

MODULATORS OF PHARMACOKINETIC PROPERTIES OF THERAPEUTICS

FIELD OF THE INVENTION

5 This application relates generally to compounds and pharmaceutical compositions which modify, e.g., improve, the pharmacokinetics of a coadministered 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

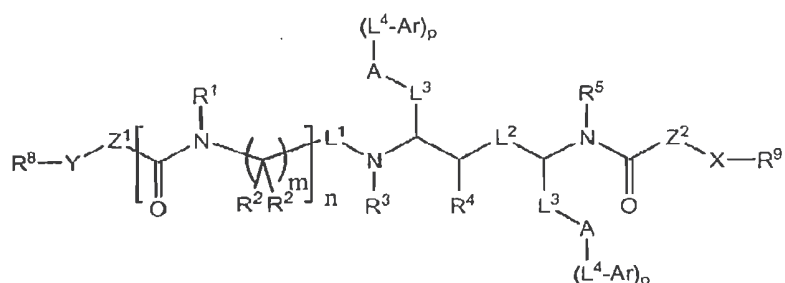
Oxidative metabolism by cytochrome P450 enzymes is one of the primary mechanisms of drug metabolism. It can be difficult to maintain therapeutically effective blood plasma levels of drugs which are rapidly metabolized by cytochrome
15 P450 enzymes. Accordingly, the blood plasma levels of drugs which 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. Known inhibitors include ritonavir, for example, disclosed in WO 97/01349 and US 5,625,523, for example.

20 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
25 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
30 protease inhibitors.

SUMMARY OF THE INVENTION

One aspect of the present application is directed to compounds and
 5 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 I:



Formula I

10

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

L¹ is selected from the group consisting of -C(R⁶)₂-, -C(O)-, -S(O)₂-, -N(R⁷)-C(O)-,
 and -O-C(O)-;

L² is a covalent bond, -C(R⁶)₂- or -C(O)-;

15 each L³ is independently a covalent bond, an alkylene, or substituted alkylene;

each L⁴ is independently selected from the group consisting of a covalent bond,
 alkylene, substituted alkylene, -O-, -CH₂-O-, and -NH-;

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

20 heterocyclyl,

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

Z¹ and Z² are each independently -O- or -N(R⁷)-;

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;

5 R¹, R³, and R⁵ are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

each R² 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;

R⁴ and R⁶ are independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl;

each R⁷ is independently selected from the group consisting of H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, and substituted heterocyclyl;

R⁸ and R⁹ 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;

20 m is 1 or 2;

n is 0 or 1; and

each p is independently 0 or 1.

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 excipient.

In another embodiment, the present application provides for a method for improving the pharmacokinetics of a drug, comprising administering to a patient
5 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
10 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
15 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
20 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
25 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.

- 5 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.

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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
15 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
20 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
25 carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, C₁-C₂₀ alkyl), 1 to 10 carbon atoms (*i.e.*, C₁-C₁₀ alkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (n-Pr, n-propyl, -CH₂CH₂CH₃),

2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (*n*-Bu, *n*-butyl, -CH₂CH₂CH₂CH₃),
 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (*s*-Bu, *s*-butyl,
 -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (*n*-
 pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl
 5 (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl
 (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl
 (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl
 (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-
 pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-
 10 methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-
 C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-
 butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl
 (-CH₂)₇CH₃).

"Alkoxy" means a group having the formula -O-alkyl, in which an alkyl
 15 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.*, C₁-C₂₀
 alkoxy), 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ alkoxy), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆
 alkoxy). Examples of suitable alkoxy groups include, but are not limited to,
 methoxy (-O-CH₃ or -OMe), ethoxy (-OCH₂CH₃ or -OEt), *t*-butoxy (-O-C(CH₃)₃ or
 20 -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.*, C₁-C₂₀ haloalkyl),
 1 to 12 carbon atoms (*i.e.*, C₁-C₁₂ haloalkyl), or 1 to 6 carbon atoms (*i.e.*, C₁-C₆ alkyl).
 25 Examples of suitable haloalkyl groups include, but are not limited to, -CF₃,
 -CHF₂, -CFH₂, -CH₂CF₃, 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.*, C₂-C₂₀ alkenyl), 2 to 12 carbon atoms (*i.e.*, C₂-C₁₂ alkenyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂), cyclopentenyl
5 (-C₅H₇), and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

"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.*, C₂-C₂₀ alkynyl), 2 to 12 carbon atoms (*i.e.*, C₂-C₁₂ alkyne), or 2 to 6 carbon atoms
10 (*i.e.*, C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡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
15 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 (-CH₂-), 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl (-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

20 "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, an 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
25 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 ($-\text{C}\equiv\text{C}-$), propargyl ($-\text{CH}_2\text{C}\equiv\text{C}-$), and 4-pentynyl ($-\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH}-$).

- 5 "Amino" means an $-\text{NH}_2$ or a $-\text{NR}_2$ group in which the "R" groups are independently H, alkyl, 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 $-\text{NH}_2$, $-\text{NH}(\text{alkyl})$, $-\text{NH}(\text{carbocyclyl})$, $-\text{NH}(\text{heterocyclyl})$, $-\text{N}(\text{alkyl})_2$, $-\text{N}(\text{carbocyclyl})_2$, $-\text{N}(\text{heterocyclyl})_2$, $-\text{N}(\text{alkyl})(\text{carbocyclyl})$, $-\text{N}(\text{alkyl})(\text{heterocyclyl})$, $-\text{N}(\text{carbocyclyl})(\text{heterocyclyl})$, 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, trifluoroacetyl, 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 $-\text{CH}_2\text{-NH}_2$, $-\text{CH}_2\text{CH}_2\text{-NH}_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-NH}_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-NH}_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{-NH}_2$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{-NH}_2$, $-\text{CH}_2\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)\text{-NH}(\text{CH}_3)$, $-\text{CH}_2\text{-N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{-N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_2\text{CH}_2\text{-N}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{-N}(\text{CH}_3)_2$,

-CH₂CH₂CH(CH₃)-N(CH₃)₂, -CH₂-NH(CH₂CH₃), -CH₂CH₂-NH(CH₂CH₃),
 -CH₂CH₂CH₂-NH(CH₂CH₃), -CH₂CH₂CH₂CH₂-NH(CH₂CH₃),
 -CH₂CH(CH₃)-NH(CH₂CH₃), -CH₂CH₂CH(CH₃)-NH(CH₂CH₃), -CH₂-N(CH₂CH₃)₂,
 -CH₂CH₂-N(CH₂CH₃)₂, -CH₂CH₂CH₂-N(CH₂CH₃)₂, -CH₂CH₂CH₂CH₂-N(CH₂CH₃)₂,
 5 -CH₂CH(CH₃)-N(CH₂CH₃)₂, -CH₂CH₂CH(CH₃)-N(CH₂CH₃)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,
 10 trifluoroacetyl, 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
 15 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 sp³ carbon atom, is
 20 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.

25 "Arylalkenyl" refers to an acyclic alkenyl radical in which one of the
 hydrogen atoms bonded to a carbon atom, typically a terminal or sp³ carbon
 atom, but also an sp² 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.

5 “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
10 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”,
15 “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 $\cdot$, =O, -OR, -SR, -S $\cdot$,
20 -NR₂, -N⁺R₃, =NR, -CX₃, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, -NO₂, =N₂, -N₃, -NHC(=O)R, -NHS(=O)₂R, -C(=O)R, -C(=O)NRR, -S(=O)₂O $\cdot$, -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 $\cdot$)₂, -P(=O)(OH)₂, -P(O)(OR)(O $\cdot$), -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O $\cdot$, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(=NR)NRR, where
25 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 C₁₋₄ substituted alkyl refers to a C₁₋₄ 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
5 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.

10 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
15 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,
20 respectively, an alkoxy group (e.g., -OCH₃, etc.), an amine (e.g., -NHCH₃, -N(CH₃)₂, etc.), or a thioalkyl group (e.g., -SCH₃). 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., -CH₂CH₂-O-CH₃, etc.), an alkyl amine (e.g., -CH₂NHCH₃, -CH₂N(CH₃)₂, etc.),
25 or a thioalkyl ether (e.g., -CH₂-S-CH₃). 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., -CH₂CH₂-OH), an aminoalkyl group (e.g., -CH₂NH₂), or an alkyl thiol group (e.g., -CH₂CH₂-SH). A heteroalkyl group can

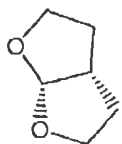
have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C₁-C₆ heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

“Heterocycle” or “heterocyclyl” as used herein includes by way of
5 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)
10 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, partially unsaturated rings, and aromatic rings (*i.e.*, heteroaromatic rings). Substituted heterocyclyls
15 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
20 pyridyl, dihydropyridyl, 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,
25 tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranlyl,

isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazolyl, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β -carbolinyl,
 5 phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanlyl, chromanyl, imidazolidinyl, imidazolyl, pyrazolidinyl, pyrazolyl, piperazinyl, indolyl, isoindolyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolyl, isatinyl, and bis-tetrahydrofuranyl:



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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,
 15 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-
 20 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,
 25 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-azetetyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

5 "Heterocyclalkyl" 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 heterocycl radical (*i.e.*, a heterocycl-alkylene-moiety). Typical heterocycl alkyl groups include, but are not limited to heterocycl- CH_2 -, heterocycl- $CH(CH_3)$ -, heterocycl- CH_2CH_2 -, 2-(heterocycl)ethan-1-yl, and the like, wherein the "heterocycl" portion includes any of the heterocycl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocycl group can be attached to the alkyl portion of the heterocycl alkyl by means of a carbon-carbon bond or a carbon-15 heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclalkyl group comprises 2 to 20 carbon atoms, *e.g.*, the alkyl portion of the heterocyclalkyl group is 1 to 6 carbon atoms and the heterocycl moiety is 1 to 14 carbon atoms. Examples of heterocyclalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolyethan-1-yl, 20 imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl, pyrazinylmethyl, etc.

25 "Heterocyclalkenyl" 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 heterocycl radical (*i.e.*, a heterocycl-alkenylene-moiety). The heterocycl portion of the heterocycl

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.

- 5 "Carbocycle" or "carbocyclyl" refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloalkenyl, 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.
- 15 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.
- 25

"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 -CH₂-pyridinyl, -CH₂-pyrrolyl,

- CH₂-oxazolyl, -CH₂-indolyl, -CH₂-isoindolyl, -CH₂-purinyl, -CH₂-furanyl,
 -CH₂-thienyl, -CH₂-benzofuranyl, -CH₂-benzothiophenyl, -CH₂-carbazolyl,
 -CH₂-imidazolyl, -CH₂-thiazolyl, -CH₂-isoxazolyl, -CH₂-pyrazolyl,
 -CH₂-isothiazolyl, -CH₂-quinolyl, -CH₂-isoquinolyl, -CH₂-pyridazolyl,
 5 -CH₂-pyrimidyl, -CH₂-pyrazyl, -CH(CH₃)-pyridinyl, -CH(CH₃)-pyrrolyl,
 -CH(CH₃)-oxazolyl, -CH(CH₃)-indolyl, -CH(CH₃)-isoindolyl, -CH(CH₃)-purinyl,
 -CH(CH₃)-furanyl, -CH(CH₃)-thienyl, -CH(CH₃)-benzofuranyl,
 -CH(CH₃)-benzothiophenyl, -CH(CH₃)-carbazolyl, -CH(CH₃)-imidazolyl,
 -CH(CH₃)-thiazolyl, -CH(CH₃)-isoxazolyl, -CH(CH₃)-pyrazolyl,
 10 -CH(CH₃)-isothiazolyl, -CH(CH₃)-quinolyl, -CH(CH₃)-isoquinolyl,
 -CH(CH₃)-pyridazolyl, -CH(CH₃)-pyrimidyl, -CH(CH₃)-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.

- 15 "Ac" means acetyl (-C(O)CH₃).
 "Ac₂O" means acetic anhydride.
 "DCM" means dichloromethane (CH₂Cl₂).
 "DIBAL" means diisobutylaluminum hydride.
 "DMAP" means dimethylaminopyridine.
 20 "EDC" means 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide.
 "Et" means ethyl.
 "EtOAc" means ethylacetate.
 "HOBT" means N-hydroxybenzotriazole.
 "Me" means methyl (-CH₃).
 25 "MeOH" means methanol.
 "MeCN" means acetonitrile.
 "Pr" means propyl.
 "i-Pr" means isopropyl (-CH(CH₃)₂).

