compound 175

Compound **175** was prepared following the procedure used to prepare Example **DV**, except that Compound **174** was used instead of Example **DU(c)**.

Compound 176

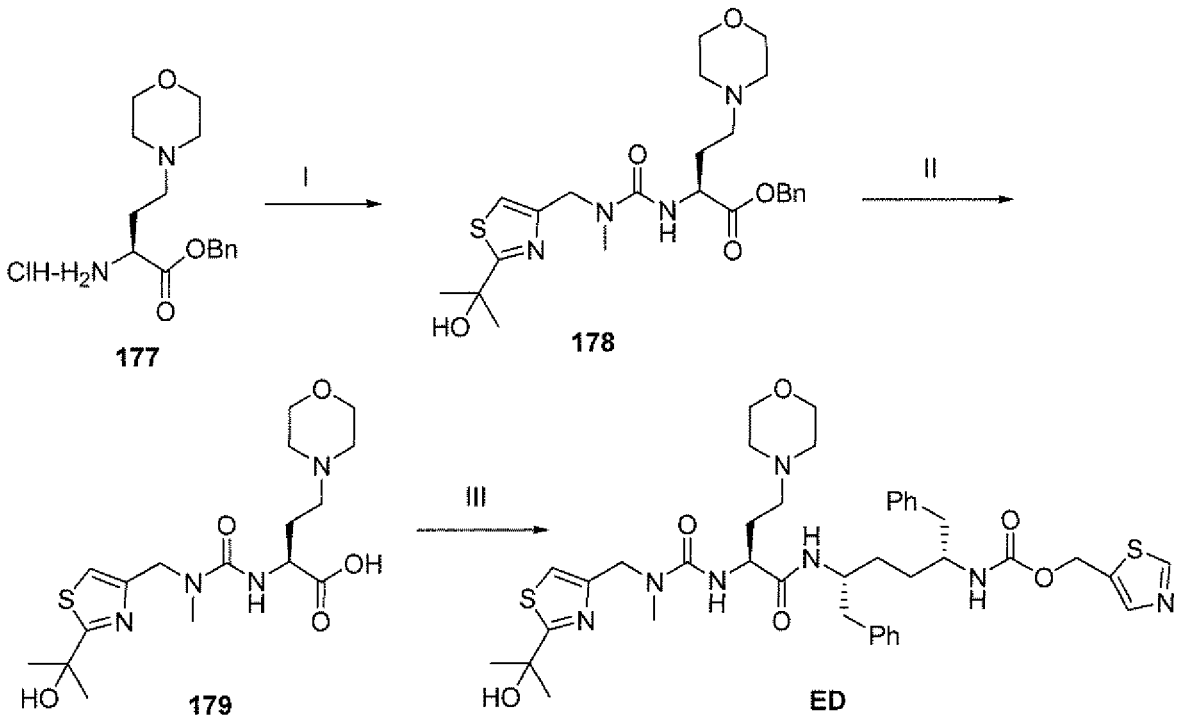
Compound **176** was prepared following the procedure used to prepare Compound **148a**, except that Compound **175** and morpholine were used instead of Compound **60** and 1-acetylpiperazine.

Compound 177

Compound **177** (3.4 g) was prepared following the procedure used to prepare example **140a**, except that Compound **176** was used instead of Compound **139a**. m/z: 279.1 $(M+H)^+$.

Preparation of Example ED

Scheme 107



I. a. CDI/DIPEA; b. cmpd **173**; II. a. NaOH; b. HCl; III. cmpd **8**/EDC/HOBt

Compound 178

Compound **178** (300 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compounds **173** and **177** were used instead of Compounds **140a** and **9**. m/z: 491.3 $(M+H)^+$.

Compound 179

Compound **179** was prepared following the procedure used to prepare Compound **149a**, except that Compound **178** was used instead of Compound **148a**.

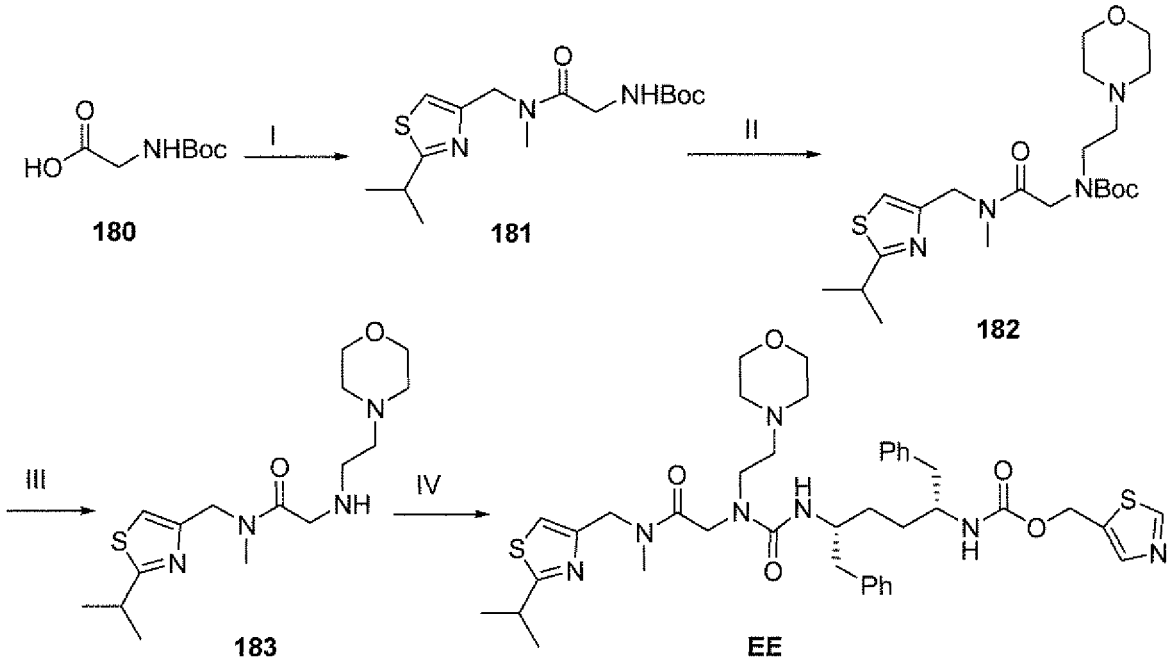
Example ED

Example **ED** (370 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **179** was used instead of Compound **138a**. m/z: 792.3 $(M+H)^+$. ^1H NMR (CD_3OD) • 8.98 (1 H, s), 7.83 (1 H, s), 7.20-7.08 (11 H, m), 5.20 (2 H, m), 4.55 (2 H, m), 4.3-4.0 (4 H, m), 3.75 (3 H, m),

3.4 (2 H, m), 3.2-3.0 (4 H, m), 2.99 (3 H, s), 2.70 (4 H, m), 2.1-1.8 (2 H, m), 1.7-1.4 (10 H, m).

Preparation of Example EE

Scheme 108



I. cmpd **9**/EDC/HOBt; II. a. NaH/DMF; b. 2-morpholineethylbromide;
III. a. TFA/DCM; b. NaOH; IV. a. triphosgene/DIPEA; b. cmpd **8**/DIPEA

Compound 180

Compound **180** was obtained from Aldrich.

Compound 181

Compound **181** (1.6 g) was prepared following the procedure used to prepare Compound **139a**, except that Compounds **180** and **9** were used instead of Compounds **8** and **138a**. m/z: 327.9 $(M+H)^+$.

Compound 182

To a suspension of sodium hydride (52 mg, 60%, 1.3 mmol) in DMF (4 mL) was added a solution of Compound **181** (327 mg, 1 mmol) in DMF (1 mL). The mixture was stirred for 90 minutes, and a solution of 2-morpholineethyl bromide (212 mg, 1.1 mmol) in DMF (1 mL) was added dropwise. The mixture was stirred for 12 hours, and quenched with water. The aqueous phase was extracted three

times with EtOAc. The combined organic phases were washed five times with water and once with brine, and dried over Na_2SO_4. The dried organic phases were concentrated and purified by flash column chromatography (0-10% MeOH in DCM) to give Compound **182** (267 mg). m/z: 441.1 $(M+H)^+$.

Compound 183

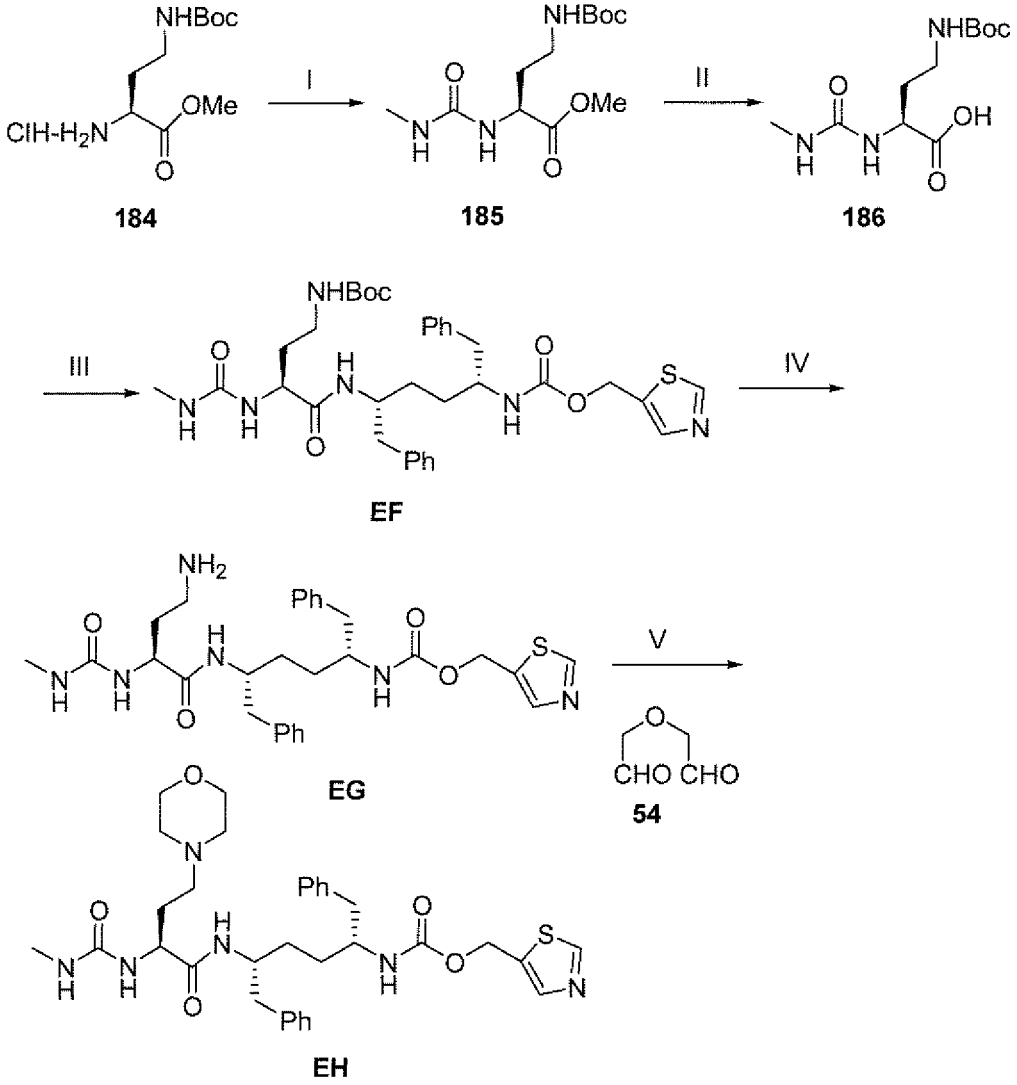
Compound **183** (175 mg) was prepared following the procedure used to prepare Compound **169**, except that Compound **182** was used instead of Compound **168**. m/z: 341.2 $(M+H)^+$.

Example EE

To a solution of triphosgene (56 mg, 0.19 mmol) in DCM (1 mL) at 0 °C was added a solution of Compound **8** (210 mg, 0.51 mmol) and DIPEA (194 •l) in DCM (1.8 mL). The mixture was stirred for 30 minutes, and a solution of Compound **183** (175 mg, 0.51 mmol) and DIPEA (194 •l) in DCM (1 mL) was added. The mixture was warmed to 25 °C and stirred for 12 hours. The mixture was diluted with EtOAc, and washed twice with saturated sodium carbonate, once with water, and once with brine, and was dried over Na_2SO_4. The dried organic phases were concentrated and purified by flash column chromatography (15% iPrOH in DCM) gave Example **EE** (150 mg). m/z: 776.3 $(M+H)^+$. ^1H NMR (CD_3OD) • 8.97 (1 H, s), 7.82 (1 H, s), 7.25-7.05 (11 H, m), 5.21 (2 H, s), 4.6 (2 H, m), 4.3-4.1 (2 H, m), 3.95 (1 H, m), 3.75 (1 H, s), 3.47 (4 H, m), 3.3 (5 H, m), 3.06/2.94 (3 H, s), 2.7 (4 H, m), 2.30 (4 H, m), 1.6-1.2 (10 H, m).

Preparation of Examples EF-EH

Scheme 109



1. a. CDI/DIPEA; b. $MeNH_2$; II.a. NaOH/THF/H_2O; b. HCl;
III.cmpd **8**/EDC/HOBt/DIPEA; IV. a. TFA/DCM; b. NaOH;
V. $NaBH(OAc)_3$/HOAc

Compound 184

Compound **184** was obtained from Aldrich.

Compound 185

Compound **185** (291 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **184** and methylamine were used instead of Compounds **140a** and **9**. m/z: 289.9 $(M+H)^+$.

Compound 186

Compound **186** was prepared following the procedure used to prepare Compound **144**, except that Compound **185** was used instead of Compound **143**. m/z: 275.9 $(M+H)^+$.

Example EF

Example **EF** (102 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **186** was used instead of Compound **138a**. m/z: 667.1 $(M+H)^+$.

Example EG

Example **EG** (144 mg) was prepared following the procedure used to prepare Compound **169**, except that Example **EF** was used instead of Compound **168** m/z: 567.2 $(M+H)^+$.