"i-PrOH" means isopropanol.

"rt" means room temperature.

"TFA" means trifluoroacetic acid.

"THF" means tetrahydrofuran.

5 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
10 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
15 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
20 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
25 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 l 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

10 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 phosphoramidate 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 sulfinat.

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.

5 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
10 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
15 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
20 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
25 according to Formula I, as described herein.

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 L² is -CH(R⁶)-, wherein R⁶ is selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl.

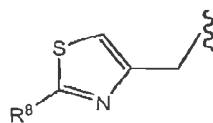
In another embodiment of the compounds of Formula I, n is 1 and L² is -CH₂-.

In another embodiment of the compounds of Formula I, n is 1 and L² is -C(O)-.

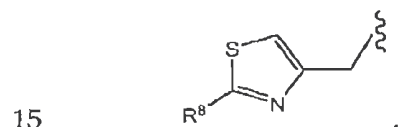
In another embodiment of the compounds of Formula I, n is 1 and Y is heterocyclylalkyl.

In another embodiment of the compounds of Formula I, n is 1 and Y-R⁸ is -CH₂-(substituted heteroaryl).

In another embodiment of the compounds of Formula I, n is 1 and Y-R⁸ is



In another embodiment of the compounds of Formula I, n is 1 and Y-R⁸ is

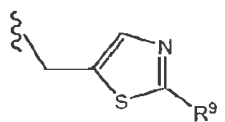


wherein R⁸ is alkyl, for example 2-propyl.

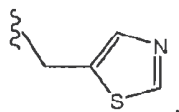
In another embodiment of the compounds of Formula I, n is 1 and X is heterocyclylalkyl.

In another embodiment of the compounds of Formula I, n is 1 and X is -CH₂-heteroaryl.

In another embodiment of the compounds of Formula I, n is 1 and X-R⁹ is



In another embodiment of the compounds of Formula I, n is 1 and X-R⁹ is



In another embodiment of the compounds of Formula I, n is 1 and Z¹ is –N(R⁷)–.

In another embodiment of the compounds of Formula I, n is 1 and Z¹ is –N(alkyl)– or –N(carbocyclyl)–.

In another embodiment of the compounds of Formula I, n is 1 and Z¹ is –N(CH₃)– or –N(cyclopropyl)–.

In another embodiment of the compounds of Formula I, n is 1 and Z¹ 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 R² is H, alkyl, substituted alkyl, or heteroalkyl.

In another embodiment of the compounds of Formula I, n is 1 and R² is 2-propyl, methyl, –CH₂–O–benzyl, –CH(CH₃)(O–t-Bu), or –CH(CH₃)(OH).

In another embodiment of the compounds of Formula I, L¹ is –C(O)–; each A is independently aryl, substituted aryl, alkyl, or substituted alkyl; R¹ is H or alkyl; each R² is independently H, alkyl, substituted alkyl, or heteroalkyl; R³, R⁴, R⁵, and R⁶ are each H; each R⁷ is independently H, alkyl, or carbocyclyl; R⁸ is H or alkyl;

R^9 is H;

X and Y are both heterocyclalkyl;

Z^2 is -O-; and

p is 0.

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

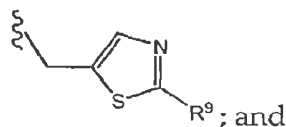
R^1 is H or -CH₃;

each R^2 is H, methyl, ethyl, 2-propyl, -CH₂-O-benzyl, -CH(CH₃)-OH, or
-CH(CH₃)(O-t-Bu);

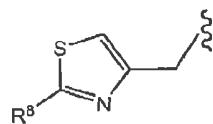
each R^7 is H, methyl or cyclopropyl;

10 R^8 is H or 2-propyl;

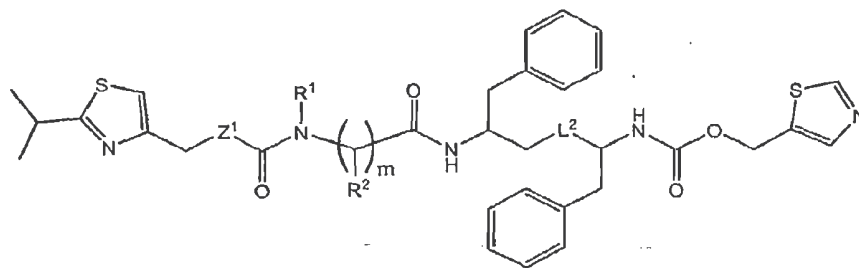
X is



Y is



15 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
20 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.

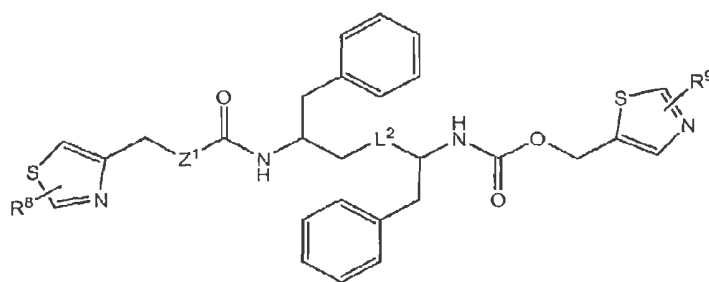
In another embodiment of the compounds of Formula IA, m is 1 and R^2 is ethyl.

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 R² is independently selected from H and alkyl.

In another embodiment of the compounds of Formula IA, m is 2 and each R² is H.

- 5 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, Z¹ is -N(R⁷)-. In
 10 a particular embodiment, R⁷ is H. In another particular embodiment, R⁷ is alkyl, for example any of the alkyl groups disclosed herein. In another particular embodiment, R⁷ is heteroalkyl, for example any of the heteroalkyl groups disclosed herein. In another particular embodiment, R⁷ is substituted or unsubstituted carbocyclyl, wherein for example, said carbocyclyl is any of the
 15 carbocyclyl groups disclosed herein. In another particular embodiment, R⁷ 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, Z¹ is -O-.

- In another embodiment of the compounds of Formula IB, L² is -C(R⁶)₂-,
 20 wherein each R⁶ is H.

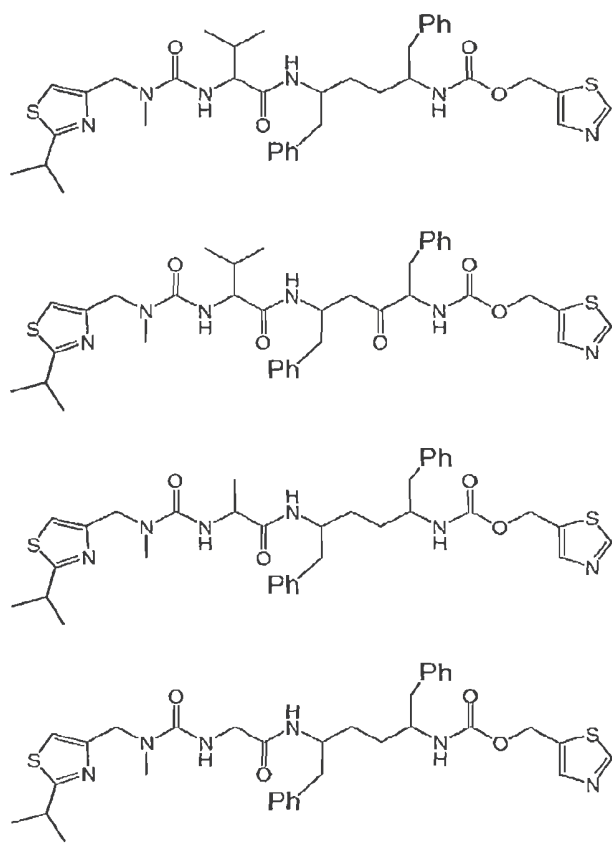
In another embodiment of the compounds of Formula IB, L² is -C(R⁶)₂-, wherein each R⁶ is independently H or alkyl, and said alkyl includes any alkyl disclosed herein.

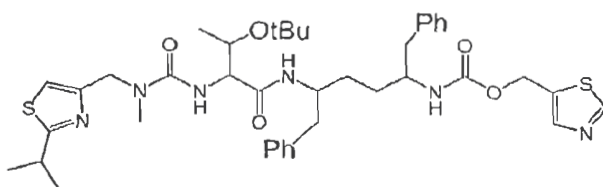
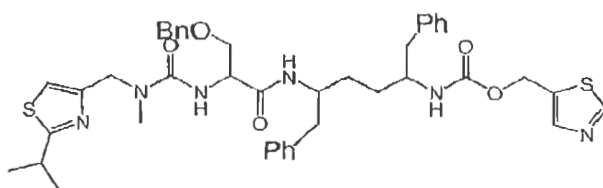
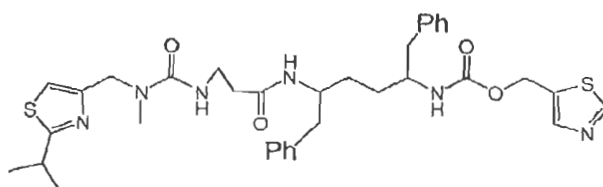
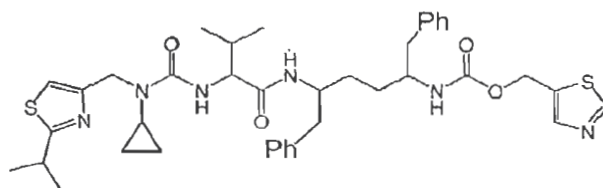
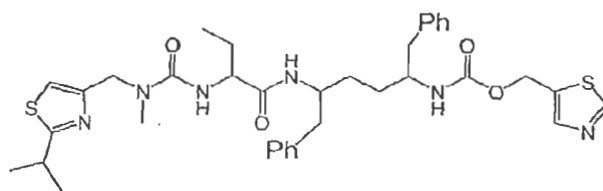
In another embodiment of the compounds of Formula IB, L^2 is $-C(R^6)_2-$, wherein one R^6 is H and the other R^6 is alkyl, wherein said alkyl includes any alkyl disclosed herein.

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

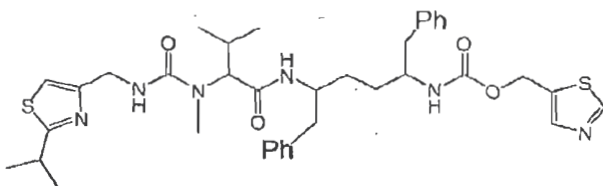
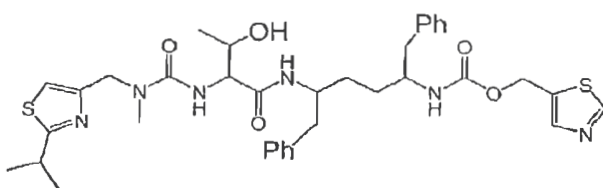
In another embodiment of the compounds of Formula IB, R^8 and R^9 are independently selected from H and alkyl, wherein said alkyl includes any alkyl disclosed herein.

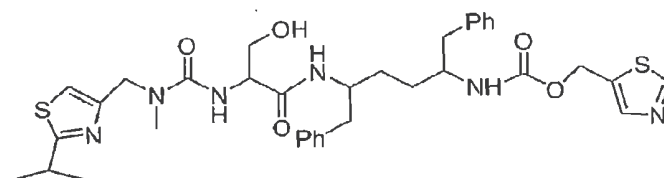
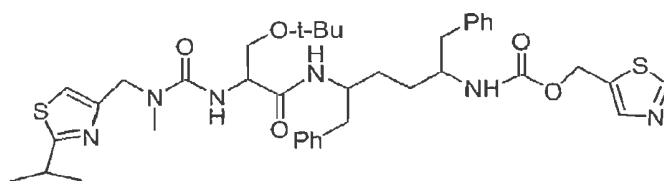
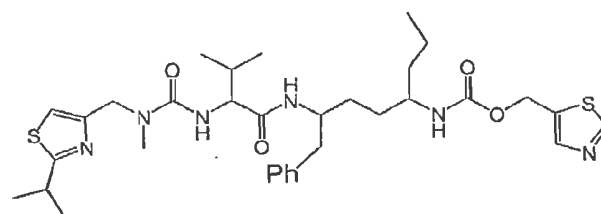
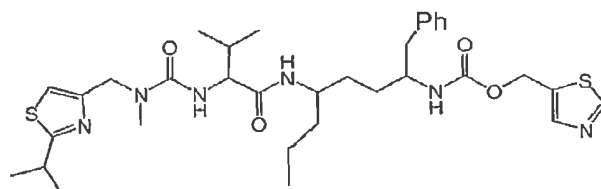
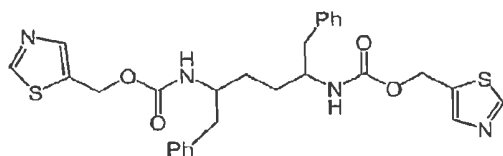
In another embodiment, the compounds of Formula I have one of the
 10 following structures:



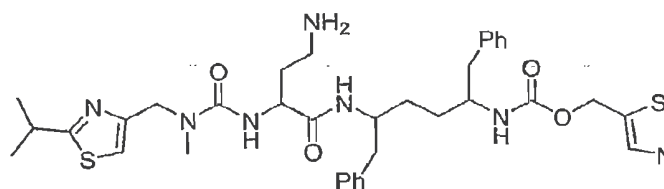
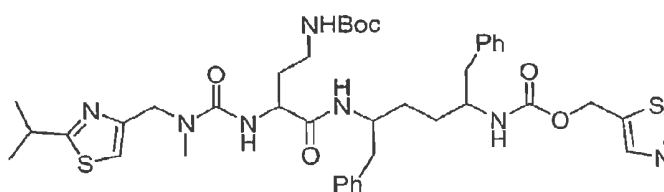


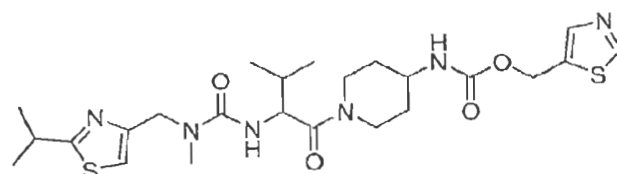
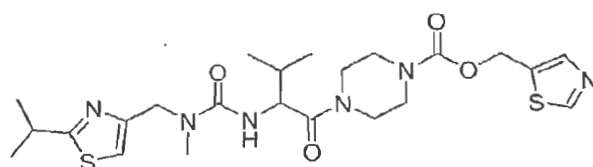
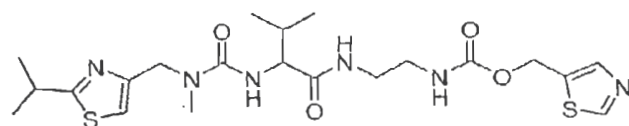
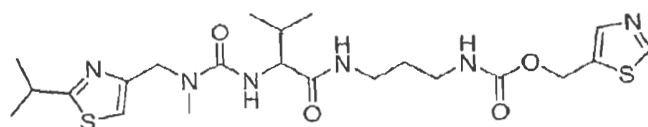
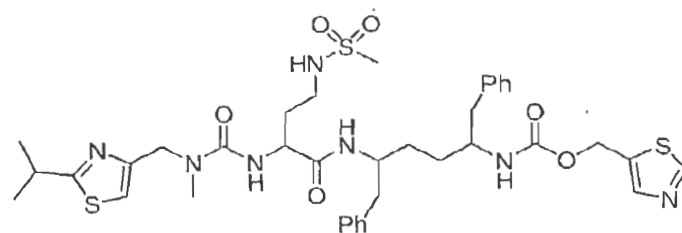
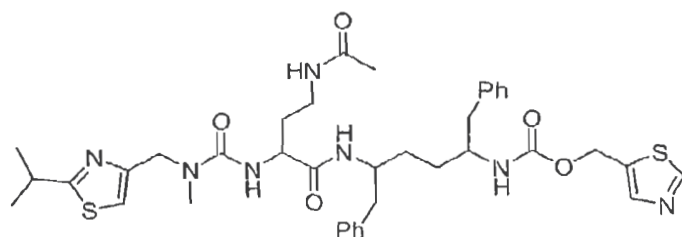
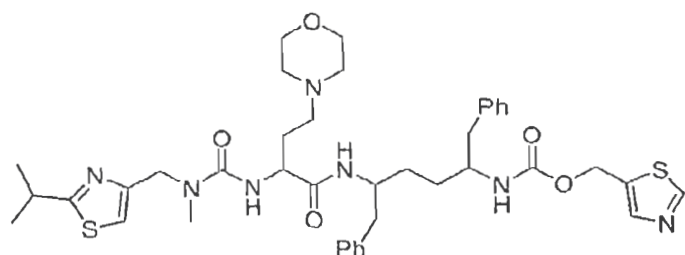
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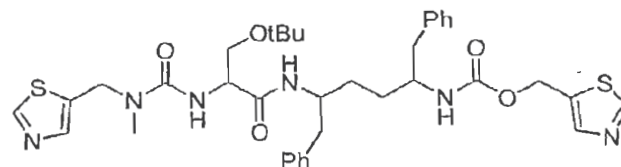
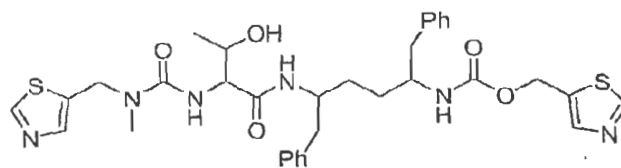
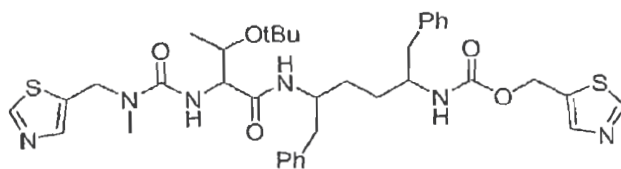
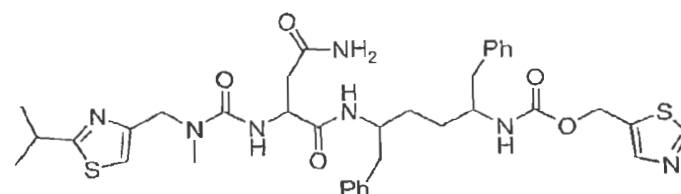
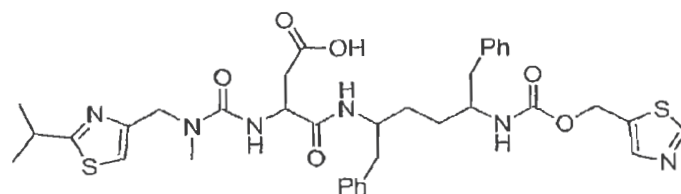
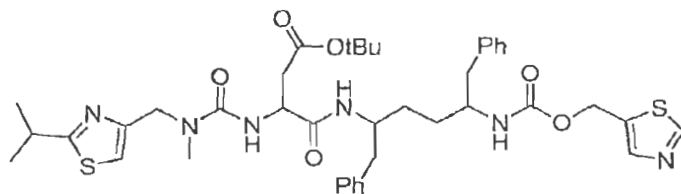
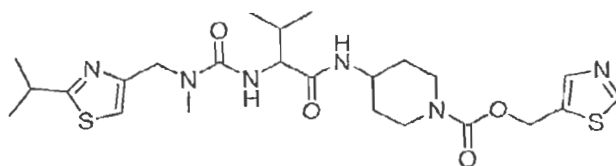




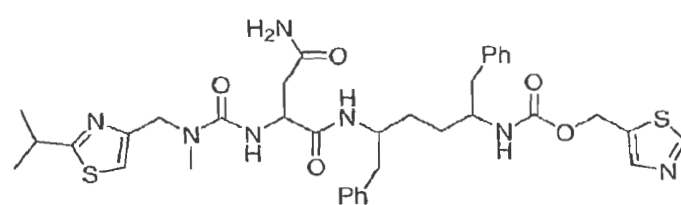
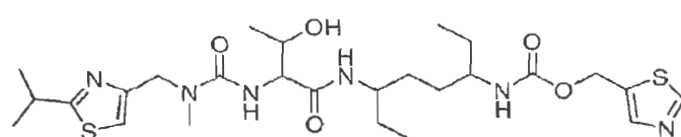
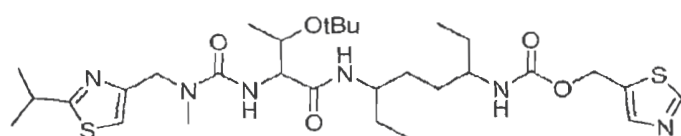
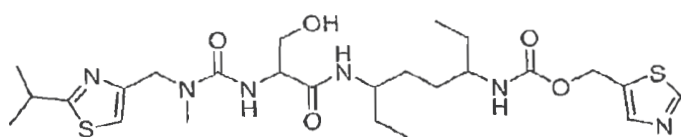
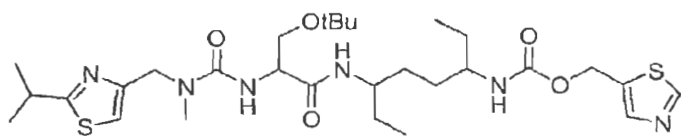
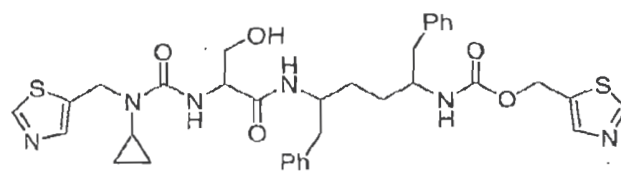
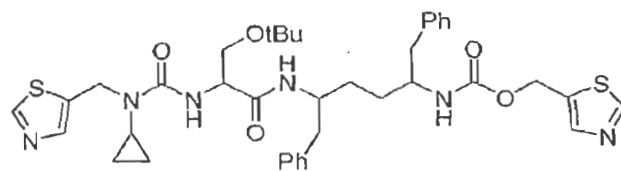
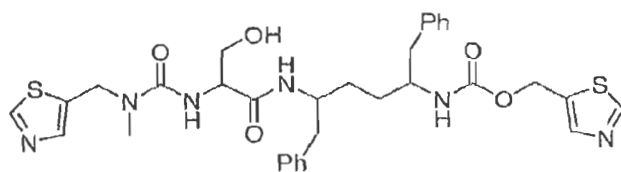
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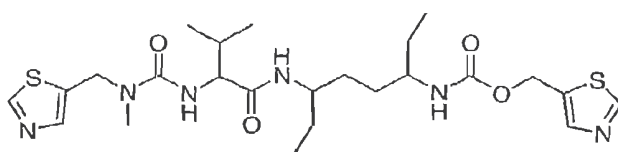
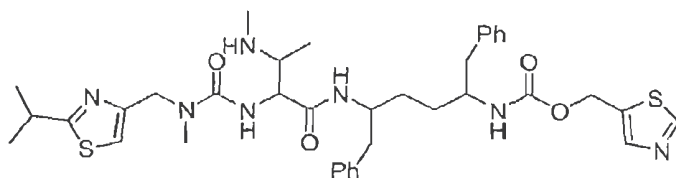
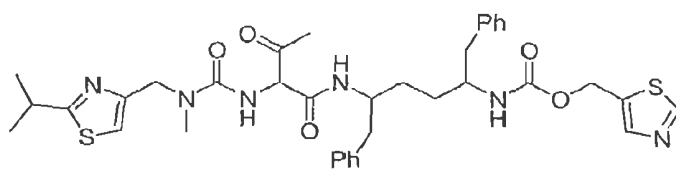
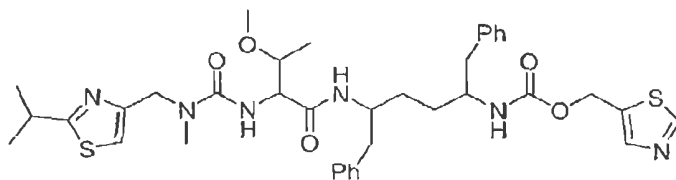
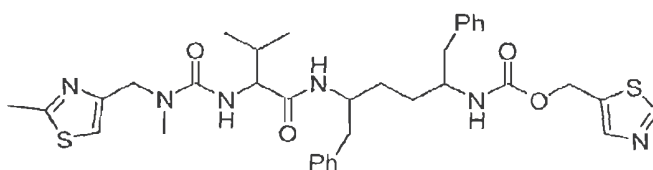
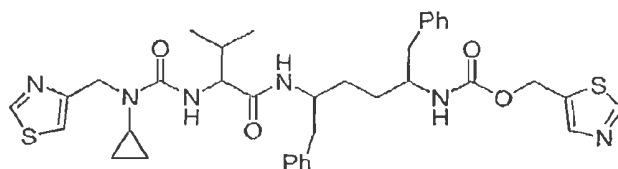
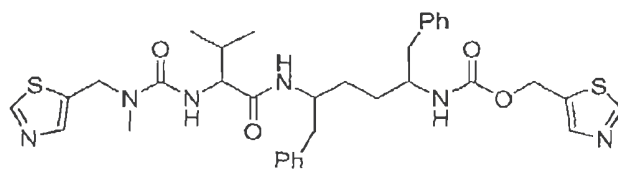
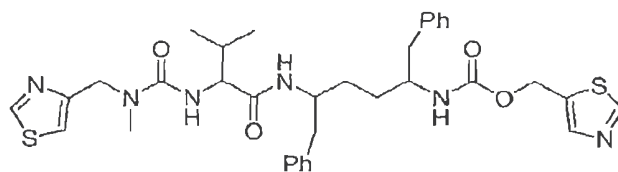