Compound 54

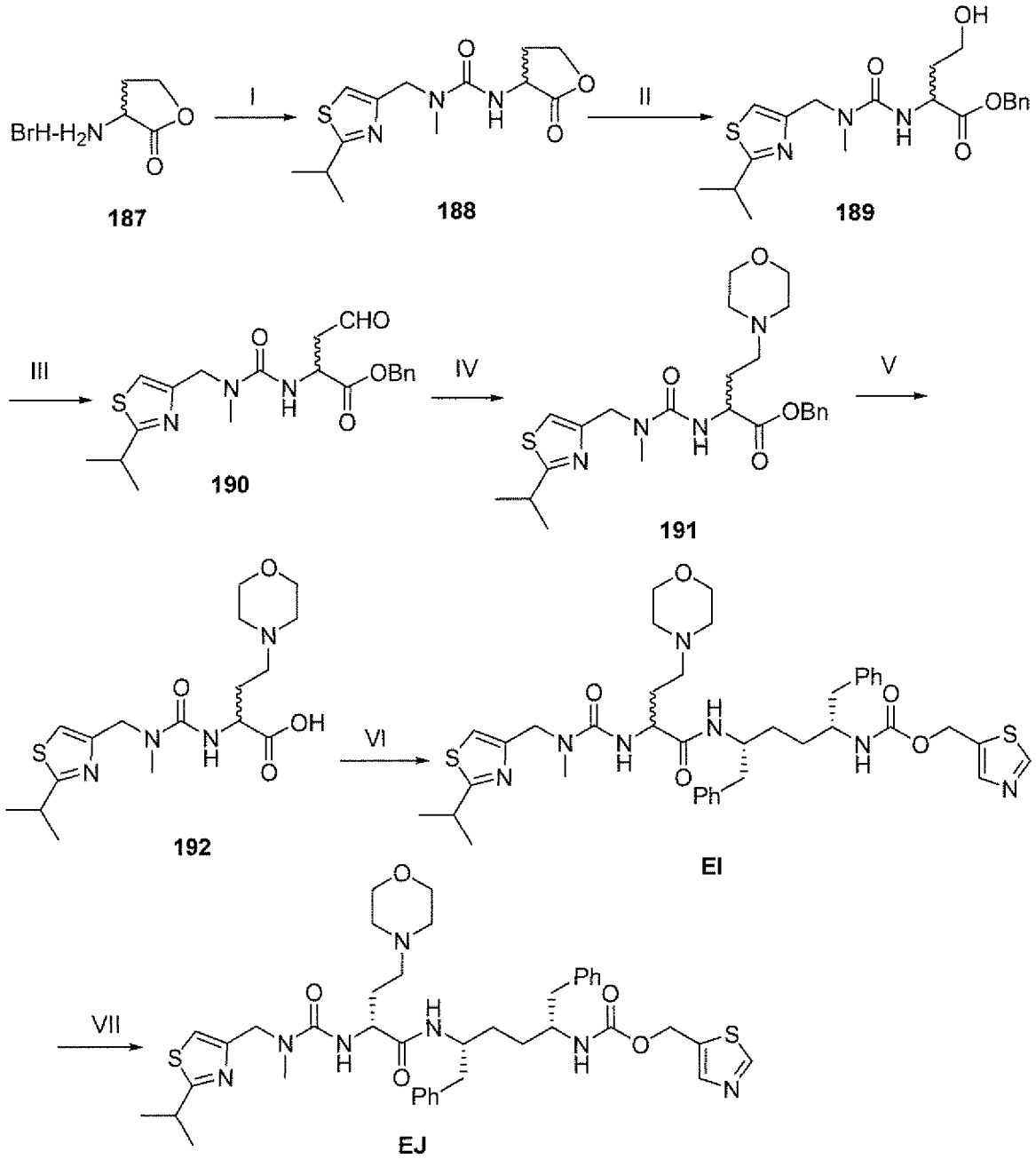
Compound **54** was synthesized following the procedure described in WO2008/010921 A2.

Example EH

Example **EH** (25 mg) was prepared following the procedure used to prepare Compound **148a**, except that Example **EG** and Compound **54** were used instead of Compound **60** and 1-acetylpiperazine. m/z: 637.3 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 9.00 (br s, 1H); 7.94 (br s, 1H); 7.72 (br s, 1H); 7.40-7.00 (m, 10H); 5.49 (m, 1H); 5.25 (s, 2H); 4.47 (m, 1H); 4.30 (m, 1H); 4.02 (br s, 1H); 3.65 (m, 2H); 3.41 (m, 2H); 2.76 (m, 9H); 2.25-1.70 (m, 4H); 1.70-1.40 (m, 6H).

Preparation of Example EI-EJ

Scheme 110



I. a. CDI/DIPEA; b. cmpd **9**; II. a. NaOH/EtOH; b. BnBr/DMF; III. SO3-pyridine/Et_3N; IV. morpholine/$NaBH(OAc)_3$/AcOH/CH_3CN; V. a. NaOH/EtOH/H_2O; b. HCl; IV.cmpd **8**/EDC/HOBt/DIPEA; VII. *chiral column separation*

Compound 187

Compound **187** was obtained from Aldrich.

Compound 188

Compound **188** (897 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compound **187** was used instead of Compound **140a**. m/z: 298.0 $(M+H)^+$.

Compound 189

Compound **189** (1.24 g) was prepared following the procedure used to prepare Compound **174**, except that Compound **188** was used instead of Compound **151**. m/z: 406.1 $(M+H)^+$.

Compound 190

Compound **190** (712 mg) was prepared following the procedure used to prepare Example **DV**, except that Compound **189** was used instead of Example **DU(c)**. m/z: 40.4.0 $(M+H)^+$.

Compound 191

Compound **191** (384 mg) was prepared following the procedure used to prepare Compound **148a**, except that Compound **190** and morpholine were used instead of Compound **60** and 1-acetylpiperazine. m/z: 475.1 $(M+H)^+$.

Compound 192

Compound **192** (900 mg) was prepared following the procedure used to prepare Compound **149a**, except that Compound **191** was used instead of Compound **148a**. m/z: 385.0 $(M+H)^+$.

Example EI

Example **EI** (151 mg) was prepared following the procedure used to prepare Compound **139a**, except that Compound **192** was used instead of Compound **138a**. m/z: 776.2 $(M+H)^+$. ^1H NMR (CD_3OD) • 8.97 (1 H, s), 7.82 (1 H, s), 7.3-7.1 (11 H, m), 5.2 (2 H, s), 4.5 (2 H, m), 4.18 (2 H, m), 3.78 (1 H, m), 3.59 (4 H, m), 3.23 (1 H, m), 2.97 (3 H, s), 2.8-2.5 (4 H, m), 2.5-2.1 (6 H, m), 1.9-1.6 (2 H, m), 1.6-1.3 (10 H, m).

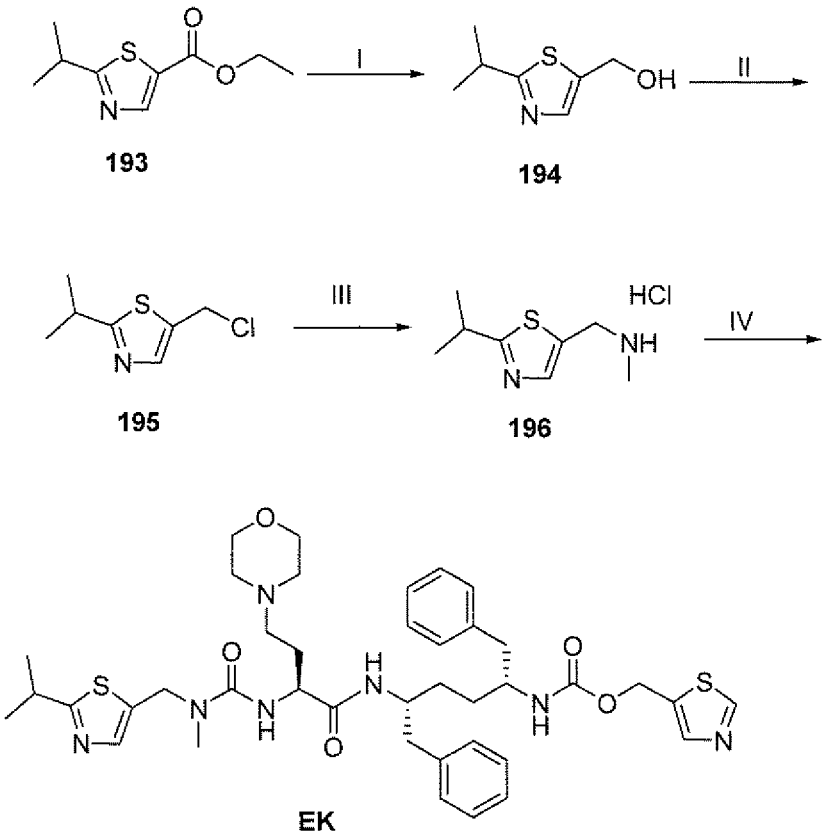
Example EJ

Example **EI** was purified with HPLC (chiral cel OD-H column by Chiral Technologies Inc, heptane/iPrOH = 70/30) to give Example **EJ**. m/z: 776.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) • 8.98 (s, 1H); 7.90 (s, 1H); 7.75 (m, 1H); 7.40-7.00 (m,

15H), 6.55 (br s, 1H); 5.92 (br s, 1H); 7.75 (d, 1H); 5.28, 5.19 (d_{AB}, J=14 Hz, 2H); 4.70-4.37 (m, 3H); 3.99 (m, 5H); 3.76 (br s, 1H); 3.65-3.30 (m, 3H); 2.97 (m, 5H); 2.90-2.60 (m, 7H); 2.28 (br s, 2H); 1.91 (br s, 2H); 1.6-1.3 (m, 12H).

Preparation of Example EK

Scheme 111



I. LiAlH4, THF; II. PCl5, toluene; III. $MeNH_2$in MeOH;
IV.a. CDI/DIPEA; b. cmpd **169**

Compound 193

Compound **193** was synthesized following the procedure from J. Med. Chem., *41(4)*, **1998**, 602-617 (herein incorporated by reference in its entirety for all purposes).

Compound 194

Compound **193** (1.4 g, 7 mmol) was dissolved in anhydrous THF (7 mL) and added dropwise over 1 hour into a 1 M $LiAlH_4$ solution in THF stirring at 0 °C under nitrogen gas. The reaction mixture was then allowed to warm to room temperature and stirred for 1 hour, at which time HPLC showed that reaction was

complete. The reaction mixture was cooled in an ice bath and methanol was slowly added. Aqueous potassium sodium tartarate solution was then added. The organic solution was extracted with ethyl acetate and then dried over anhydrous sodium sulfate and concentrated under reduced pressure to give Compound **194** (1 g, 91%), which was used in the next reaction without further purification.

Compound 195

Compound **194** (1 g, 6.37 mmol) was dissolved in anhydrous toluene (6 mL). To the resulting solution was added PCl_5 (1.3 g, 6.37 mmol). After the reaction mixture was stirred for 1 hour, the reaction was complete. Solid sodium bicarbonate was added to the reaction mixture, which was then diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution, followed by saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to yield Compound **195** (0.91 g, 81%).

Compound 196

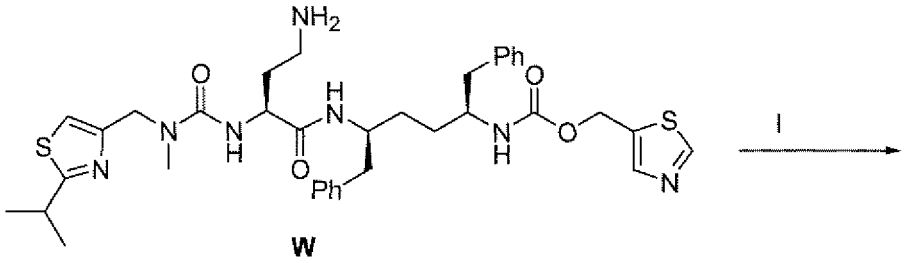
Compound **195** (0.91 g, 5.2 mmol) was dissolved in 2 M methylamine in methanol (15 mL). The reaction mixture was stirred for 15 hours, then concentrated under reduced pressure. The resulting oil was dissolved in dilute aqueous HCl solution to give a solution with a pH of 2. The solution was then washed with ethyl acetate. The aqueous layer was concentrated under reduced pressure. The residue was purified by preparative HPLC to give Compound **196** (0.6 g, 56%).