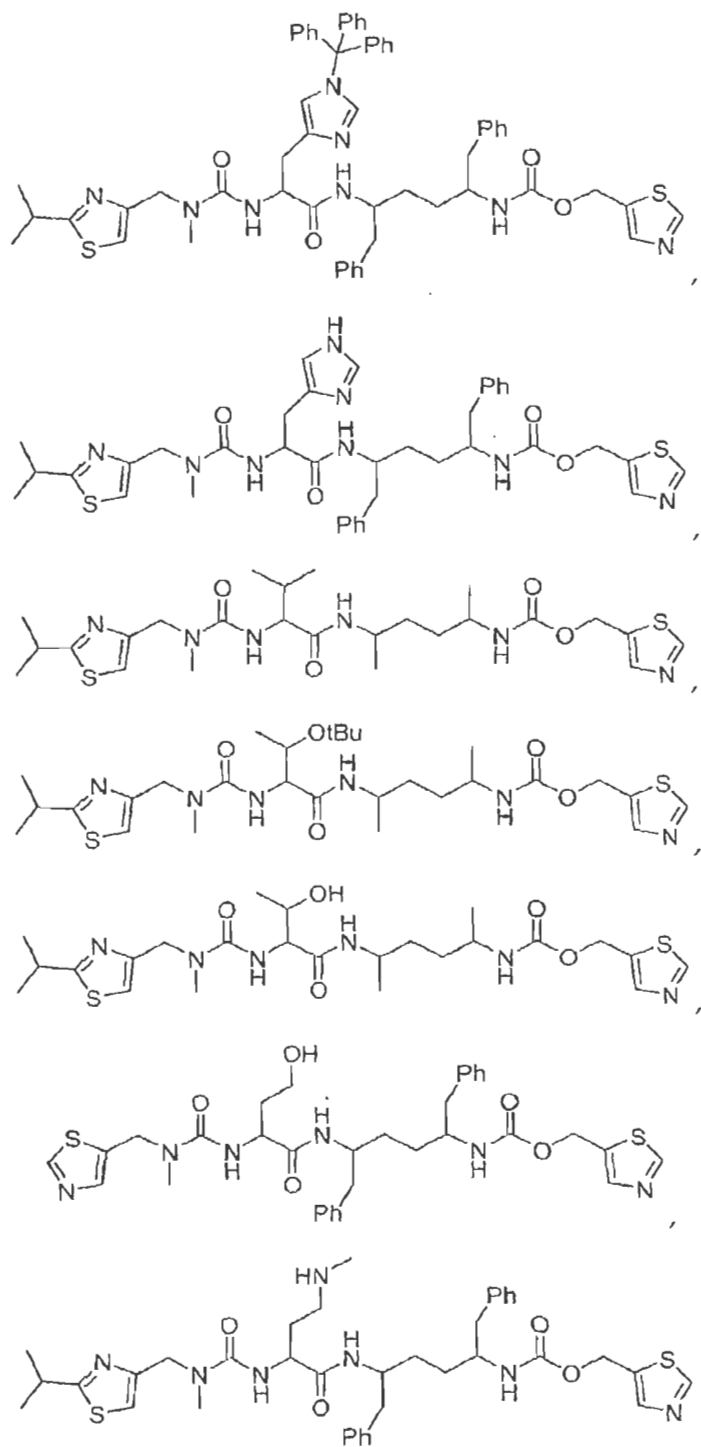




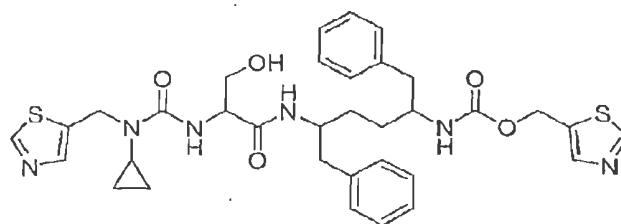
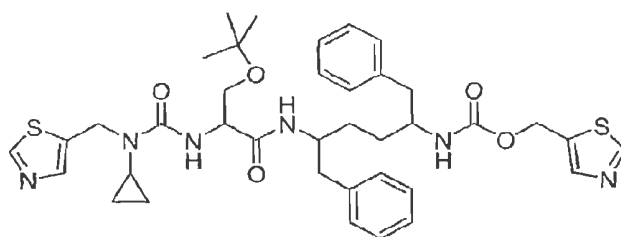
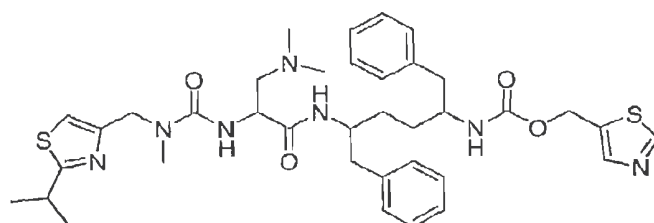
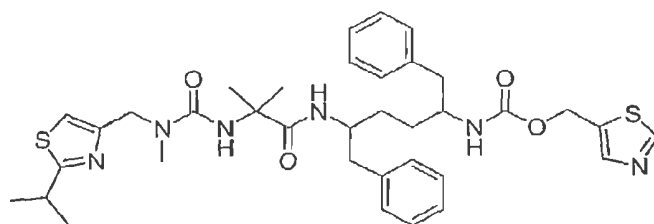
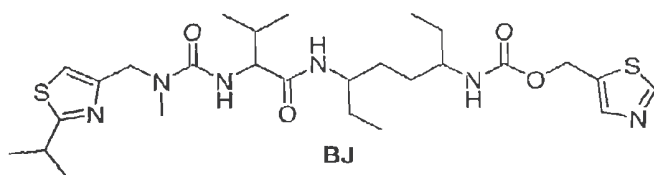
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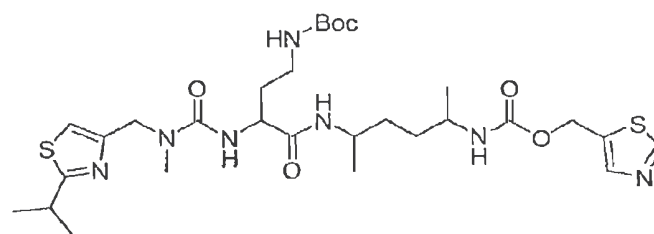


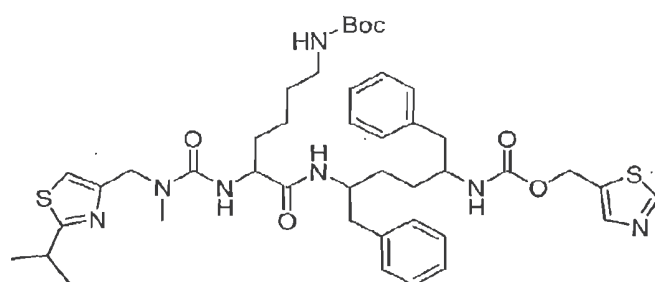
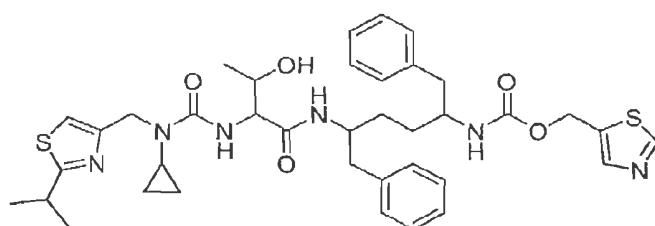
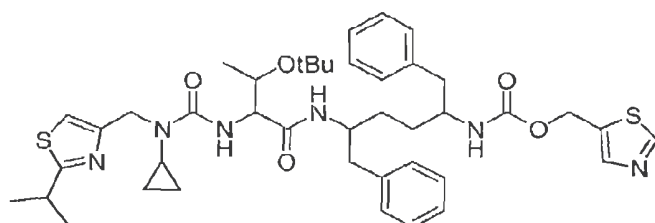
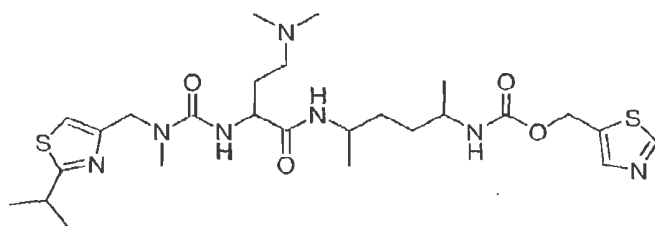
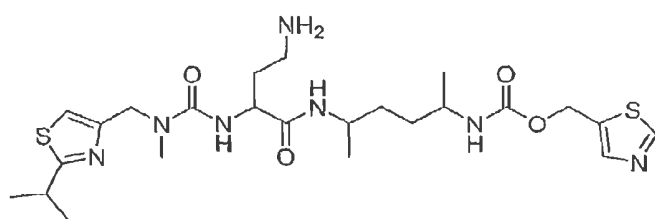