Example EK

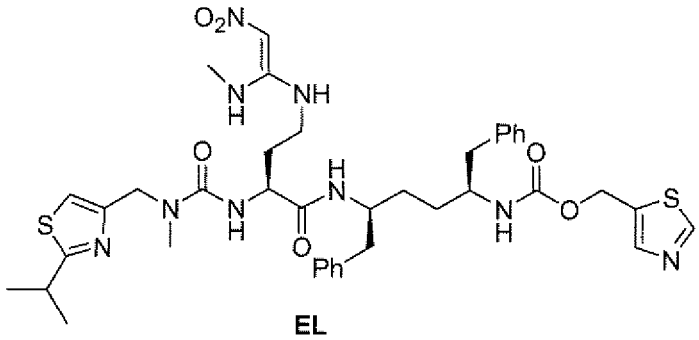
Example **EK** (14 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compounds **169** and **196** were used instead of Compounds **140a** and **9**. ^{1}H NMR (CD_3OD): • 8.98 (s, 1H), 7.82 (s, 1H), 7.55 (s, 1H), 7.19 (m, 10H), 5.21 (m, 2H), 4.68 (m, 2H), 4.20 (m, 1H), 4.15 (m, 1H), 3.79 (m, 1H), 3.64 (m, 4H), 3.25 (m, 1H), 2.98 (s, 3H), 2.73 (m, 4H), 2.23-2.40 (m, 6H), 1.90-1.70 (m, 2H), 1.51 (m, 4H), 1.36 (d, J=6.9 Hz, 6H). Mass Spectrum (*m/e*): $(M+H)^+$ 776.3, $(M-H)^-$ 773.9

Preparation of Example EL

Scheme 112



W



EL

I. a. 1,1-bis(methylthio)-2-nitroethylene/DMF; b. $MeNH_2$/MeOH

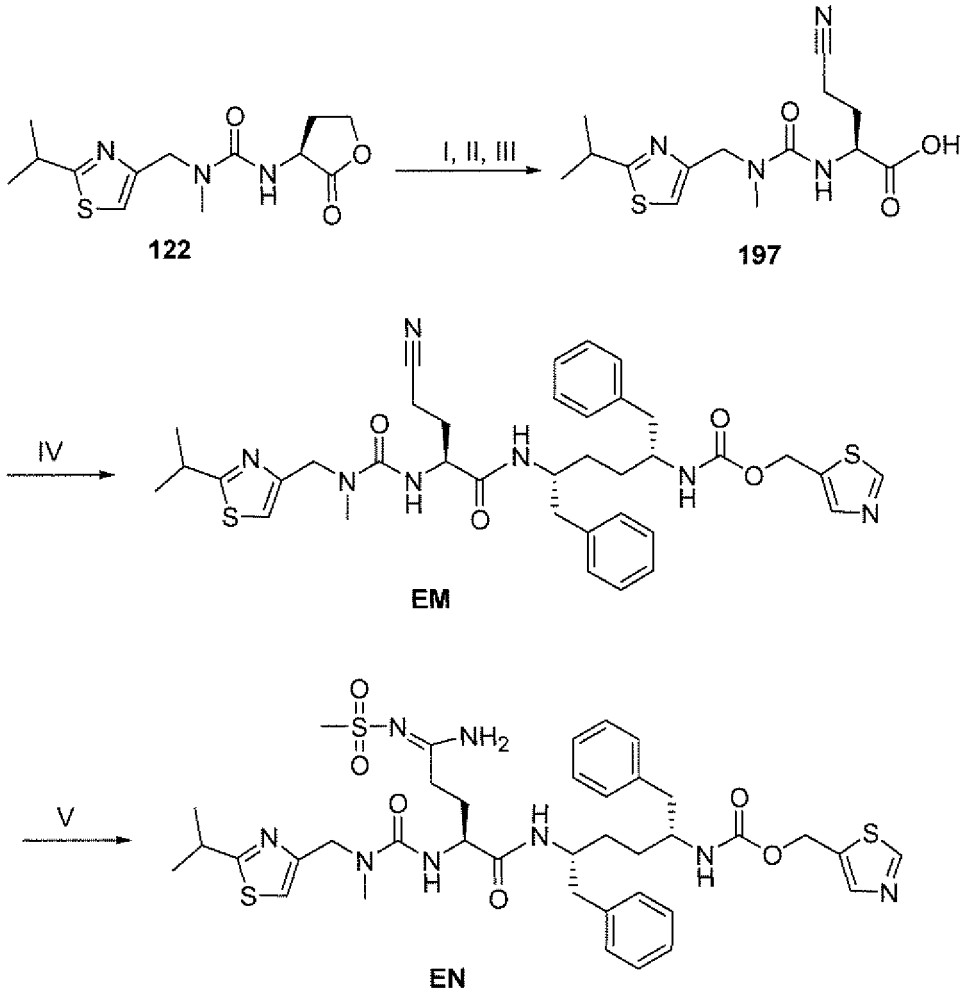
Example EL

Example **W** (71 mg, 0.1 mmol) and 1,1-bis(methylthio)-2-nitroethylene (17 mg, 0.1 mmol) was dissolved in anhydrous DMF (2 mL). The resulting mixture was stirred at room temperature for 90 minutes, followed by another 16 hours at 40 °C. An additional 10% of 1,1-bis(methylthio)-2-nitroethylene was added and the mixture was stirred at 60 °C for 8 hours. A solution of 2 M methylamine in methanol (1.2 mL, 2.4 mmol) was added and the mixture was stirred for 3 hours at room temperature. The mixture was diluted with ethyl acetate and washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude product obtained was purified by flash silica gel column chromatography (3-10% MeOH in DCM). Final purification with C_{18}-reverse phase prep HPLC gave Example **EL** (55 mg, 68%). ^{1}H NMR (CD_3OD): • 8.97 (s, 1H), 7.81 (s, 1H), 7.16 (m, 10H), 6.66 (s, 1H), 5.20 (s, 2H), 4.54 (m, 2H), 4.17 (m, 2H), 3.80 (m, 1H), 3.35 (s, 3H), 3.23 (m, 1H),

3.00-2.80 (m, 9H), 2.63 (m, 3H), 1.60-1.43 (m, 6H), 1.33 (d, J=7.2 Hz, 6H). Mass Spectrum (*m/e*): $(M+H)^+$ 806.3, $(M-H)^-$ 804.1.

Preparation of Examples EM-EN

Scheme 113



I. TMS-I/EtOH; II. KCN/DMSO; III. $NaOH/H_2O/EtOH$; IV. EDC,/HOBt/TEA/THF; V.a. HCl/MeOH; b. $H_2NSO_2NH_2$

Compound 197

Compound **122** (460 mg, 1.5 mmol) was dissolved in anhydrous DCM. To the resulting solution was added EtOH (540 •L, 9.28 mmol), followed by TMS-I (663 •L, 4.6 mmol) dropwise. The mixture was stirred for 2 hours at room temperature. Additional TMS-I (200 •L) was added and the mixture was stirred for 1 hour. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOH and concentrated under reduced pressure. The

residue was again dissolved in another portion of EtOH. The resulting oil was dissolved in anhydrous DMSO (5 mL). KCN was added, and the resulting mixture was stirred at room temperature for 16 hours. The mixture was diluted with ethyl acetate and washed sequentially with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with flash silica gel column chromatography (EtOAc). The product (260 mg, 0.74 mmol) was dissolved in EtOH and stirred in an ice bath. NaOH (33 mg, 0.82 mmol) was dissolved in water and added to the EtOH solution in portions. The reaction mixture was acidified with 10% citric acid to a pH of 2-3 and extracted with EtOAc. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The resulting Compound **197** (228 mg, 47%) was used in the next step without further purification.

Example EM

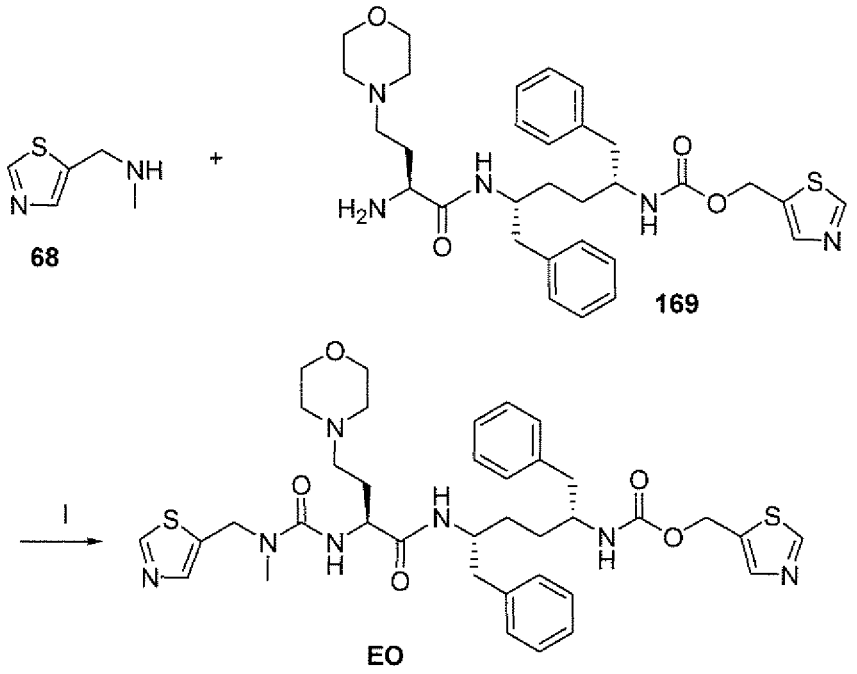
Compound **197** (228 mg, 0.7 mmol) was dissolved in anhydrous THF (5 mL). EDC (202 mg, 1.05 mmol) and HOBt (162 mg, 1.05 mmol) were added to the solution and the resulting mixture was stirred for 30 minutes. Compound **8** (214 mg, 0.7 mmol) was added to the reaction mixture along with anhydrous DMF (3 mL) and TEA (294 •L, 2.11 mmol). The mixture was stirred for 90 minutes, then diluted with EtOAc and washed sequentially with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified with flash silica gel column chromatography (0-10% MeOH in DCM). Final purification with C_{18}–reverse phase prep HPLC gave Example **EM** (291mg, 58%). ^{1}H NMR (CD_3OD): • 8.97 (s, 1H), 7.83 (s, 1H), 7.17 (m, 10H), 5.22 (s, 2H), 4.53 (s, 2H), 4.23 (m, 1H), 4.06 (m, 1H), 3.77 (m, 1H), 3.27 (m, 1H), 2.96 (s, 3H), 2.72 (m, 4H), 2.37 (m, 2H), 1.88 (m, 2H), 1.52 (m, 4H), 1.38 (d, J=7.2 Hz, 6H). Mass Spectrum (*m/e*): $(M+H)^+$ 716.2, $(M-H)^-$ 713.9.

Example EN

Example **EM** (120 mg, 0.168 mmol) was dissolved in anhydrous MeOH (5 mL) and concentrated under reduced pressure. This process was repeated twice with fresh portions of MeOH. The residue was dissolved in MeOH (5 mL) and stirred in an ice bath under nitrogen gas. HCl gas was bubbled into the MeOH solution for 5-10 minutes to saturate the solution. The reaction vessel was sealed and the reaction mixture was stirred at 0 °C for 8 hours. The reaction mixture was then concentrated under reduced pressure at room temperature. The residue was dissolved in EtOAc and washed twice with 10% aqueous sodium carbonate solution, followed by saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in 2-methoxy ethanol (5 mL). Sulfamide (161 mg, 1.68 mmol) was added to the solution, which was stirred at 80 °C for 8 hours and then at room temperature for 16 hours. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed with saturated aqueous sodium bicarbonate solution, followed by saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified with flash silica gel column chromatography (0-10% MeOH in DCM). Final purification with C_{18}-reverse phase prep HPLC gave Example **EN** (16 mg, 12%). ^{1}H NMR (CD_3OD): • 8.98 (s, 1H), 7.83 (s, 1H), 7.67 (m, 1H), 7.16 (m, 10H), 6.82 (m, 1H), 5.21 (s, 2H), 4.53 (m, 2H), 4.15 (m, 2H), 3.77 (m, 1H), 3.28 (m, 1H), 2.96 (s, 3H), 2.68 (m, 4H), 2.21 (m, 2H), 1.88 (m, 2H), 1.45 (m, 4H), 1.35 (d, J=7.2 Hz, 6H). Mass Spectrum (*m/e*): $(M+H)^+$ 812.1, $(M-H)^-$ 810.0.

Preparation of Example EO

Scheme 114



I. a. cmpd **169**/CDI/DIPEA; b. cmpd **68**

Compound 68

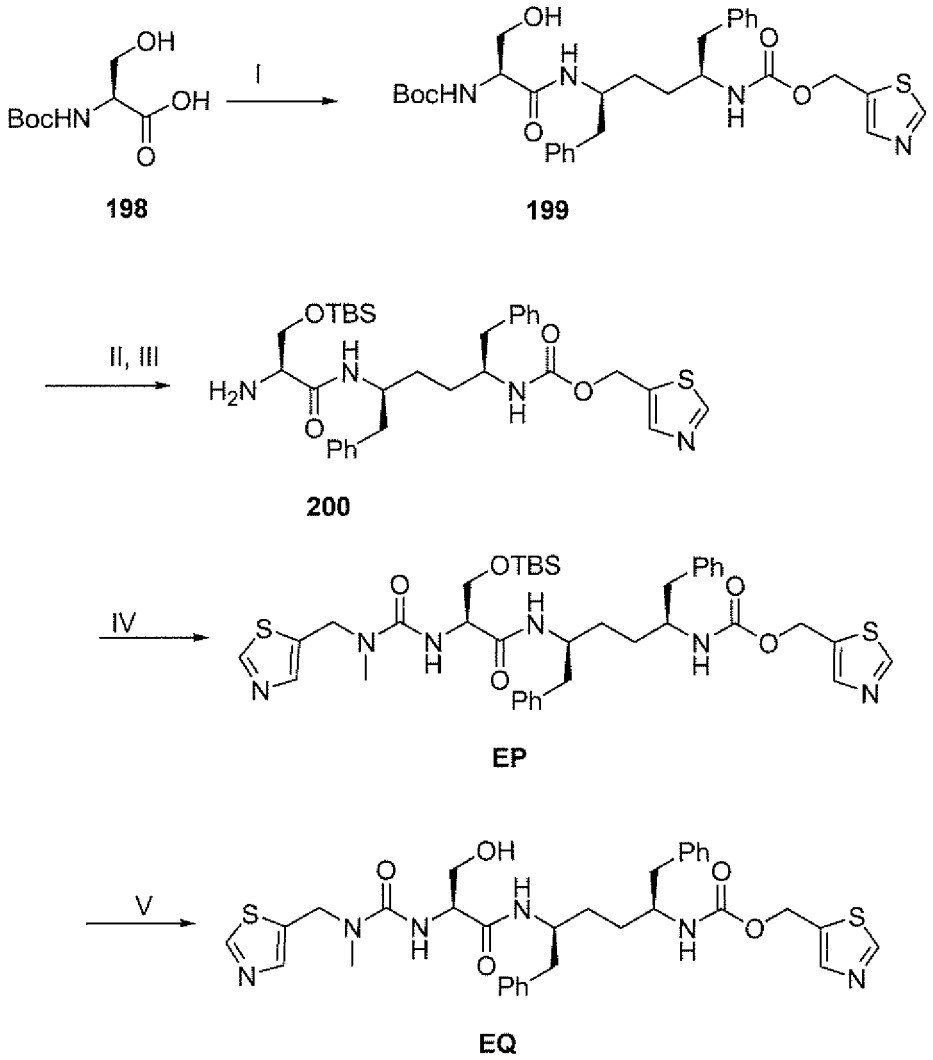
Compound **68** was synthesized following the procedure described in WO2008/010921 A2.

Example EO

Example **EO** (39 mg) was prepared following the procedure used to prepare Example **DM(a)**, except that Compounds **68** and **169** were used instead of Compounds **140a** and **9**. ^{1}H NMR (CD_3OD): • 8.98 (s, 1H), 8.93 (s, 1H), 7.82 (s, 2H), 7.19 (m, 10H), 5.21 (s, 2H), 4.60 (m, 2H), 4.20 (m, 1H), 4.10 (m, 1H), 3.77 (m, 1H), 3.64 (m, 4H), 2.93 (s, 3H), 2.74 (m, 4H), 2.38-2.28 (m, 6H), 1.84-1.70 (m, 2H), 1.50 (m, 4H). Mass Spectrum (*m/e*): $(M+H)^+$ 734.3, $(M-H)^-$ 731.9

Preparation of Example EP-EQ

Scheme 115



I. cmpd **46**/EDC/HOBt/DIPEA; II. HCl/dioxane; III. TBSCl/pyridine;
IV. a. CDI/DIPEA; b.cmpd **68**; V. HCl/dioxane

Compound 198

Compound **198** was obtained from Aldrich.

Compound 199

Compound **198** (205 mg, 1 mmol) was mixed with Compound **46** (446 mg, 1 mmol) and HOBt (230 mg, 1.5 mmol) in anhydrous DMF (5 mL). EDC (230mg, 1.2 mmol) was then added. The resulting mixture was stirred for 30 minutes. DIPEA (348 •L, 2 mmol) was added. The mixture was stirred for 2 hours, then diluted with EtOAc, washed sequentially with saturated aqueous sodium

bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified with flash silica gel column chromatography (0-100% EtOAc in DCM) to give Compound **199** (345 mg, 58%).

Compound 200

Compound **199** (345 mg, 0.58 mmol) was dissolved in a small amount of MeOH. A solution of 4 N HCl in dioxane (5 mL) was added. The resulting mixture was stirred for 1 hour and concentrated under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was dissolved in anhydrous DCM (10 mL). Pyridine (163 •L, 2 mmol) and t-butyldimethylsilyl chloride (166 mg, 1.1 mmol) were added. The resulting mixture was stirred for 15 hours. More pyridine (163 •L) and TBS-Cl (60 mg) were added. The resulting mixture was stirred for another 24 hours. The mixture was concentrated under reduced pressure. The residue was dissolved in EtOAc and washed sequentially with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude material was purified by flash silica gel column chromatography (0-5% MeOH in DCM) to give Compound **200** (248 mg, 69%).

Example EP

Example **EP** was prepared following the procedure used to prepare Example **DM(a)**, except that Compounds **200** and **68** were used instead of Compounds **140a** and **9**.

Example EQ

To Example **EP** was added 4 N HCl in dioxane (4 mL). The mixture was stirred for 1 hour and the solvent was evaporated. The residue was diluted with EtOAc, and washed sequentially with saturated aqueous sodium carbonate, water, and brine. The organic layer was dried over Na_2SO_4, then concentrated.

The residue was purified by flash column chromatography (10% iPrOH in DCM) to give Example **EQ** (35 mg). ^{1}H NMR (CD_3OD): δ 8.97 (s, 1H), 8.89 (s, 1H), 7.81 (s, 2H), 7.70 (m, 1H), 7.19 (m, 10H), 6.92 (m, 1H), 5.20 (s, 2H), 4.73 (m, 2H), 4.22 (m, 1H), 4.13 (m, 1H), 3.78 (m, 1H), 3.56 (d, J=5.4Hz, 2H), 3.31 (m, 1H), 2.94 (s, 3H), 2.67 (m, 4H), 1.45 (m, 4H). Mass Spectrum (*m/e*): $(M+H)^+$ 651.2, $(M-H)^-$ 648.8.

IC_{50} Determinations for Human Liver Cytochrome P450

Materials and General Methods

Pooled (n ≥ 15 donors) human hepatic microsomal fraction was obtained from BD-Gentest (Woburn, MA) who also supplied hydroxy-terfenadine, 4'-hydroxydiclofenac and NADPH regenerating system. Ritonavir was prepared from commercial Norvir® oral solution (Abbott Laboratories, Abbott Park, IL). Other reagents were from Sigma-Aldrich (St. Louis, MO) and included terfenadine, fexofenadine, BRL 15572, diclofenac and mefenamic acid.

Incubations were performed in duplicate in 50 mM potassium phosphate buffer, pH 7.4 with NADPH regenerating system used as described by the manufacturer. The final microsomal protein concentrations had previously been determined to be within the linear range for activity and resulted in less than 20% consumption of substrate over the course of the incubation. The final substrate concentrations used were equal to the apparent Km values for the activities determined under the same conditions. Inhibitors were dissolved in DMSO, and the final concentration of DMSO, from both substrate and inhibitor vehicles, was 1% (v/v). Incubations were performed at 37°C with shaking and were initiated by addition of substrate. Aliquots were then removed at 0, 7 and 15 minutes. Samples were quenched by treatment with an acetonitrile, formic acid, water (94.8%/0.2%/5%, v/v/v) mixture containing internal standard. Precipitated protein

was removed by centrifugation at 3000 rpm for 10 min and aliquots of the supernatant were then subjected to LC-MS analysis.

The LC-MS system consisted of a Waters Acquity UPLC, with a binary solvent manager and a refrigerated (8°C) sample organizer and sample manager, interfaced to a Micromass Quattro Premier tandem mass spectrometer operating in electrospray ionization mode. The column was a Waters Acquity UPLC BEH C_{18} 2.1 x 50 mm, 1.7 μm pore size. Mobile phases consisted of mixtures of acetonitrile, formic acid and water, the composition for mobile phase A being 1%/0.2%/98.8% (v/v/v) and that for mobile phase B being 94.8%/0.2%/5% (v/v/v). The injection volumes were 5 μL and the flow rate was 0.8 mL/min. Concentrations of metabolites were determined by reference to standard curves generated with authentic analytes under the same conditions as the incubations.

IC_{50} values (the concentration of inhibitor reducing CYP3A activity by 50%) were calculated by non-linear regression using GraphPad Prism 4.0 software and a sigmoidal model.

CYP3A Inhibition Assay

The potencies of the compounds as inhibitors of human hepatic cytochromes P450 of the CYP3A subfamily (particularly CYP3A4) were assessed using terfenadine oxidase, a well-characterized CYP3A-selective activity described in Ling, K.-H.J., et al *Drug Metab. Dispos.* **23,** 631-636, (1995) and Jurima-Romet, et al *Drug Metab. Dispos.* **22,** 849-857, (1994). The final concentrations of microsomal protein and terfenadine substrate were 0.25 mg/mL and 3 μM, respectively. Metabolic reactions were terminated by treatment with seven volumes of quench solution containing 0.1 μM BRL 15572 as internal standard. A further 8 volumes of water were added before centrifugation and aliquots of the supernatant were removed for analysis.

For LC-MS analysis chromatographic elution was achieved by a series of linear gradients starting at 20% B and holding for 0.1 minutes, then increasing to 80% B over 1.5 minutes, holding for 0.4 minutes and then returning to the starting conditions for 0.05 min. The system was allowed to re-equilibrate for at least 0.25 minutes prior to the next injection. The mass spectrometer was operated in positive ion mode and the following precursor ($[M+H]^+$)/product ion pairs were monitored and quantified using MassLynx 4.0 (SP4, 525) software: hydroxy-terfenadine 488.7/452.4, fexofenadine 502.7/466.4 and BRL 15572 407.5/209.1. Terfenadine oxidase activity was determined from the sum of hydroxy-terfenadine and carboxy-terfenadine (fexofenadine) metabolites.

CYP2C9 Inhibition Assay

The potencies of the compounds as inhibitors of human hepatic CYP2C9 were assessed using diclofenac 4′-hydroxylase, an activity specific for this enzyme, as described in Leeman, T., et al *Life Sci.* **52,** 29-34, (1992). The final concentrations of microsomal protein and diclofenac substrate were 0.08 mg/mL and 4 μM, respectively. Metabolic reactions were terminated by treatment with three volumes of quench solution containing 1 μM mefenamic acid as internal standard. After centrifugation a further 4 volumes of water were added. Aliquots of the supernatant were then subjected to LC-MS analysis.

For LC-MS analysis chromatographic elution was achieved by a series of linear gradients starting at 20% B and holding for 0.3 minutes, then increasing to 99% B over 1.2 minutes, holding for 0.5 minutes and then returning to the starting conditions for 0.25 min. The system was allowed to re-equilibrate for at least 0.25 minutes prior to the next injection. The mass spectrometer was operated in negative ion mode and the following precursor ($[M-H]^-$)/product ion pairs were monitored and quantified: 4′-hydroxy-diclofenac 312.4/294.2 and mefenamic acid 242.4/224.2.

Biological Assays Used for the Characterization of HIV Protease Inhibitors

HIV-1 Protease Enzyme Assay (*Ki*)

The assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage by HIV-1 protease in a defined reaction buffer as initially described by M.V. Toth and G.R.Marshall, Int. J. Peptide Protein Res. 36, 544 (1990) (herein incorporated by reference in its entirety for all purposes).

The assay employed (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg as the substrate and recombinant HIV-1 protease expressed in E.Coli as the enzyme. Both of the reagents were supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-2992). The buffer for this reaction was 100 mM ammonium acetate, pH 5.3, 1 M sodium chloride, 1 mM ethylendiaminetetraacetic acid, 1 mM dithiothreitol, and 10% dimethylsulfoxide.

To determine the inhibition constant K_i, a series of solutions were prepared containing identical amount of the enzyme (1 to 2.5 nM) and the inhibitor to be tested at different concentrations in the reaction buffer. The solutions were subsequently transferred into a white 96-well plate (190 μl each) and preincubated for 15 min at 37 °C The substrate was solublized in 100% dimethylsulfoxide at a concentration of 800 μM and 10 μl of 800 μM substrate was added into each well to reach a final substrate concentration of 40 μM. The real-time reaction kinetics was measured at 37 °C using a Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at λ(Ex) = 330 nm and λ(Em) = 420 nm. Initial velocities of the reactions with different inhibitor concentrations were determined and the K_i value (in picomolar concentration units) was calculated by using EnzFitter program (Biosoft, Cambridge, U.K.) according to an algorithm for tight-binding competitive inhibition described by Ermolieff J., Lin X., and Tang J., Biochemistry **36**, 12364 (1997).

HIV-1 Protease Enzyme Assay (IC50)

As for the K_i assay, above, the IC_{50} assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage by HIV-1 protease in a defined reaction buffer as initially described by M.V. Toth and G.R.Marshall, Int. J. Peptide Protein Res. 36, 544 (1990).

The assay employed (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg as the substrate and recombinant HIV-1 protease expressed in E.Coli as the enzyme. Both of the reagents were supplied by Bachem California, Inc. (Torrance, CA; Cat. nos. H-2992 and H-9040, respectively). The buffer for this reaction was 100 mM ammonium acetate, pH 5.5, 1 M sodium chloride, 1 mM ethylendiaminetetraacetic acid, and 1 mM dithiothreitol, and 10% dimethylsulfoxide.

To determine the IC50 value, 170 μL of reaction buffer was transferred into the wells of a white 96-well microtiter plate. A series of 3-fold dilutions in DMSO of the inhibitor to be tested was prepared, and 10 μL of the resulting dilutions was transferred into the wells of the microtiter plate. 10 μL of a 20-50 nM enzyme stock solution in reaction buffer was added to each well of the 96-well plate to provide a final enzyme concentration of 1-2.5 nM. The plates were then preincubated for 10 minutes at 37°C. The substrate was solublized in 100% dimethylsulfoxide at a concentration of 400 μM and 10 μl of the 400 μM substrate was added into each well to reach a final substrate concentration of 20 μM. The real-time reaction kinetics were measured using a Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at λ(Ex) = 330 nm and λ(Em) = 420 nm. Initial velocities of the reactions with different inhibitor concentrations were determined and the IC_{50} value (in nanomolar concentration units) was calculated by using GraphPad Prism™ software to fit nonlinear regression curves.

Anti-HIV-1 Cell Culture Assay (EC50)

The assay is based on quantification of the HIV-1-associated cytopathic

effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. HIV-1-induced cell death was determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. **81**, 577 (1989) (herein incorporated by reference in its entirety for all purposes).

MT2 cells (NIH AIDS reagent program, Cat # 237) maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics were infected with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37 °C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01. The infected cells in culture media were distributed into a 96-well plate (20,000 cells in 100 µl/well), and incubated in the presence of a set of solutions containing 5-fold serial dilutions of the tested inhibitor (100 µl/well) for 5 days at 37 °C. Samples with untreated infected and untreated mock-infected control cells were also distributed to the 96-well plate and incubated under the same conditions.

To determine the antiviral activity of the tested inhibitors, a substrate XTT solution (6 mL per assay plate) at a concentration of 2 mg/mL in a phosphate-buffered saline pH 7.4 was heated in water-bath for 5 min at 55 °C before 50 µl of N-methylphenazonium methasulfate (5 µg/mL) was added per 6 mL of XTT solution. After removing 100 µl media from each well on the assay plate, 100 µl of the XTT substrate solution was added to each well. The cells and the XTT solution were incubated at 37 °C for 45 to 60 min in a CO_2 incubator. To inactivate the virus, 20 µl of 2% Triton X-100 was added to each well. Viability, as determined by the amount of XTT metabolites produced, was quantified spectrophotometrically by the absorbance at 450 nm (with subtraction of the

background absorbance at 650 nm). Data from the assay was expressed as the percentage absorbance relative to untreated control and the fifty percent effective concentration (EC_{50}) was calculated as the concentration of compound that effected an increase in the percentage of XTT metabolite production in infected, compound treated cells to 50% of that produced by uninfected, compound-free cells.

Anti-HIV-1 Cell Culture Assay (EC_{50}) in presence of 40% Human Serum or Human Serum Proteins

This assay is almost identical to the Anti-HIV-1 Cell Culture Assay described above, except that the infection was made in the presence or absence of 40% human serum (Type AB Male Cambrex 14-498E) or human serum proteins (Human α-acid Glycoprotein, Sigma G-9885; Human Serum Albumin, Sigma A1653, 96-99%) at physiological concentration. The HIV-1-induced cell death was determined as described above, except that the infected cells distributed in the 96-well plate were incubated in 80% Human Serum (2X concentration) or in 2 mg/mL Human α-acid Glycoprotein + 70 mg/mL HSA (2X concentration) rather than in culture media.