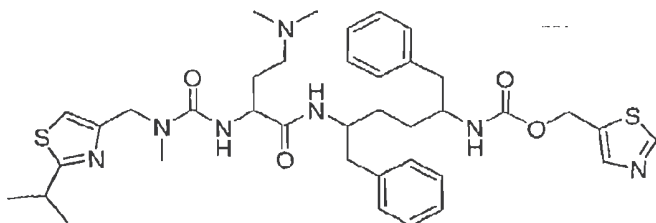
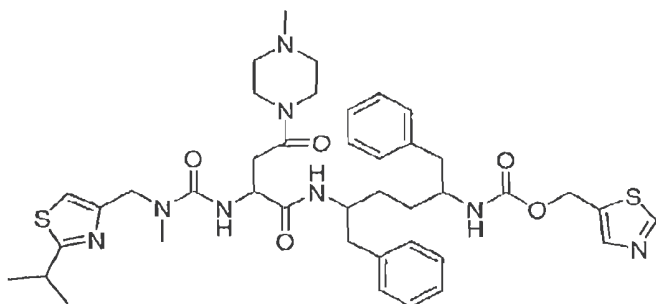
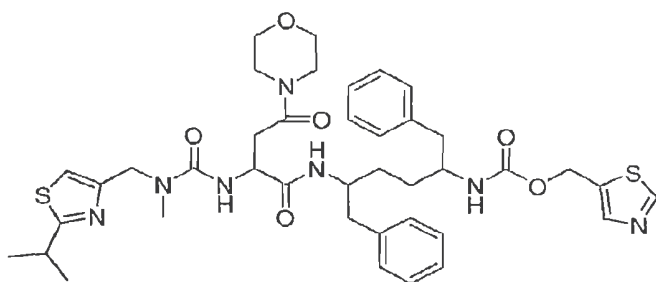
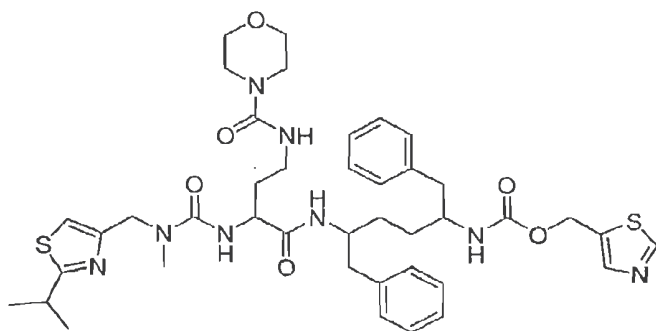
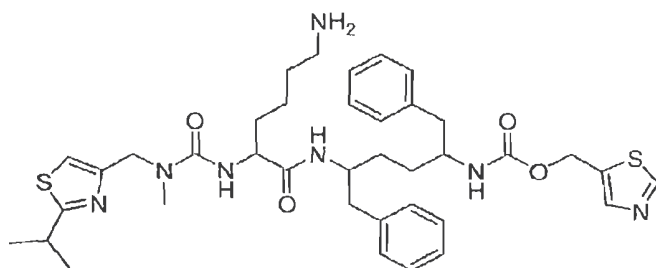
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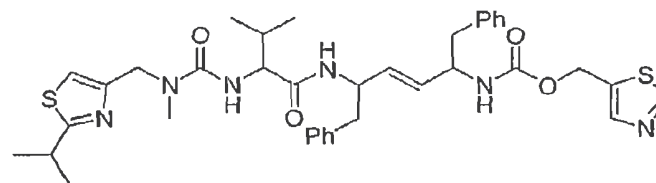
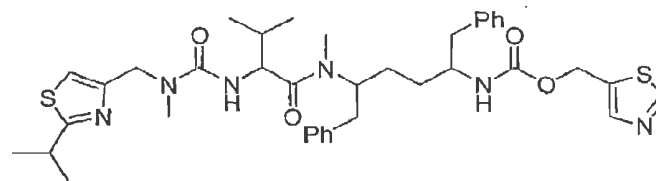
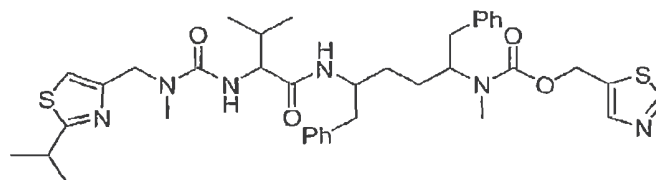
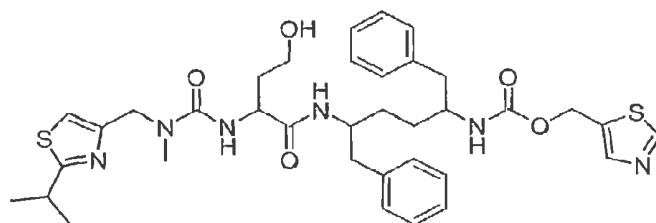
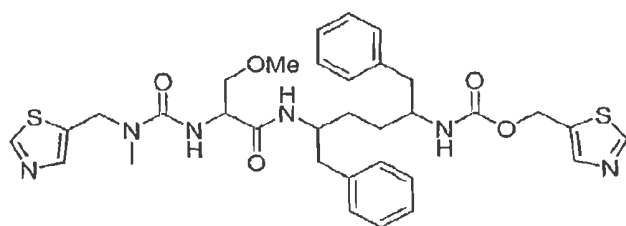
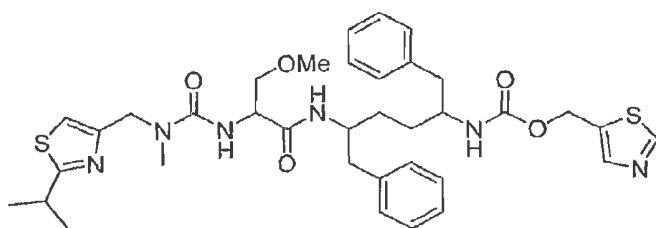


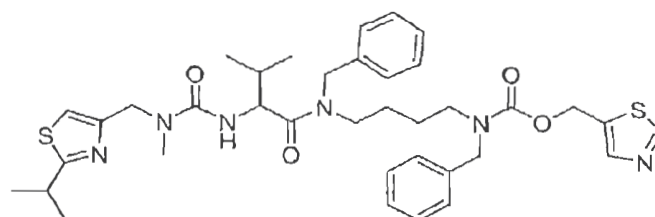
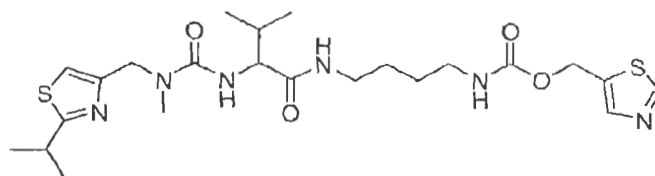
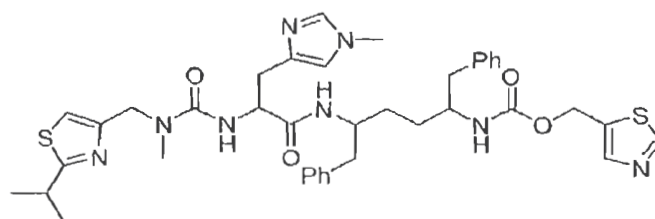
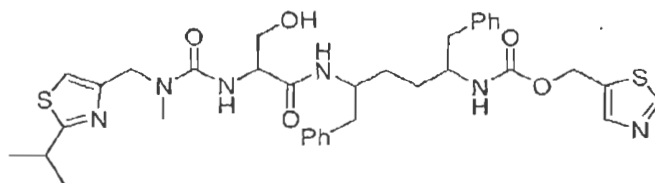
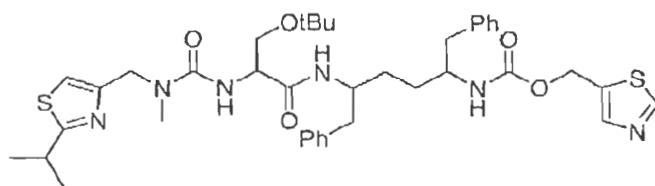
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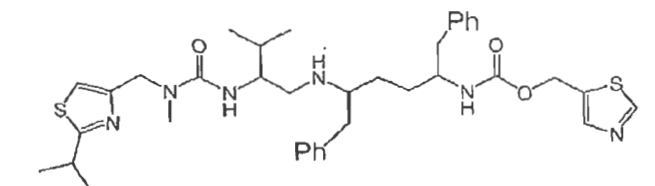
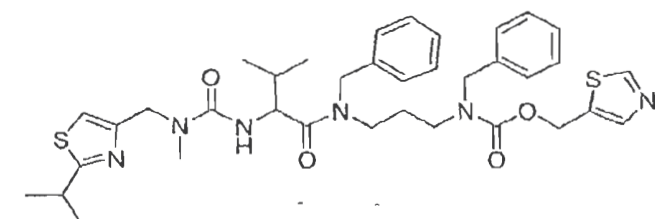


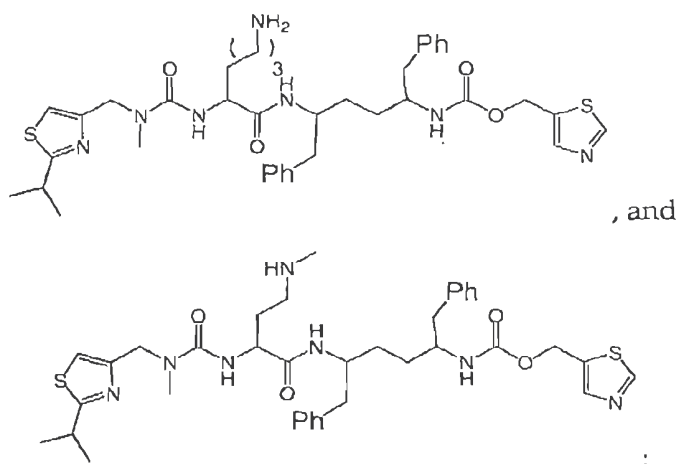




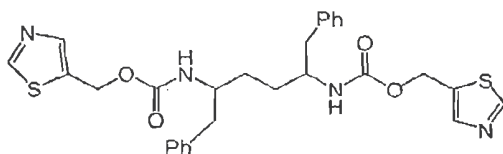


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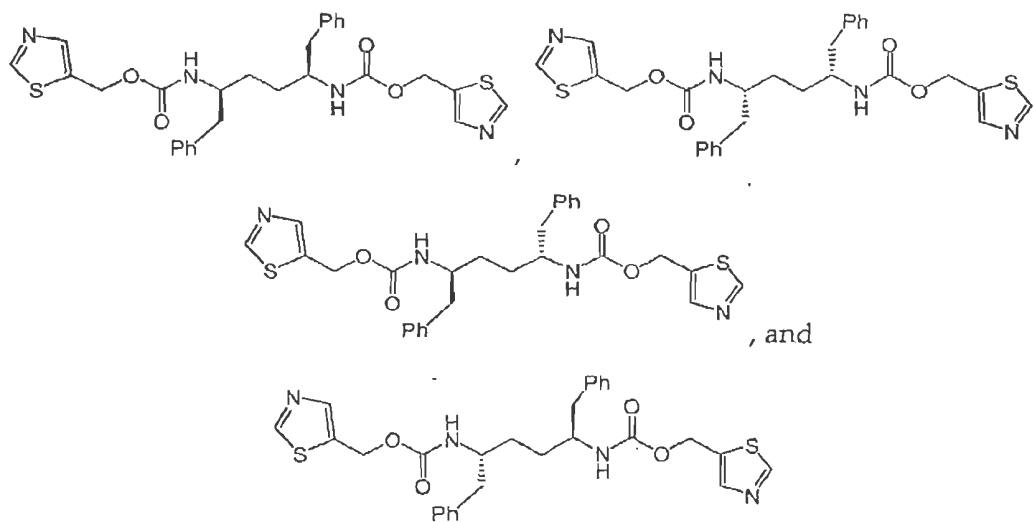




including stereoisomers or mixtures of stereoisomers thereof. One skilled in the art will recognize that stereoisomers or mixtures of stereoisomers of the
 5 compounds of the present application include enantiomers, diastereomers, and other stereoisomers. For example, for:



contemplated stereoisomers include at least:



10

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

In still another embodiment of the compounds of Formula I, L¹ is -C(R⁶)₂-, -C(O)-, -S(O₂)-, -N(R⁷)-C(O)-, or -O-C(O)-. When L¹ is -C(R⁶)₂-, each R⁶ 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(R⁶)₂- include -CH₂-,
5 -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
10 L¹ is -N(R⁷)-C(O)-, R⁷ 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, L² is -C(R⁶)₂- or -C(O)-. When L² is -C(R⁶)₂-, each R⁶ 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(R⁶)₂- include -CH₂-,
15 -CH(CH₃)-, -CH(-CH₂CH₃)-, -CH(-CH₂CH₂CH₃)-, -CH(-CH(CH₃)₂)-, -CH(-CH₂CH₂CH₂CH₃)-, -CH(-CH₂CH(CH₃)₂)-, -CH(-CH(CH₃)CH₂CH₃)-, -CH(-C(CH₃)₃)-, -C(CH₃)₂-, -CH(OCH₃)-, -CH(CH₂OH)-, -CH(CH₂CH₂OH)-, etc.
20

In still another embodiment of the compounds of Formula I, each L³ is independently a covalent bond, an alkylene or substituted alkylene. When any L³ is an alkylene, non-limiting examples of alkylene includes any of the alkenes defined or disclosed herein. When any L³ is a substituted alkylene, non-limiting examples of substituted alkylene includes any of the substituted alkenes defined or disclosed herein. For example, substituted alkenes include alkenes substituted with one or more -OH group, alkenes substituted with one or more
25

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 L³ is the same, i.e., each L³ is the same alkylene or substituted alkylene group.

In still another embodiment of the compounds of Formula I, each L³ is different, i.e., one L³ is an alkylene and the other L³ is a substituted alkylene, one L³ is an alkylene and the other L³ is a different alkylene, or one L³ is a substituted alkylene, and the other L³ is a different substituted alkylene.