Cytotoxicity Cell Culture Assay (CC_{50})

The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. **81,** 577 (1989). This assay is almost identical to the previous assay described (Anti-HIV-1 Cell Culture Assay), except that the cells were not infected. The compound induced cell death (or growth reduction) was determined as previously described.

MT-2 cells maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics were distributed into a 96-well plate (20,000 cells in 100

μl/well) and incubated in the presence or absence of 5-fold serial dilutions of the tested inhibitor (100 μl/well) for 5 days at 37 °C. Controls included untreated infected cells and infected cells protected by 1 μM of P4405 (Podophyllotoxin, Sigma Cat # P4405).

To determine cytotoxicity, an XTT solution (6 mL per assay plate) at a concentration of 2 mg/mL in phosphate-buffered saline pH 7.4 was heated in the dark in a water-bath for 5 min at 55 °C before 50 μl of N-methylphenazonium methasulfate (5 μg/mL) was added per 6 mL of XTT solution. After removing 100 μL media from each well on the assay plate, 100 μL of the XTT substrate solution was added to each well. The cells and the XTT solution were incubated at 37 °C for 45 to 60 min in a CO_2 incubator. To inactivate the virus, 20 μl of 2% Triton X-100 was added to each well. Viability, as determined by the amount of XTT metabolites produced, is quantified spectrophotometrically by the absorbance at 450 nm (with subtraction of the background absorbance at 650 nm). Data from the assay is expressed as the percentage absorbance relative to untreated control, and the fifty percent cytotoxicity concentration (EC_{50}) was calculated as the concentration of compound that effected an increase in the percentage of cell growth in compound treated cells to 50% of the cell growth provided by uninfected, compound-free cells.

Experimental data based on representative Examples **A-EQ** demonstrate that the compounds of Formula (IV) of the present invention can have a CYP450 3A4 inhibition activity in a range represented by an IC_{50} from about 100 nM to about 4700 nM, and a CYP450 2C9 inhibition activity in a range represented by an IC_{50} from about 100 nM to about 10,000 nM.

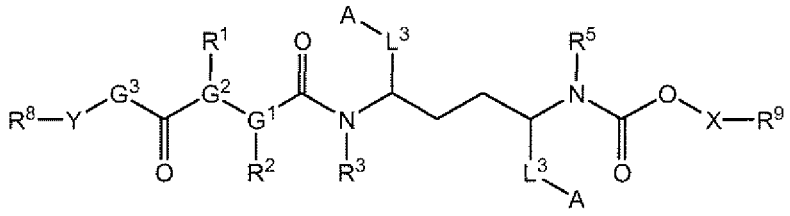
Experimental data based on representative Examples **A-EQ** demonstrate that the compounds of Formula (IV) of the present invention can have a protease

inhibition activity in a range represented by HIV EC_{50} from about 140 nM to greater than about 30000 nM.

Experimental data based on representative Examples **P**, **S**, and **T** have a CYP450 3A4 inhibition activity in a range represented by an IC_{50} from about 80-150 nM, a CYP450 2C9 inhibition activity in a range represented by an IC_{50} from about 1000-10,000 nM, and a protease inhibition activity in a range represented by HIV EC_{50} greater than about 30,000 nM.

What is Claimed:

1. A compound of formula IV,



Formula IV

or a pharmaceutically acceptable salt, solvate, and/or ester thereof, wherein,

each L^3 is independently an alkylene or substituted alkylene;

each A is independently an aryl or substituted aryl;

X is heterocyclylalkyl;

Y is heterocyclylalkyl or alkyl;

G^1 and G^2 are independently CH or N, with the proviso that G^1 and G^2 are different;

G^3 is $-NR^7-$ or $-O-$;

R^1, R^3, R^5, and R^7 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

R^2 is independently selected from the group consisting of substituted alkyl, alkoxyalkyl, hydroxyalkyl, trialkylsiloxyalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-$N(R^a)$-C(O)-alkyl, -alkylene-NR^a-C(O)-$N(R^a)_2$, -alkylene-NR^a-C(=N-R^b)-$N(R^a)_2$, -alkylene-C(=N-R^b)-$N(R^a)_2$, -alkylene-C(O)-OH, -alkylene-C(O)-Oalkyl, and -alkylene-C(O)-$N(R^c)_2$;

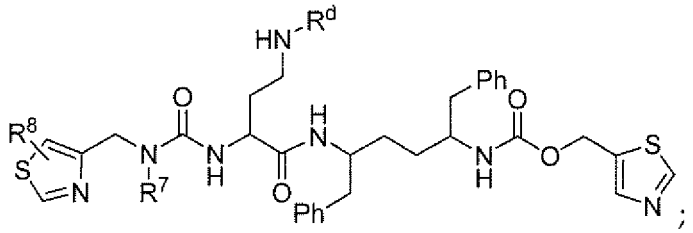
R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, and –CN;

each R^a is independently selected from the group consisting of H, alkyl, and substituted alkyl;

R^b is selected from the group consisting of H, alkyl, substituted alkyl, CN, and –$S(O_2)$-alkyl; and

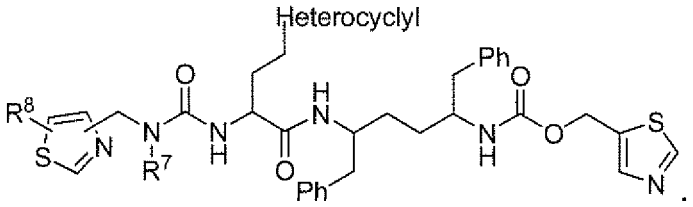
each R^c is independently selected from the group consisting of H, alkyl, substituted alkyl, heterocyclyl, substituted heterocyclyl, –$S(O_2)$-alkyl, –$S(O_2)$-aryl, and substituted –$S(O_2)$-aryl.

2. The compound of claim 1, having the following formula:



wherein R^d is selected from the group consisting of H, haloalkyl, –C(O)-$N(R^a)_2$, -C(=N-R^b)-$N(R^a)_2$, hydroxyalkyl, -$C(N(R^a)_2)$=$CHNO_2$, -C(O)-alkyl.

3. The compound of claim 1, having the following formula:



4. The compound of claim 3, wherein said Heterocyclyl is a substituted or unsubstituted heteroaryl.

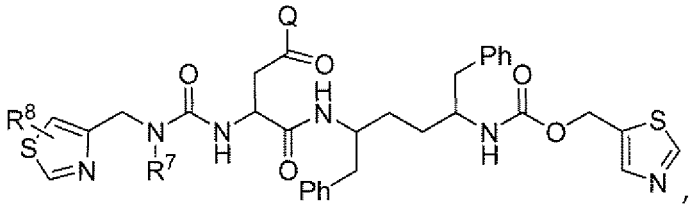
5. The compound of claim 4, wherein said heteroaryl is selected from the group consisting of triazolyl, pyrrolyl, imidazolyl, pyridyl, pyrazolyl, and imidazolidin-dionyl.

6. The compound of claim 3, wherein said Heterocyclyl is a substituted or unsubstituted heterocycloalkyl.

7. The compound of claim 6, wherein said heterocycloalkyl is selected from the group consisting of pyrrolidinonyl, pyrrolidine-dionyl, oxazolidinonyl, pyrrolidinyl, piperidinyl, piperidinonyl, piperazinyl, thiomorpholinyl, and morpholinyl.

8. The compound of claim 7, wherein said heterocycloalkyl is morpholinyl.

9. The compound of claim 1, having the following formula:

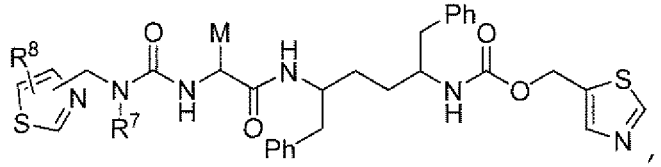


wherein Q is –OH or -N(R^a)$_2$.

10. The compound of claim 9, wherein Q is –OH.

11. The compound of claim 9, wherein Q is -NHR^a, and R^a is substituted or unsubstituted heterocyclyl or sulfonylalkyl.

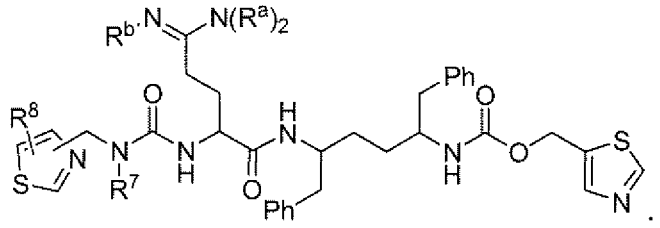
12. The compound of claim 1, having the following formula:



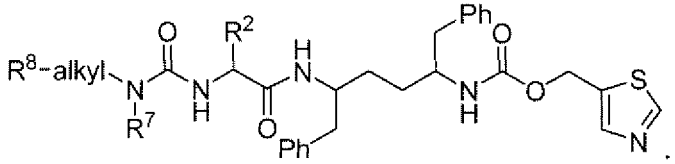
wherein M is substituted alkyl.

13. The compound of claim 12, wherein said substituted alkyl is selected from hydroxyalkyl, substituted hydroxyalkyl, cyanoalkyl, substituted cyanoalkyl, and trialkylsiloxyalkyl.

14. The compound of claim 1, having the following formula:



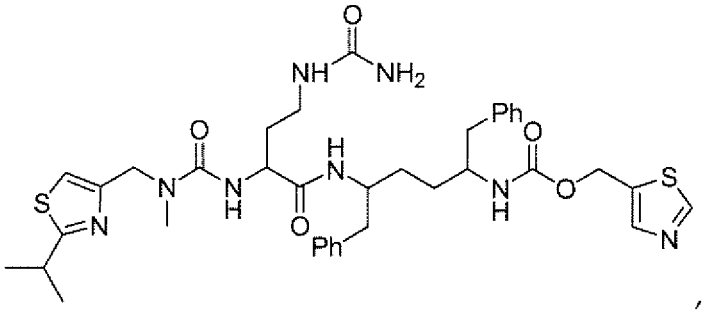
15. The compound of claim 1, having the following formula:



16. The compound of claim 15, wherein R^8 is H.

17. The compound of claim 15, wherein R^2 is aminoalkyl or heterocyclylalkyl.

18. The compound of claim 1, selected from the group consisting of:



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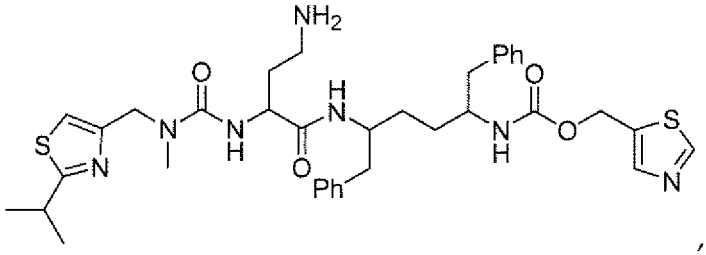

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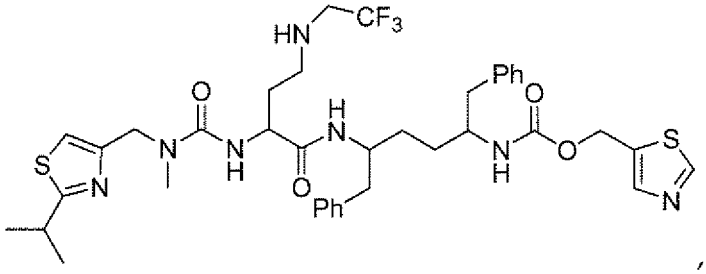

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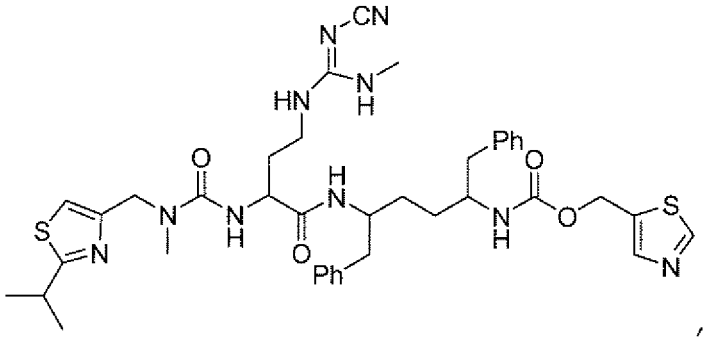

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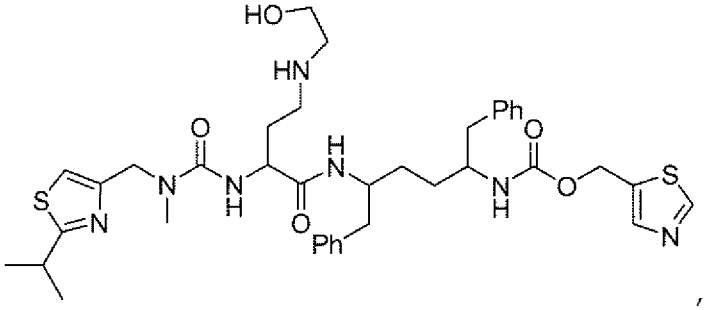

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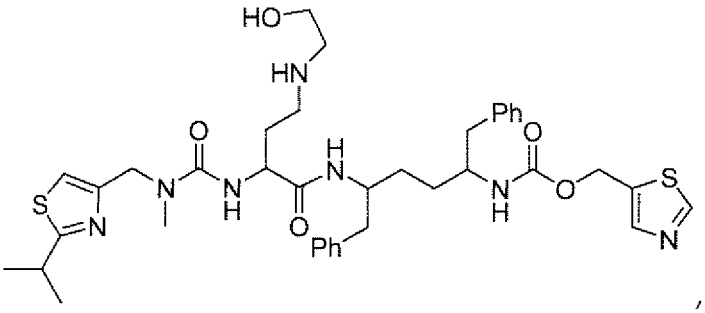

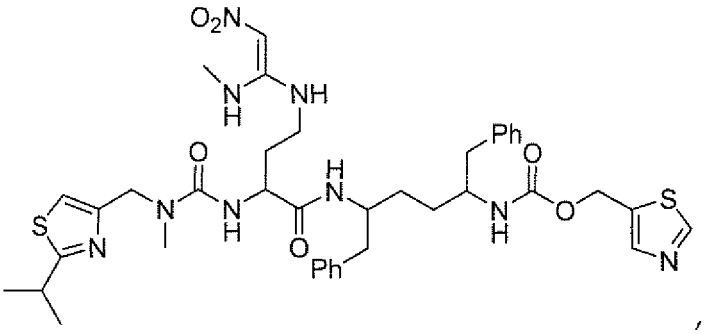

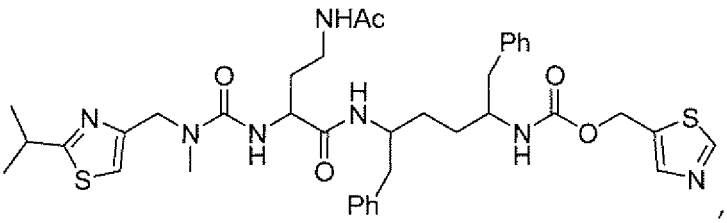

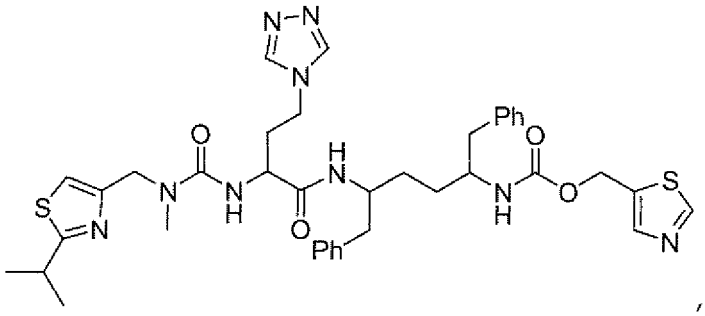

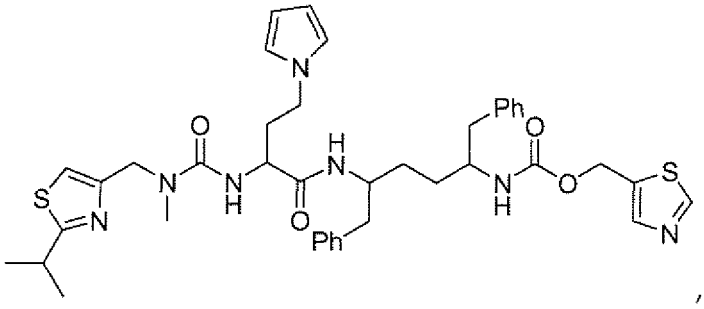

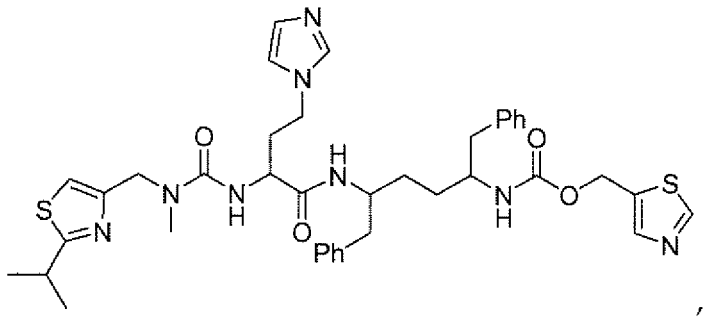

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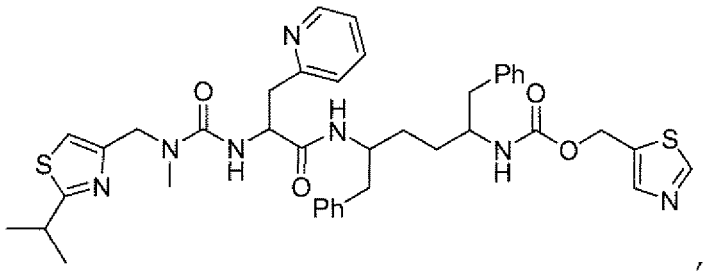

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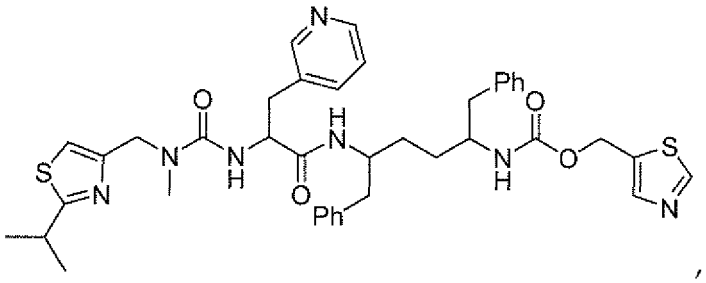

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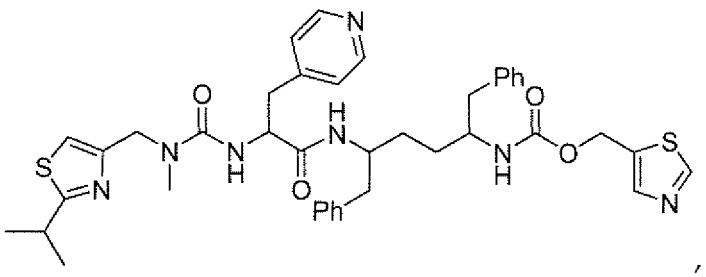

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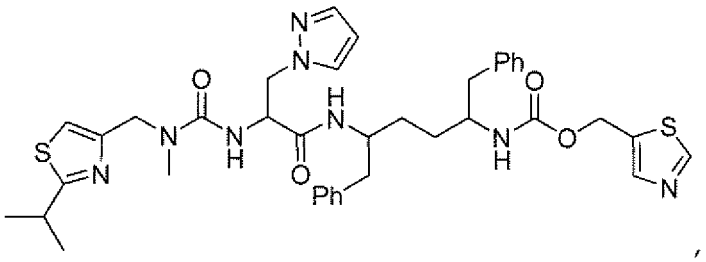

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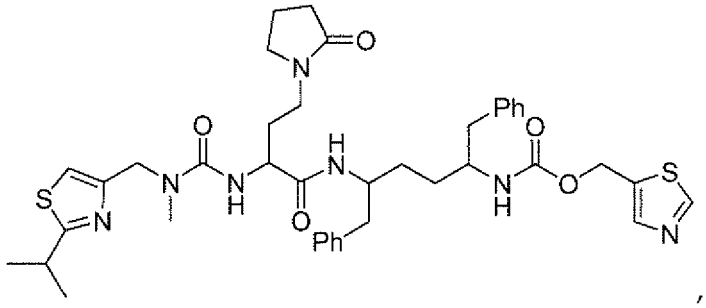

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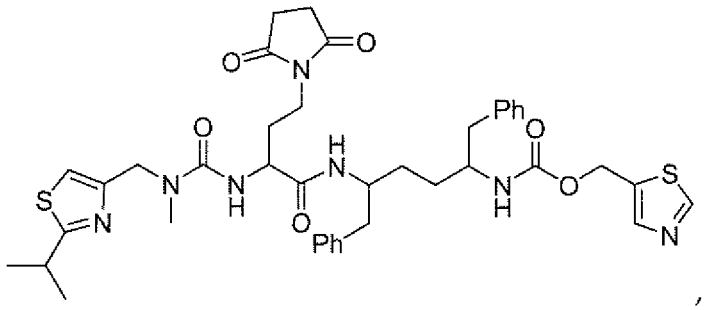

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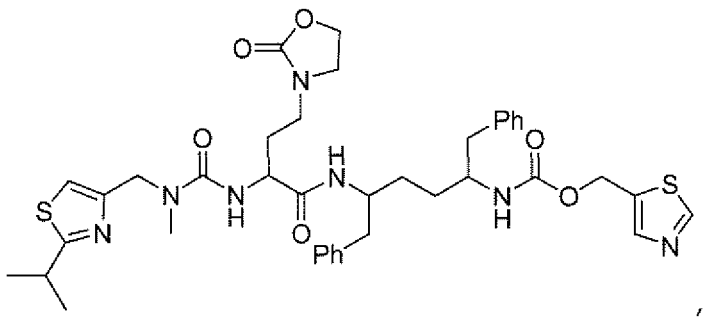

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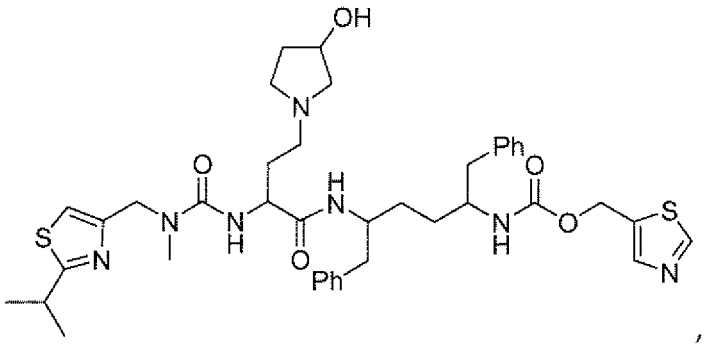

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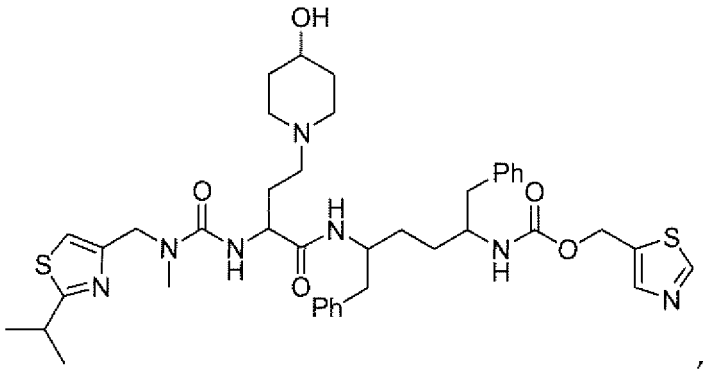

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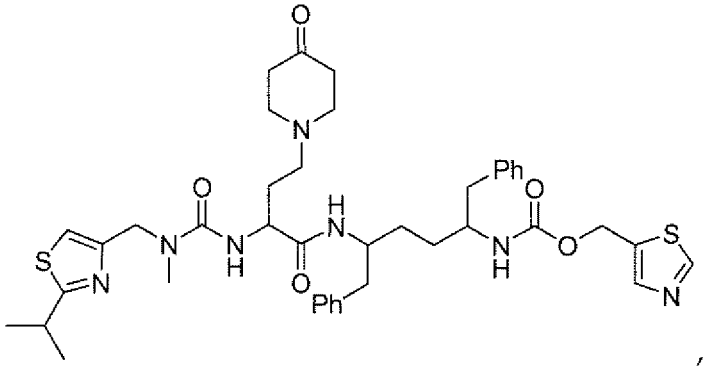

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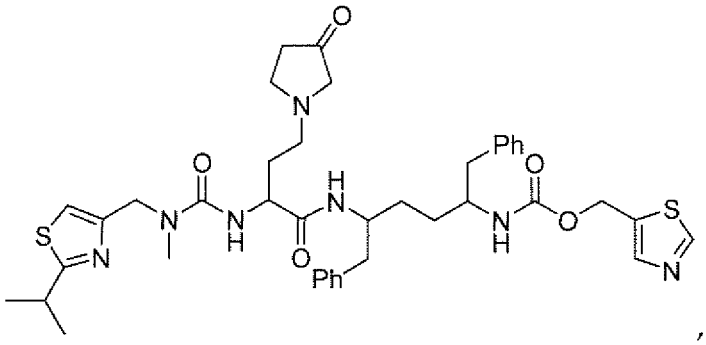

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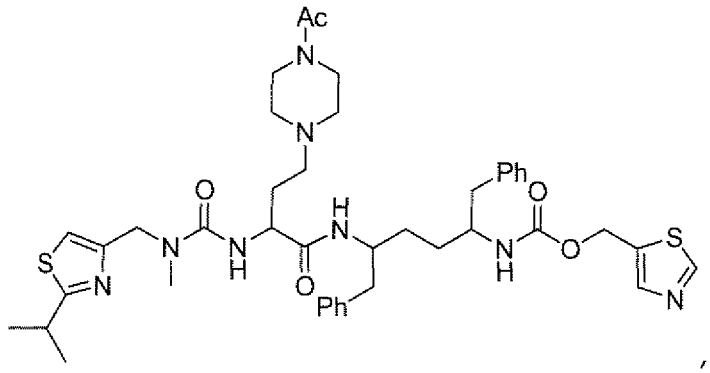

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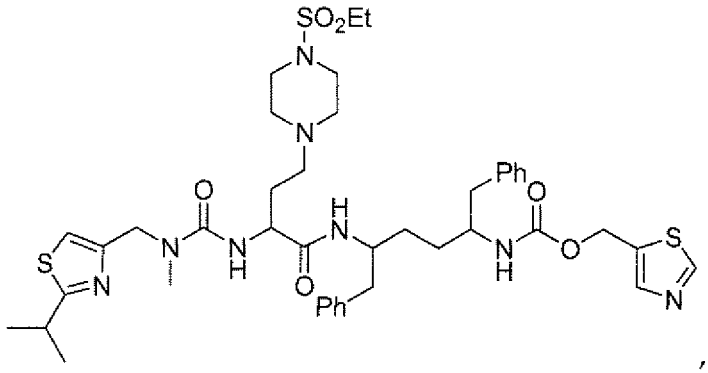

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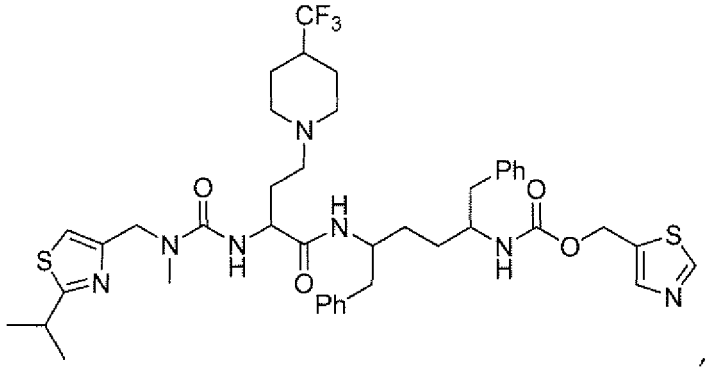