In still another embodiment of the compounds of Formula I, each L⁴ is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, -CH₂-O-, and -NH-. When L⁴ is alkylene, said alkylene includes any alkylene defined or exemplified herein. When L⁴ 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 L⁴ groups are the same, i.e. both L⁴ groups are a covalent bond, both are -O-, both are -CH₂-O-, (wherein the CH₂ 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 L⁴ is different. For example, one L⁴ is a covalent bond and the other L⁴ is -O-, one L⁴ is a covalent bond and the other L⁴ is -CH₂-O- (wherein the CH₂ group is attached to either the "A" moiety or the "Ar" moiety of Formula I), one L⁴ is a covalent bond and the other L⁴ is -NH-, one L⁴ is a -O- and the other L⁴ is -CH₂-O- (wherein the CH₂ group is attached to either the "A" moiety or the "Ar" moiety of Formula I), one L⁴ is -O- and the other L⁴ is -NH-, one L⁴ is -CH₂-O- (wherein the CH₂ group is attached to either the "A" moiety or the "Ar" moiety of Formula

I) and the other L⁴ is -NH-, one L⁴ is a covalent bond and the other L⁴ is a substituted or unsubstituted alkylene, one L⁴ is a substituted alkylene and the other L⁴ is a unsubstituted alkylene, one L⁴ is a substituted or unsubstituted alkene and the other L⁴ is -O-, one L⁴ is a substituted or unsubstituted alkylene and the other L⁴ is -CH₂-O- (wherein the CH₂ group is attached to either the "A" moiety or the "Ar" moiety of Formula I), or one L⁴ is substituted or unsubstituted alkylene and the other L⁴ 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, Z¹ is -O- or -N(R⁷)-. When Z¹ is -N(R⁷)-, R⁷ 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, Z² is -O- or -N(R⁷)-. When Z² is -N(R⁷)-, R⁷ 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, Z¹ and Z² are the same, e.g., Z¹ and Z² are both -O-, or Z¹ and Z² are both -N(R⁷)-, where R⁷ 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
5 herein.

In still another embodiment of the compounds of Formula I, Z¹ and Z² are different, e.g. Z¹ is -O- and Z² is -N(R⁷)-, Z¹ is -N(R⁷)- and Z² is -O-, or Z¹ and Z² are both -N(R⁷)- but in Z¹ the R⁷ is different from the R⁷ in Z². When either Z¹ of
10 Z² is -N(R⁷)-, R⁷ 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
15 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
20 (-CH₂-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.

25 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

heterocyclalkyl are any heterocycl or heterocyclalkyl 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 heterocyclalkyls, e.g.
5 thiazolymethyl.

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
10 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
15 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.

20 In still another embodiment of the compounds of Formula I, R¹, R³, and R⁵ 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, R¹, R³, and R⁵
25 are each the same. In a particular embodiment R¹, R³, and R⁵ are each H. in another particular embodiment R¹, R³, and R⁵ are each alkyl, e.g. one of the alkyl groups defined or disclosed herein.

In still another embodiment of the compounds of Formula I, R¹, R³, and R⁵ are each different.

In still another embodiment of the compounds of Formula I, one of R¹, R³, and R⁵ is different from the other two groups.

5 In still another embodiment of the compounds of Formula I, n and m are both 1, and each R² is independently H, alkyl, substituted alkyl, arylheteroalkyl, arylalkyl, or heterocyclalkyl, wherein alkyl, substituted alkyl, arylheteroalkyl, aryl alkyl, or heterocyclalkyl is any alkyl, substituted alkyl, arylheteroalkyl, aryl alkyl, or heterocyclalkyl defined or disclosed herein.

10 In still another embodiment of the compounds of Formula I, n and m are both 1, and R² is H.

In still another embodiment of the compounds of Formula I, n is 1, m is 2, and R² is H.

In still another embodiment of the compounds of Formula I, n and m are
15 both 1, and at least one R² is alkyl. In a particular embodiment at least one R² is methyl. In another particular embodiment at least one R² is ethyl. In another particular embodiment at least one R² is i-propyl. In another particular embodiment at least one R² is t-butyl. In another particular embodiment, one R² is H, and the other R² is methyl. In another particular embodiment, one R² is H,
20 and the other R² is ethyl. In another particular embodiment, one R² is H, and the other R² is i-propyl. In another particular embodiment, one R² is H, and the other R² is t-butyl.

In still another embodiment of the compounds of Formula I, n and m are both 1, and R² is substituted alkyl. In a particular embodiment at least one R² is –
25 CH(CH₃)OH or –CH(CH₃)O(t-Bu)

In still another embodiment of the compounds of Formula I, n and m are both 1, and at least one R² is arylheteroalkyl. In particular embodiment n and m are both 1, and at least one R² is selected from the group consisting of H, methyl,

ethyl, benzyl-O-CH₂-, i-propyl, -CH(CH₃)OBn, -CH₂CH(CH₃)-O-tBu, -CH(CH₃)OH, -CH₂OH, -CH₂OtBu, -CH₂CH₂NH₂, -CH₂CH₂NH-P (where P is a protecting group such as Boc, Ac, methanesulfonyl, etc.), -CH₂CH₂-morpholine, -CH₂C(O)OH, -CH₂C(O)OtBu, and -CH₂C(O)-NH₂.

5 In still another embodiment of the compounds of Formula I, n and m are both 1, and at least one R² is arylheteroalkyl. In particular embodiment n and m are both 1, one R² is H and one R² is selected from the group consisting of H, methyl, ethyl, benzyl-O-CH₂-, i-propyl, -CH(CH₃)OBn, -CH₂CH(CH₃)-O-tBu, -CH(CH₃)OH, -CH₂OH, -CH₂OtBu, -CH₂CH₂NH₂, -CH₂CH₂NH-P (where P is a
10 protecting group such as Boc, Ac, methanesulfonyl, etc.), -CH₂CH₂-morpholine, -CH₂C(O)OH, -CH₂C(O)OtBu, and -CH₂C(O)-NH₂.

In still another embodiment of the compounds of Formula I, R⁴ is H, alkyl, substituted alkyl, and heteroalkyl, wherein alkyl, substituted alkyl, and heteroalkyl are any alkyl, substituted alkyl, or heteroalkyl defined or disclosed
15 herein. A particular embodiment, R⁴ is H.

In still another embodiment of the compounds of Formula I, R⁶ 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, R⁶ is H.

20 In still another embodiment of the compounds of Formula I, R⁸ and R⁹ 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 R⁸ or R⁹ are alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, or substituted heterocyclyl,
25 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, R⁸ and R⁹ are the same. In a particular embodiment R⁸ and R⁹ 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
5 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
10 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
15 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
20 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
25 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
5 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
10 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
15 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
20 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
25 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
5 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
10 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-CH₂-O-heterocyclyl group,
15 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-OCH₂-heterocyclyl group,
20 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.

25 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
5 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
10 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
15 the $-L^3-A-(L^4-Ar)_p$ moieties is an -alkylene-heterocyclyl-CH₂-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
20 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-OCH₂-aryl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the
25 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.

5 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
10 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
15 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-CH₂-O-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally
20 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-OCH₂-heterocyclyl group, wherein said alkylene, aryl, and heterocyclyl moieties are any alkylene, aryl, and heterocyclyl moieties defined or exemplified herein, optionally substituted on the
25 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
5 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
10 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
15 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-CH₂-O-heteroaryl group, wherein
20 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-OCH₂-heteroaryl group, wherein
25 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
5 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
10 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
15 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
20 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-CH₂-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
25 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-OCH₂-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.

5 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
10 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
15 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
20 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-CH₂-O-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and
25 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-OCH₂-heteroaryl group, wherein said alkylene, aryl, and heteroaryl moieties are any alkylene, aryl, and heteroaryl moieties defined or exemplified herein, optionally substituted on the
5 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
10 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.

15 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 -CH₂-phenyl and X and Y are both -CH₂-heterocyclyl.

20 In yet another embodiment of the compounds of Formula I, both $-L^3-A-(L^4-Ar)_p$ moieties are -CH₂-phenyl and Y is -CH₂-heterocyclyl.

In yet another embodiment of the compounds of Formula I, both $-L^3-A-(L^4-Ar)_p$ moieties are -CH₂-phenyl and X is -CH₂-heterocyclyl.

In yet another embodiment of the compounds of Formula I, both $-L^3-A-$
25 $(L^4-Ar)_p$ moieties are -CH₂-phenyl and Y is -CH₂-thiazolyl.

In yet another embodiment of the compounds of Formula I, both $-L^3-A-(L^4-Ar)_p$ moieties are -CH₂-phenyl and X is -CH₂-thiazolyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl and X and Y are both -CH₂-thiazolyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, and n and m are both 1.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₁-C₆ alkyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₁-C₆ hydroxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₂-C₁₀ alkoxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₇-C₁₄ arylalkyloxyalkyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₁-C₆ aminoalkyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a C₁-C₆ aminoalkyl substituted on the nitrogen with an amine protecting group selected from acyl, alkylsulfonyl, arylsulfonyl, heterocyclacyl, and benzyl.

In yet another embodiment of the compounds of Formula I, both -L³-A-(L⁴-Ar)_p moieties are -CH₂-phenyl, X and Y are both -CH₂-thiazolyl, n and m are both 1, and at least one R² is a substituted or unsubstituted heterocyclalkyl.

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
5 $-L^3-A-(L^4-Ar)_p$ 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.

10 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 heterocyclalkyl.

In yet another embodiment of the compounds of Formula I, X and Y are
15 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 $-$
20 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
25 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, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, and Z¹ is -N(alkyl)-.

5 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, and Z¹ is -N(CH₃)-

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(alkyl)-, and Z² is -O-.

10 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(CH₃)-, and Z² is -O-.

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(alkyl)-, Z² is -O-, and Y is substituted or unsubstituted -CH₂-4-thiazole.

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(alkyl)-, Z² is -O-, and R⁸-Y is -CH₂-(2-alkyl-4-thiazole).

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, and R⁸-Y is -CH₂-(2-iPr-4-thiazole).

25 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(alkyl)-, Z² is -O-, Y is substituted or

unsubstituted $-\text{CH}_2\text{-4-thiazole}$, and X is substituted or unsubstituted $-\text{CH}_2\text{-5-thiazole}$.

In another embodiment of the compounds of Formula I, L^1 is $-\text{C}(\text{O})-$, R^4 is H, both $-\text{L}^3\text{-A-(L}^4\text{-Ar)}_p$ groups are substituted or unsubstituted benzyl, L^2 is $-\text{CH}_2-$, m and n are both 1, R^1 is H, Z^1 is $-\text{N(alkyl)-}$, Z^2 is $-\text{O-}$, Y is substituted or unsubstituted $-\text{CH}_2\text{-4-thiazole}$, and X is unsubstituted $-\text{CH}_2\text{-5-thiazole}$.

In another embodiment of the compounds of Formula I, L^1 is $-\text{C}(\text{O})-$, R^4 is H, both $-\text{L}^3\text{-A-(L}^4\text{-Ar)}_p$ groups are substituted or unsubstituted benzyl, L^2 is $-\text{CH}_2-$, m and n are both 1, R^1 is H, Z^1 is $-\text{N(H)-}$, Z^2 is $-\text{O-}$, $\text{R}^8\text{-Y}$ is $-\text{CH}_2\text{-(2-iPr-4-thiazole)}$, and X is unsubstituted $-\text{CH}_2\text{-5-thiazole}$.

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 heterocyclalkyl.

In another embodiment of the compounds of Formula I, each R^2 is independently H or $-\text{CH}_2\text{-heterocyclyl}$, 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 $-\text{CH}_2\text{-heterocyclyl}$, 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 $-\text{CH}_2\text{-heterocyclyl}$, wherein said heterocyclyl is a 6-membered ring having at least one ring nitrogen atom, where the $-\text{CH}_2-$ 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 $-\text{CH}_2\text{-heterocyclyl}$, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholinyl.

In another embodiment of the compounds of Formula I, each R² is independently H or -CH₂-heterocyclyl, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholinyl, and the -CH₂-moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl.

5 In another embodiment of the compounds of Formula I, each R² is independently H or aminoalkyl.

In another embodiment of the compounds of Formula I, each R² is independently H or aminoalkyl substituted with an amine protecting group selected from the group consisting of acetyl, alkylsulfonyl, Boc, Cbz, and Fmoc.

10 In another embodiment of the compounds of Formula I, each R² is independently H or ethylacetamide (-CH₂CH₂NHC(O)CH₃).

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-
15 thiazole), X is unsubstituted -CH₂-5-thiazole, and R² is independently H or hydroxyalkyl.