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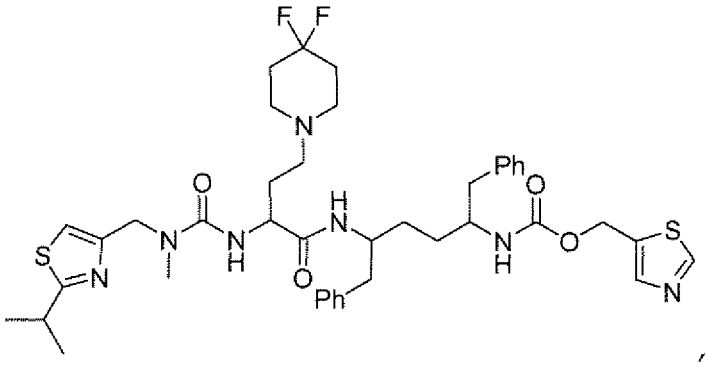

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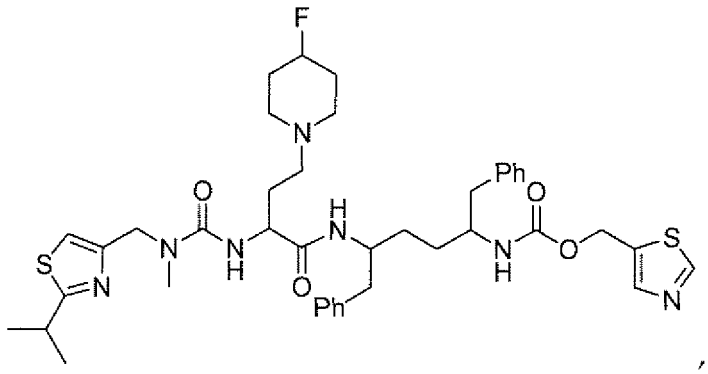

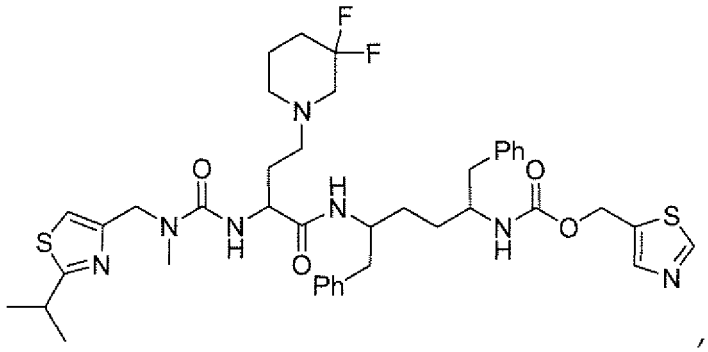

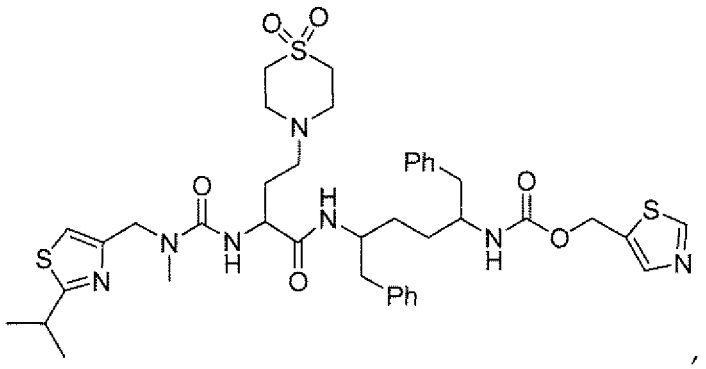

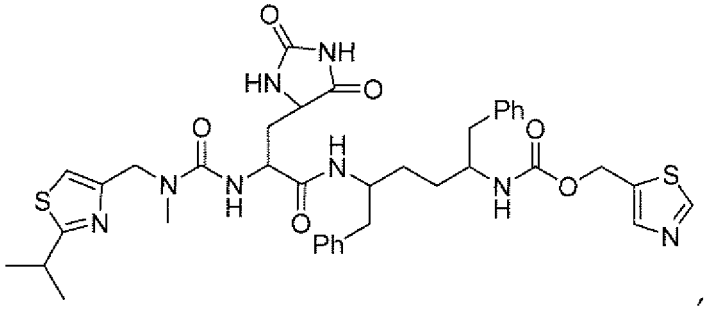

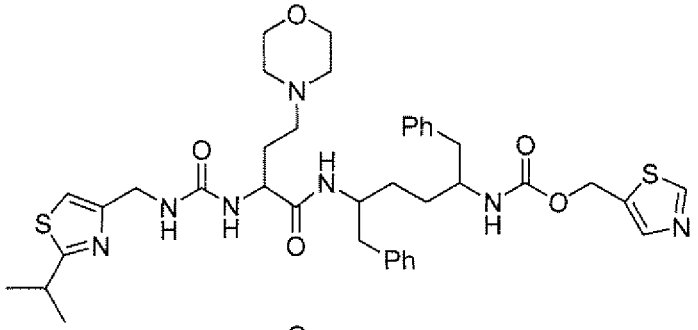

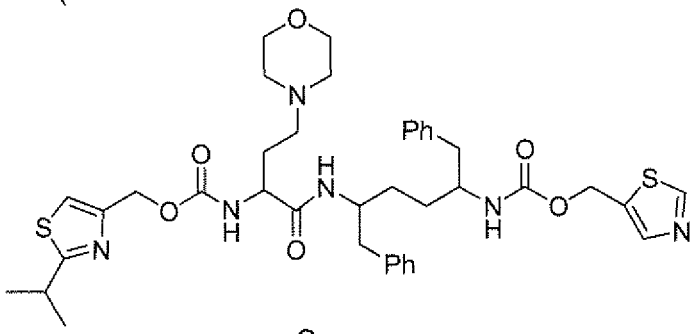

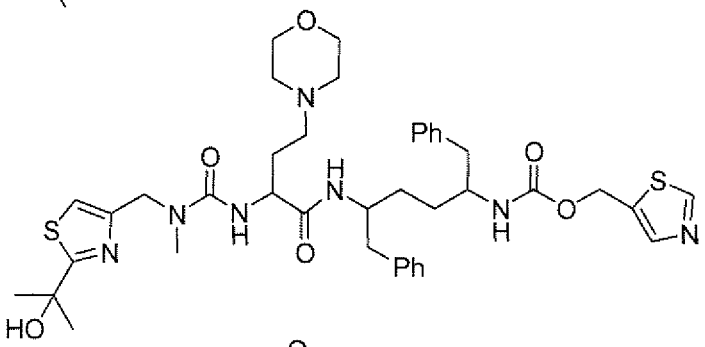

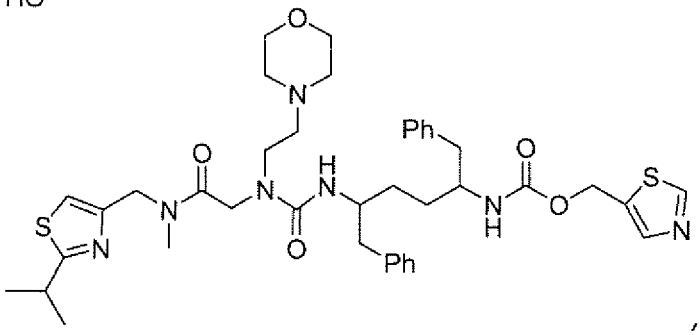

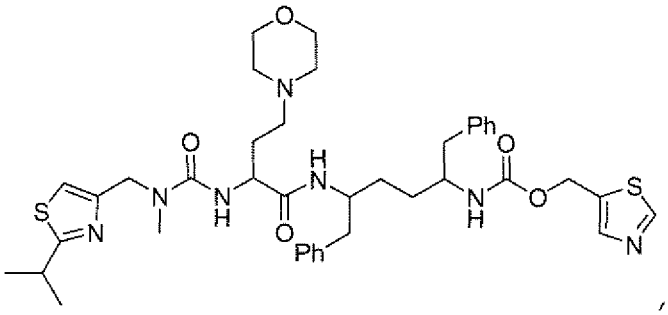

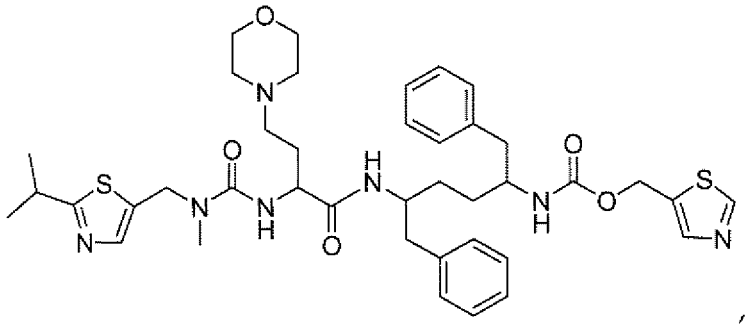

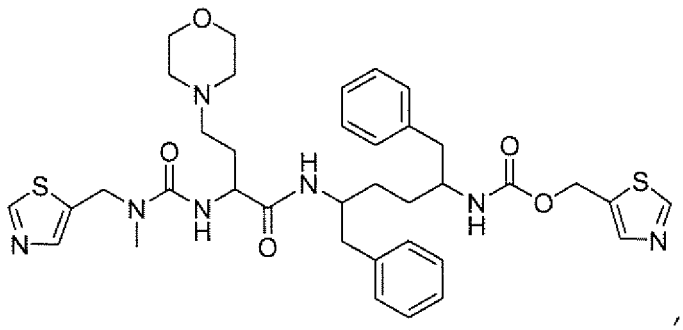

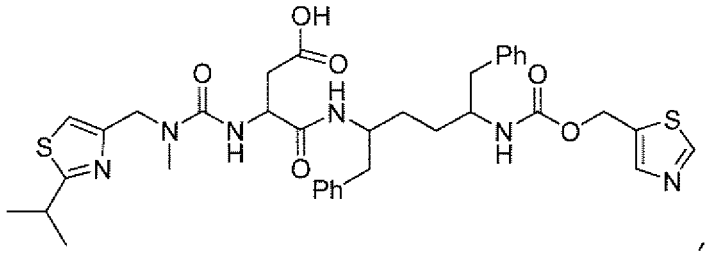

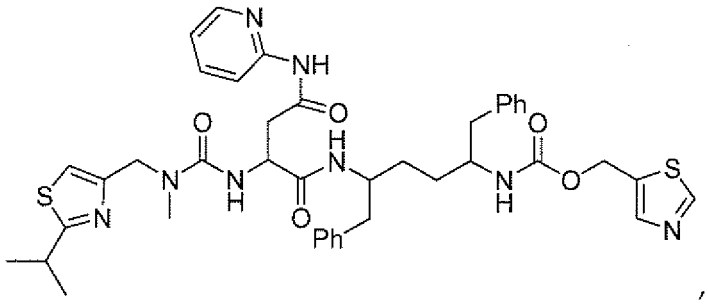

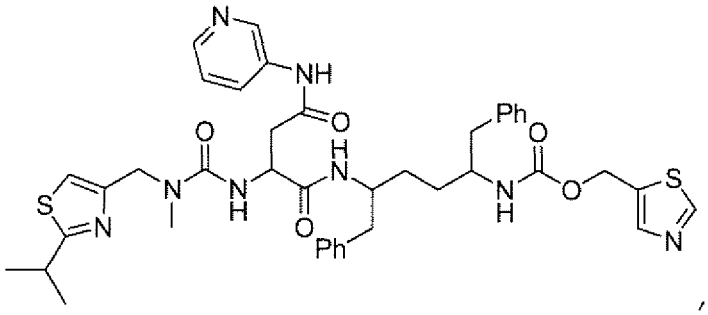

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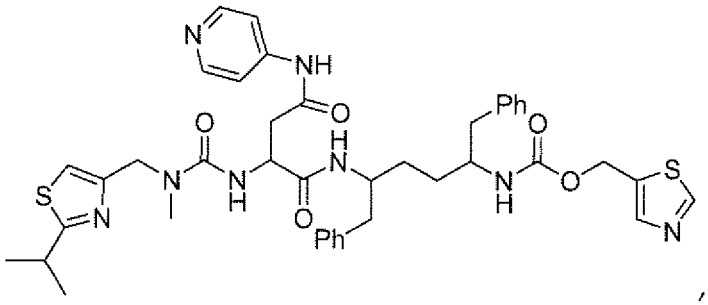

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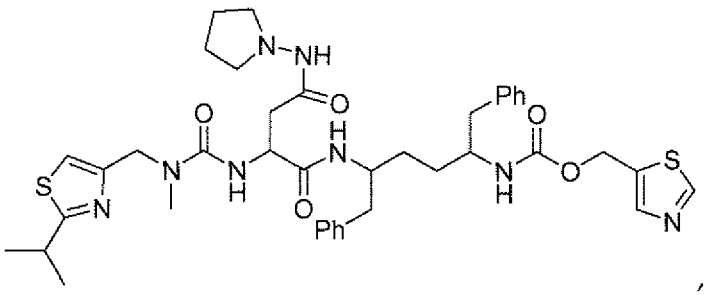

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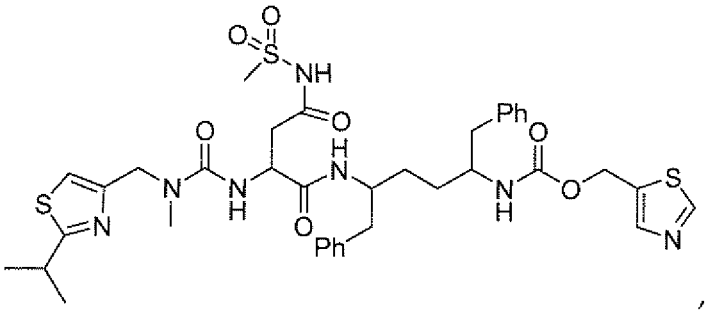

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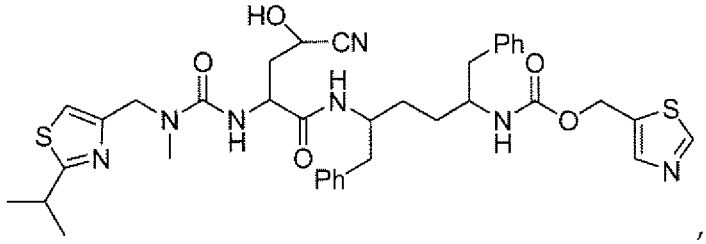

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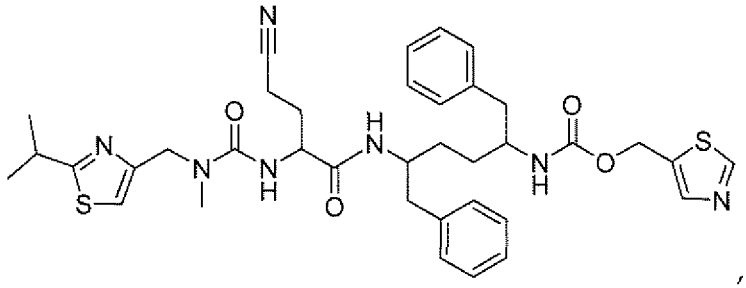

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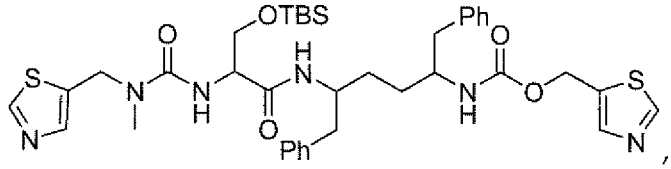

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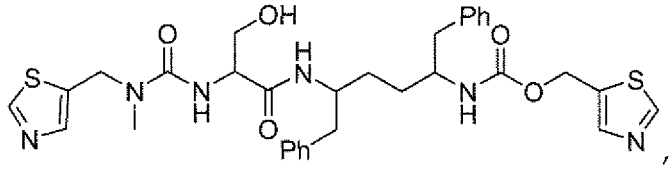

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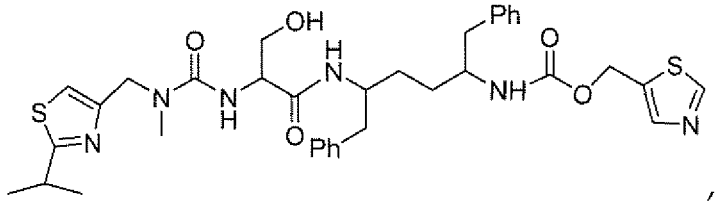

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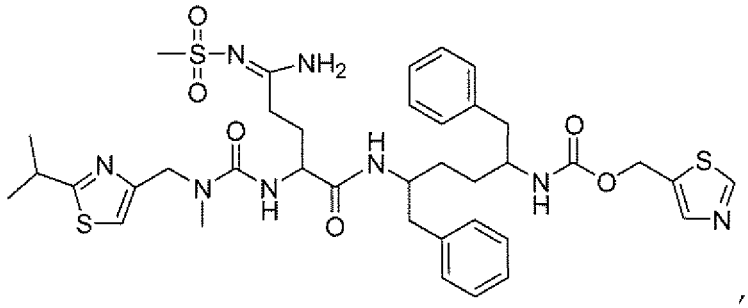

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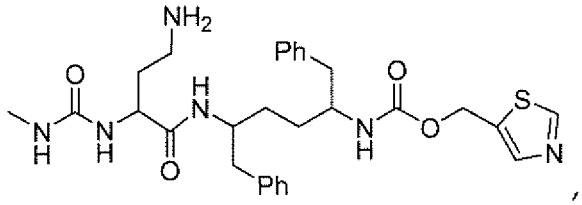
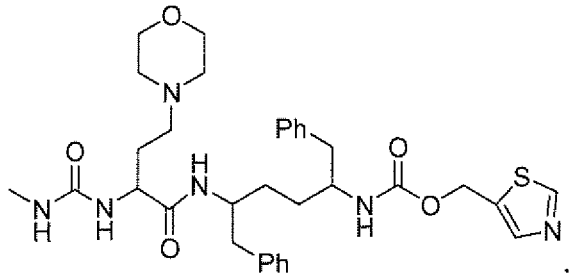
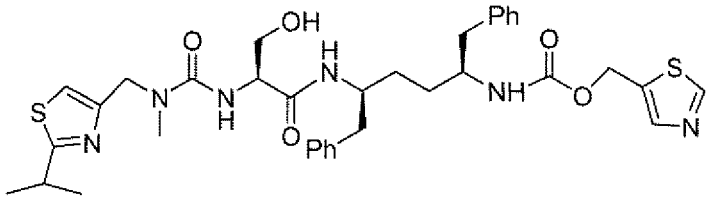


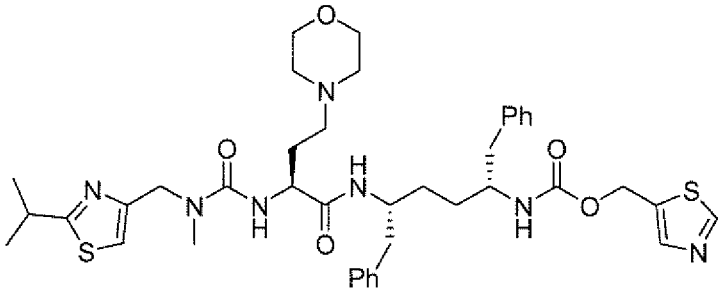


19. A compound which is:



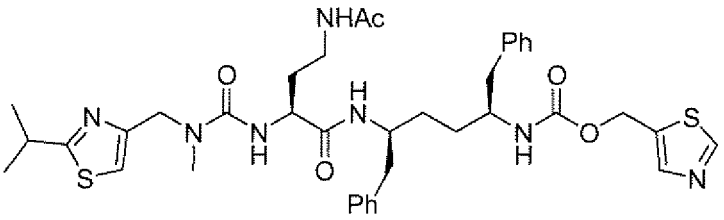
or a pharmaceutically acceptable salt, ester, and/or solvate thereof.

20. A compound which is



or a pharmaceutically acceptable salt, ester, and/or solvate thereof.

21. A compound which is



or a pharmaceutically acceptable salt, ester, and/or solvate thereof.

22. A method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, comprising administering to a patient treated with said drug, a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

23. The method of claim 22 wherein said administering comprises administering a therapeutically effective amount of a combination comprising said drug and the compound of Formula IV or a pharmaceutically acceptable salt, solvate, and/or ester of the compound of Formula IV.

24. The method of claim 22, wherein the drug metabolized by cytochrome P450 is an HIV protease inhibiting compound, an HIV non-nucleoside inhibitor of reverse transcriptase, an HIV nucleoside inhibitor of reverse transcriptase, HIV nucleotide inhibitor of reverse transcriptase, an HIV integrase inhibitor, a gp41 inhibitor, a CXCR4 inhibitor, a gp120 inhibitor, a CCR5 inhibitor, capsid polymerization inhibitors, other drugs for treating HIV, an interferon, ribavirin analog, NS3 protease inhibitor, alpha-glucosidase 1 inhibitor, hepatoprotectant, non-nucleoside inhibitor of HCV, NS5a inhibitors, NS5b polymerase inhibitors, other drugs for treating HCV, or mixtures thereof.

25. The method of claim 23, wherein the drug and the compound or pharmaceutically acceptable salt, solvate, and/or ester thereof of claim 1 is administered as a single composition to the patient.

26. The method of claim 22, wherein said improving is increasing blood plasma levels of the drug which is metabolized by cytochrome P450 monooxygenase.

27. A method for inhibiting cytochrome P450 monooxygenase in a patient comprising administering to a patient in need thereof an amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase.

28. A method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, CCR5 inhibitors, other drugs for treating HIV, and mixtures thereof.

29. The method of claim 28, wherein:

(1) said HIV protease inhibitors are selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) said HIV non-nucleoside inhibitors of reverse transcriptase are selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, TMC-278 (rilpivirene), BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

(3) said HIV nucleoside inhibitors of reverse transcriptase are selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003);

(4) said HIV nucleotide inhibitors of reverse transcriptase are selected from the group consisting of tenofovir disoproxil fumarate, GS-9131, and adefovir dipivoxil;

(5) said HIV integrase inhibitors are selected from the group consisting of curcumin, derivatives of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;

(6) said gp41 inhibitor are selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

(7) said CXCR4 inhibitor is AMD-070;

(8) said entry inhibitor is SP01A;

(9) said gp120 inhibitor is BMS-488043 or BlockAide/ CR;

(10) said G6PD and NADH-oxidase inhibitor is immunitin;

(11) said CCR5 inhibitors are selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) said other drugs for treating HIV are selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

30. A method for treating an HCV infection comprising administering to a patient in need thereof a therapeutically effective amount of a compound of claim 1, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, or mixtures thereof.

31. The method of claim 30, wherein:

(1) said interferons are selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta;

(2) said ribavirin analogs are selected from the group consisting of rebetol, copegus, and viramidine (taribavirin);

(3) said NS5b polymerase inhibitors are selected from the group consisting of NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;

(4) said NS3 protease inhibitor are selected from the group consisting of SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;

(5) said alpha-glucosidase 1 inhibitors are selected from the group consisting of MX-3253 (celgosivir) and UT-231B;

(6) said hepatoprotectants are selected from the group consisting of IDN-6556, ME 3738, LB-84451, and MitoQ;

(7) said non-nucleoside inhibitors of HCV are selected from the group consisting of benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, and A-689; and

(8) said other drugs for treating HCV are selected from the group consisting of zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

32. A pharmaceutical composition comprising a compound of claim 1, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable carrier or exipient.

33. The pharmaceutical composition of claim 32, further comprising at least one additional therapeutic agent metabolized by cytochrome P450.

34. The pharmaceutical composition of claim 33, wherein the at least one additional therapeutic agent is selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, other drugs for treating HCV, and combinations thereof.

35. The pharmaceutical composition of claim 34, wherein:

(1) said HIV protease inhibitors are selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) said HIV non-nucleoside inhibitors of reverse transcriptase are selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

(3) said HIV nucleoside inhibitors of reverse transcriptase are selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), ;

(4) said HIV nucleotide inhibitors of reverse transcriptase are selected from the group consisting of tenofovir disoproxil fumarate, GS-9131, and adefovir dipivoxil;

(5) said HIV integrase inhibitors are selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;

(6) said gp41 inhibitor are selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

(7) said CXCR4 inhibitor is AMD-070;

(8) said entry inhibitor is SP01A;

(9) said gp120 inhibitor is BMS-488043 or BlockAide/ CR;

(10) said G6PD and NADH-oxidase inhibitor is immunitin;

(11) said CCR5 inhibitors are selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) said other drugs for treating HIV are selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040);

(13) said interferons are selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus

IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta;

(14) said ribavirin analogs are selected from the group consisting of rebetol, copegus, and viramidine (taribavirin);

(15) said NS5b polymerase inhibitors are selected from the group consisting of NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;

(16) said NS3 protease inhibitor are selected from the group consisting of SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;

(17) said alpha-glucosidase 1 inhibitors are selected from the group consisting of MX-3253 (celgosivir) and UT-231B;

(18) said hepatoprotectants are selected from the group consisting of IDN-6556, ME 3738, LB-84451, and MitoQ;

(19) said non-nucleoside inhibitors of HCV are selected from the group consisting of benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, and A-689; and

(20) said other drugs for treating HCV are selected from the group consisting of zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

36. A new pharmaceutical composition or use for the preparation of a medicament, comprising a compound of claim 1.

37. A compound of claim 1 as a therapeutic substance.

38. The use of a compound of claim 1 for the manufacture of a medicament for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, increasing the blood plasma level of a drug which is metabolized by cytochrome P450 monooxygenase, inhibiting cytochrome P450 monooxygenase, treating an HIV infection, or treating an HCV infection in a patient.

39. The use of claim 38, wherein said drug which is metabolized by cytochrome P450 monooxygenase is an HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, CCR5 inhibitors, other drugs for treating HIV, an interferon, ribavirin analog, NS3 protease inhibitor, alpha-glucosidase 1 inhibitor, hepatoprotectant, non-nucleoside inhibitor of HCV, and other drugs for treating HCV, or mixtures thereof.

40. The use of claim 39, wherein said medicament is a combination of a compound of claim 1 and one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, G6PD and NADH-

oxidase inhibitors, CCR5 inhibitors, other drugs for treating HIV, interferons, ribavirin analogs, NS5b polymerase inhibitors, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and mixtures thereof.

41. The use of claim 40, wherein:

(1) said HIV protease inhibitors are selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;

(2) said HIV non-nucleoside inhibitors of reverse transcriptase are selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

(3) said HIV nucleoside inhibitors of reverse transcriptase are selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), ;

(4) said HIV nucleotide inhibitors of reverse transcriptase are selected from the group consisting of tenofovir disoproxil fumarate, GS-9131, and adefovir dipivoxil;

(5) said HIV integrase inhibitors are selected from the group consisting of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-

dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, and L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;

(6) said gp41 inhibitor are selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;

(7) said CXCR4 inhibitor is AMD-070;

(8) said entry inhibitor is SP01A;

(9) said gp120 inhibitor is BMS-488043 or BlockAide/ CR;

(10) said G6PD and NADH-oxidase inhibitor is immunitin;

(11) said CCR5 inhibitors are selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(12) said other drugs for treating HIV are selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040);

(13) said interferons are selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta;

(14) said ribavirin analogs are selected from the group consisting of rebetol, copegus, and viramidine (taribavirin);

(15) said NS5b polymerase inhibitors are selected from the group consisting of NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;

(16) said NS3 protease inhibitor are selected from the group consisting of SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;

(17) said alpha-glucosidase 1 inhibitors are selected from the group consisting of MX-3253 (celgosivir) and UT-231B;

(18) said hepatoprotectants are selected from the group consisting of IDN-6556, ME 3738, LB-84451, and MitoQ;

(19) said non-nucleoside inhibitors of HCV are selected from the group consisting of benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, and A-689; and

(20) said other drugs for treating HCV are selected from the group consisting of zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).