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-
20 thiazole), X is unsubstituted -CH₂-5-thiazole, and one R² is H and the other R² is hydroxyalkyl.

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-
25 thiazole), X is unsubstituted -CH₂-5-thiazole, and one R² is H and the other R² is hydroxymethyl.

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -

CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-thiazole), X is unsubstituted -CH₂-5-thiazole, and each R² is independently H or -CH₂-heterocyclyl, wherein said heterocyclyl is a 5- or 6-membered ring having at least one ring nitrogen atom.

5 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-thiazole), X is unsubstituted -CH₂-5-thiazole, and each R² is independently H or -CH₂-heterocyclyl, wherein said heterocyclyl is selected from the group consisting
10 of piperadyl, piperazyl, and morpholiny, and the -CH₂- moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl

 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-
15 thiazole), X is unsubstituted -CH₂-5-thiazole, and one R² is H and the other R² is -CH₂-heterocyclyl, wherein said heterocyclyl is selected from the group consisting of piperadyl, piperazyl, and morpholiny, and the -CH₂- moiety thereof is bonded to a ring nitrogen atom of the heterocyclyl

 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is
20 H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-thiazole), X is unsubstituted -CH₂-5-thiazole, and each R² is independently H or aminoalkyl substituted with an amine protecting group selected from the group consisting of acetyl, alkylsulfonyl, Boc, Cbz, and Fmoc.

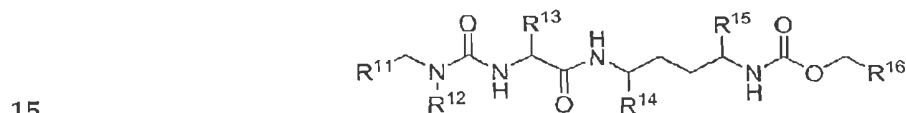
25 In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-thiazole), X is unsubstituted -CH₂-5-thiazole, and one R² is H and the other R² 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, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(H)-, Z² is -O-, R⁸-Y is -CH₂-(2-iPr-4-thiazole), X is unsubstituted -CH₂-5-thiazole, and one R² is H and the other R² is ethylacetamide (-CH₂CH₂NHC(O)CH₃).

In another embodiment of the compounds of Formula I, L¹ is -C(O)-, R⁴ is H, both -L³-A-(L⁴-Ar)_p groups are substituted or unsubstituted benzyl, L² is -CH₂-, m and n are both 1, R¹ is H, Z¹ is -N(alkyl)-, Z² is -O-, and Y is substituted or unsubstituted -CH₂-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 R¹¹ and R¹⁶ are each independently heterocyclyl or substituted heterocyclyl; and R¹², R¹³, R¹⁴, and R¹⁵ are each independently H, -C₁₋₄ alkyl or -C₁₋₄ substituted alkyl.

20 In still another embodiment of the compounds of Formula IIA, R¹³ is H, -C₁₋₄ alkyl, -(CH₂)₀₋₁CR¹⁷R¹⁸OR¹⁹, -(CH₂)₀₋₃CR¹⁷R¹⁸NR²⁰R²¹, -(CH₂)₀₋₃CR¹⁷R¹⁸NR¹⁷C(O)-NR²⁰R²¹, -(CH₂)₁₋₃C(O)R²², -(CH₂)₁₋₃S(O)₂R²² or -(CH₂)₁₋₃-R²³; R¹⁴ and R¹⁵ are each independently H, -C₁₋₄ alkyl or arylalkyl; R¹⁷ and R¹⁸ are each independently H or -C₁₋₃ alkyl; R¹⁹ is H, -C₁₋₄ alkyl or arylalkyl; R²⁰ and R²¹ are each independently H, -C₁₋₃ alkyl, -C(O)R¹⁷ or -S(O)₂R¹⁷; or R²⁰ and R²¹, taken together with the nitrogen atom to which they are attached, form an unsubstituted or substituted 5-6

25

membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O; R²² is H, -C₁₋₃ alkyl, -OR¹⁹ or -NR²⁰R²¹; and R²³ is an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O.

5 In still another embodiment of the compounds of Formula IIA, R¹³ is - (CH₂)₀₋₃CR¹⁷R¹⁸NR²⁰R²¹, -(CH₂)₀₋₃CR¹⁷R¹⁸NR¹⁷C(O)-NR²⁰R²¹, or -(CH₂)₁₋₃-R²³ wherein R²⁰ and R²¹ form a 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O or R²³ 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 C₁₋₂ alkyl.

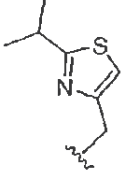
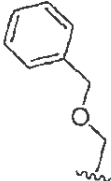
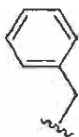
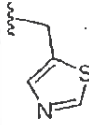
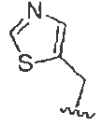
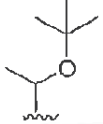
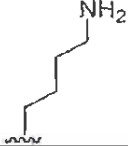
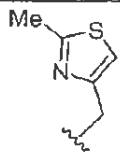
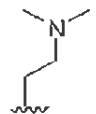
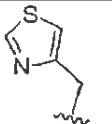
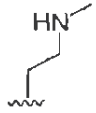
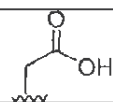
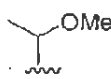
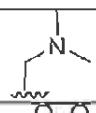
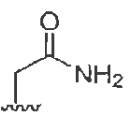
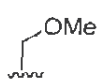
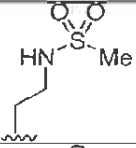
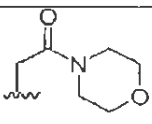
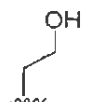
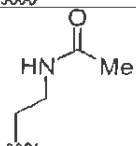
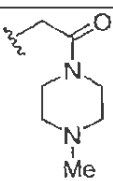
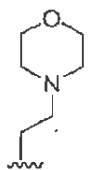
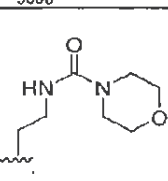
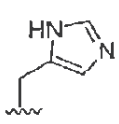
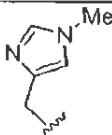
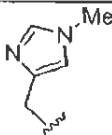
In still another embodiment of the compounds of Formula IIA, R¹³ is - (CH₂)₀₋₁CR¹⁷R¹⁸OR¹⁹. In a particular embodiment, R¹³ is a C₁₋₂ hydroxyalkyl or a C₁₋₆ alkoxyalkyl group.

15 In still another embodiment of the compounds of Formula IIA, R¹³ is - (CH₂)₀₋₃CR¹⁷R¹⁸NR²⁰R²¹. In a particular embodiment, R¹³ is a C₁₋₄alkylene-NH₂ group, C₁₋₄alkylene-NHP (wherein P is a protecting group such as Boc, Fmoc, Cbz, Ac, trifluoroacetyl, toluenesulfonyl group, benzyl, etc.), or C₁₋₄alkylene-N(alkyl)₂ group.

20 In still another embodiment of the compounds of Formula IIA, R¹³ is - (CH₂)₀₋₃CR¹⁷R¹⁸NR¹⁷C(O)-NR²⁰R²¹. In a particular embodiment, R¹³ is a C₁₋₄alkylene-C(O)NH₂ group or C₁₋₄alkylene-C(O)N(alkyl)₂ group.

In still another embodiment of the compounds of Formula IIA, R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶ are each independently selected from the groups shown in the Table, below:

R ¹¹	R ¹²	R ¹³	R ¹⁴	R ¹⁵	R ¹⁶
-----------------	-----------------	-----------------	-----------------	-----------------	-----------------

	H						
	Me	Me					
		H			Et	Et	
		Et			Me	Me	
					H	H	
							
							
							
							

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted or unsubstituted heterocyclyl, R¹² is alkyl, R¹³ is substituted or

unsubstituted heterocyclalkyl, R¹⁴ and R¹⁵ are each independently substituted or unsubstituted arylalkyl, and R¹⁶ is substituted or unsubstituted heterocyclalkyl.

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted heterocyclalkyl, R¹² is alkyl, R¹³ is unsubstituted heterocyclalkyl, R¹⁴ and R¹⁵ are both unsubstituted arylalkyl, and R¹⁶ is unsubstituted heterocyclalkyl.

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted or unsubstituted heterocyclalkyl, R¹² is alkyl, R¹³ is hydroxyalkyl, R¹⁴ and R¹⁵ are each independently substituted or unsubstituted arylalkyl, and R¹⁶ is substituted or unsubstituted heterocyclalkyl.

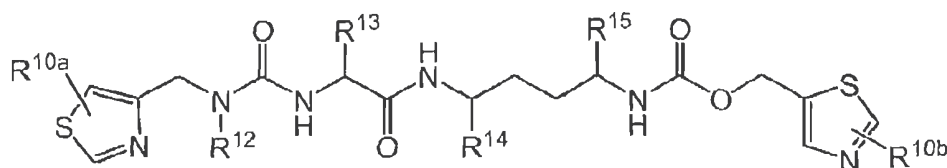
In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted heterocyclalkyl, R¹² is alkyl, R¹³ is hydroxyalkyl, R¹⁴ and R¹⁵ are both unsubstituted arylalkyl, and R¹⁶ is unsubstituted heterocyclalkyl.

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted or unsubstituted heterocyclalkyl, R¹² is alkyl, R¹³ is protected or unprotected aminoalkyl, R¹⁴ and R¹⁵ are each independently substituted or unsubstituted arylalkyl, and R¹⁶ is substituted or unsubstituted heterocyclalkyl.

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted heterocyclalkyl, R¹² is alkyl, R¹³ is protected aminoalkyl, R¹⁴ and R¹⁵ are both unsubstituted arylalkyl, and R¹⁶ is unsubstituted heterocyclalkyl.

In still another embodiment of the compounds of Formula IIA, R¹¹ is substituted heterocyclalkyl, R¹² is alkyl, R¹³ is acylated aminoalkyl, R¹⁴ and R¹⁵ are both unsubstituted arylalkyl, and R¹⁶ is unsubstituted heterocyclalkyl.

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

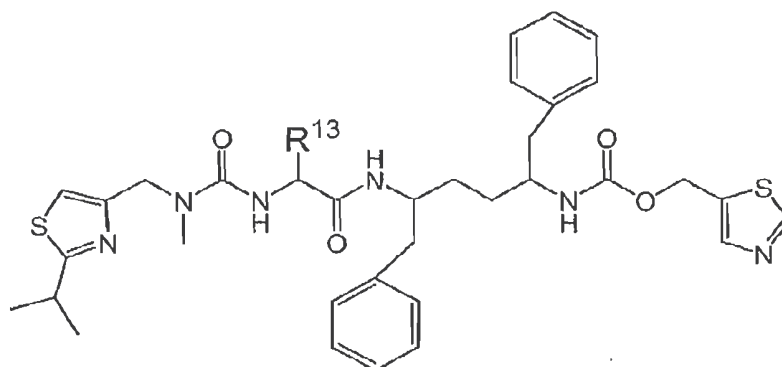


Formula IIB

- 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
 5 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
 10 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
 15 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.

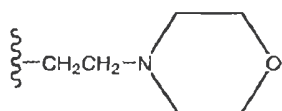
In still another embodiment of the compounds of Formula IIC, R^{13} is $-(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$. In a particular embodiment, R^{13} is a C_{1-4} alkylene- NH_2
 20 group, C_{1-4} alkylene-NHP (wherein P is a protecting group such as Boc, Fmoc,

Cbz, Ac, trifluoroacetyl, toluenesulfonyl group, benzyl, etc.), or C₁₋₄alkylene-N(alkyl)₂ group.

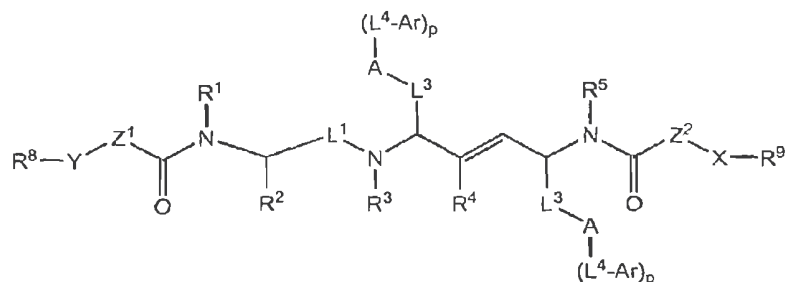
In still another embodiment of the compounds of Formula IIC, R¹³ is - (CH₂)₀₋₃CR¹⁷R¹⁸NR¹⁷C(O)-NR²⁰R²¹. In a particular embodiment, R¹³ is a

- 5 C₁₋₄alkylene-C(O)NH₂ group or C₁₋₄alkylene-C(O)N(alkyl)₂ group.

In still another embodiment of the compounds of Formula IIC, R¹³ is - CH₂OH, -CH₂CH₂NHC(O)CH₃ or



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



Formula IID

wherein,

- 15 L¹ is selected from the group consisting of -C(R⁶)₂-, -C(O)-, -S(O₂)-, -N(R⁷)-C(O)-, and -O-C(O)-;
- each L³ is independently a covalent bond, an alkylene, or substituted alkylene;
- each L⁴ is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, -CH₂-O-, and -NH-;
- 20 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;

Z¹ and Z² are each independently -O- or -N(R⁷)-;

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

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

R¹, R³, and R⁵ are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;

10 R² 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;

15 R⁴ and R⁶ are independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl;

each R⁷ is independently selected from the group consisting of H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, and substituted heterocyclyl;

20 R⁸ and R⁹ 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, L¹ is -C(R⁶)₂-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂-.

25 In another embodiment of the compounds of Formula IID, each L³ is alkylene.

In another embodiment of the compounds of Formula IID, each L³ is -CH₂-.

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.

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

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

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

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

In another embodiment of the compounds of Formula IID, Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, Z¹ is -NH-.

15 In another embodiment of the compounds of Formula IID, Z¹ is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, Z¹ is -N(CH₃)-.

In another embodiment of the compounds of Formula IID, Z² is -O-.

In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂- and X and Y are heterocyclalkyl.

20 In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and X and Y are heterocyclalkyl.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and X and Y are thiazolymethyl.

25 In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂- and Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and Z¹ is -NH-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and Z¹ is -N(alkyl)-.

5 In another embodiment of the compounds of Formula IID, L¹ is -CH₂- and Z¹ is -N(CH₃)-.

In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂- and Z² is -O-.

10 In another embodiment of the compounds of Formula IID, each L³ is alkylene and each A is aryl or substituted aryl.

In another embodiment of the compounds of Formula IID, each L³ is -CH₂- and each A is aryl or substituted aryl.

In another embodiment of the compounds of Formula IID, each L³-A is benzyl or substituted benzyl.

15 In another embodiment of the compounds of Formula IID, X and Y are heterocyclalkyl and Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z¹ is -N(R⁷)-.

20 In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z¹ is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z¹ is -N(CH₃)-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z¹ is -NH-.

25 In another embodiment of the compounds of Formula IID, X and Y are heterocyclalkyl and Z² is -O-.

In another embodiment of the compounds of Formula IID, X and Y are thiazolylmethyl and Z² is -O-.

In another embodiment of the compounds of Formula IID, Z¹ is -N(R⁷)- and Z² is -O-.

In another embodiment of the compounds of Formula IID, Z¹ is -N(alkyl)- and Z² is -O-.

5 In another embodiment of the compounds of Formula IID, Z¹ is -N(CH₃)- and Z² is -O-.

In another embodiment of the compounds of Formula IID, Z¹ is -NH- and Z² is -O-.

10 In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂-, X and Y are heterocyclalkyl, and Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are heterocyclalkyl, and Z¹ is -N(R⁷)-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are thiazolylmethyl, and Z¹ is -N(R⁷)-.

15 In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are thiazolylmethyl, and Z¹ is -N(alkyl)-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are thiazolylmethyl, and Z¹ is -N(CH₃)-.

20 In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are thiazolylmethyl, and Z¹ is -NH-.

In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂-, X and Y are heterocyclalkyl; and Z² is -O-.

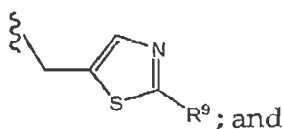
In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are heterocyclalkyl; and Z² is -O-.

25 In another embodiment of the compounds of Formula IID, L¹ is -CH₂-, X and Y are thiazolylmethyl; and Z² is -O-.

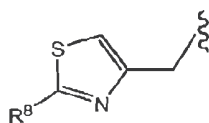
In another embodiment of the compounds of Formula IID, L¹ is -C(R⁶)₂-; each L³ is alkylene; each A is aryl or substituted aryl; X and Y are heterocyclalkyl; Z¹ is -N(R⁷)-; and Z² is -O-.

In another embodiment of the compounds of Formula IID, L¹ is -CH₂-; each L³-A is benzyl or substituted benzyl; X and Y are thiazolylmethyl; Z¹ is -N(CH₃)-; and Z² is -O-.

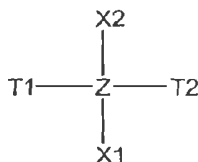
In another embodiment of the compounds of Formula IID, L¹ is -CH₂-; each L³-A is benzyl or substituted benzyl; Z¹ is -N(CH₃)-; Z² is -O-; X is



10 Y is



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



15

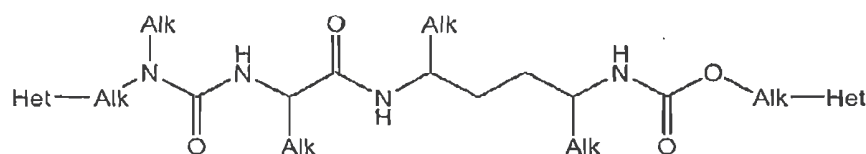
Formula II.

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

20

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:

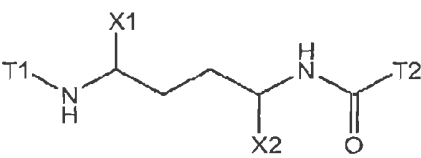
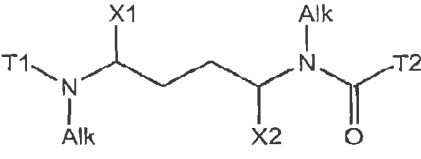
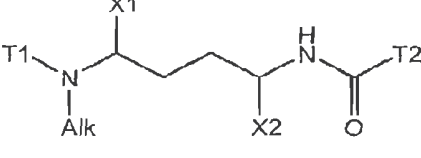
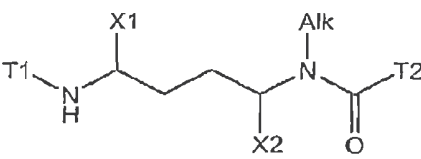
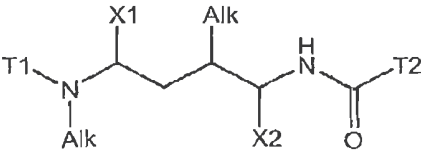
5 Z.T1.T2.X1.X2. Thus, for example, Z1.T1A.T2B.X1A.X2A represents the following structure:



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
- 5 "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	
Z4	
Z5	

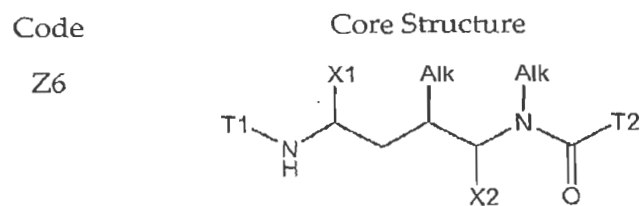
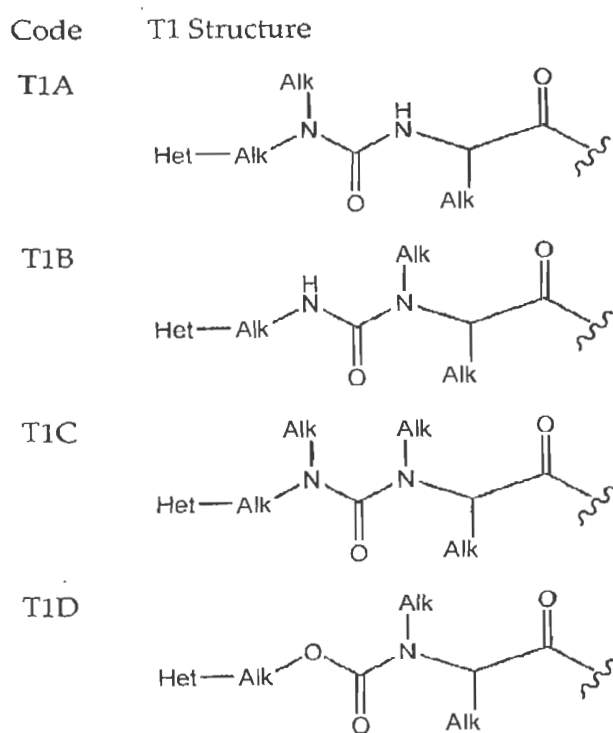
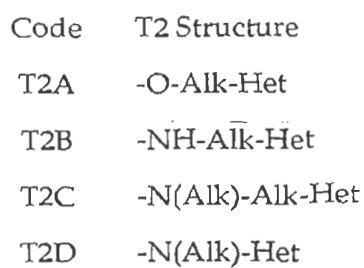
Table 2: T1 StructuresTable 3: T2 Structures

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

5 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,
 10 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,
 Z1.T1D.T2A.X1A.X2A, Z2.T1D.T2A.X1A.X2A, Z3.T1D.T2A.X1A.X2A,
 Z4.T1D.T2A.X1A.X2A, Z5.T1D.T2A.X1A.X2A, Z6.T1D.T2A.X1A.X2A,
 Z1.T1A.T2B.X1A.X2A, Z2.T1A.T2B.X1A.X2A, Z3.T1A.T2B.X1A.X2A,
 15 Z4.T1A.T2B.X1A.X2A, Z5.T1A.T2B.X1A.X2A, Z6.T1A.T2B.X1A.X2A,

Z1.T1B.T2B.X1A.X2A, Z2.T1B.T2B.X1A.X2A, Z3.T1B.T2B.X1A.X2A,
 Z4.T1B.T2B.X1A.X2A, Z5.T1B.T2B.X1A.X2A, Z6.T1B.T2B.X1A.X2A,
 Z1.T1C.T2B.X1A.X2A, Z2.T1C.T2B.X1A.X2A, Z3.T1C.T2B.X1A.X2A,
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 Z4.T1D.T2B.X1A.X2A, Z5.T1D.T2B.X1A.X2A, Z6.T1D.T2B.X1A.X2A,
 Z1.T1A.T2C.X1A.X2A, Z2.T1A.T2C.X1A.X2A, Z3.T1A.T2C.X1A.X2A,
 Z4.T1A.T2C.X1A.X2A, Z5.T1A.T2C.X1A.X2A, Z6.T1A.T2C.X1A.X2A,
 Z1.T1B.T2C.X1A.X2A, Z2.T1B.T2C.X1A.X2A, Z3.T1B.T2C.X1A.X2A,
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 Z1.T1C.T2C.X1A.X2A, Z2.T1C.T2C.X1A.X2A, Z3.T1C.T2C.X1A.X2A,
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 20 Z4.T1C.T2D.X1A.X2A, Z5.T1C.T2D.X1A.X2A, Z6.T1C.T2D.X1A.X2A,
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 Z4.T1B.T2A.X1B.X2A, Z5.T1B.T2A.X1B.X2A, Z6.T1B.T2A.X1B.X2A,
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 5 Z1.T1B.T2B.X1B.X2A, Z2.T1B.T2B.X1B.X2A, Z3.T1B.T2B.X1B.X2A,
 Z4.T1B.T2B.X1B.X2A, Z5.T1B.T2B.X1B.X2A, Z6.T1B.T2B.X1B.X2A,
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 Z1.T1D.T2B.X1B.X2A, Z2.T1D.T2B.X1B.X2A, Z3.T1D.T2B.X1B.X2A,
 10 Z4.T1D.T2B.X1B.X2A, Z5.T1D.T2B.X1B.X2A, Z6.T1D.T2B.X1B.X2A,
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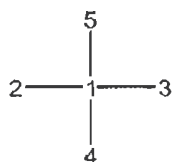
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 Z4.T1D.T2D.X1E.X2E, Z5.T1D.T2D.X1E.X2E, and Z6.T1D.T2D.X1E.X2E.

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:

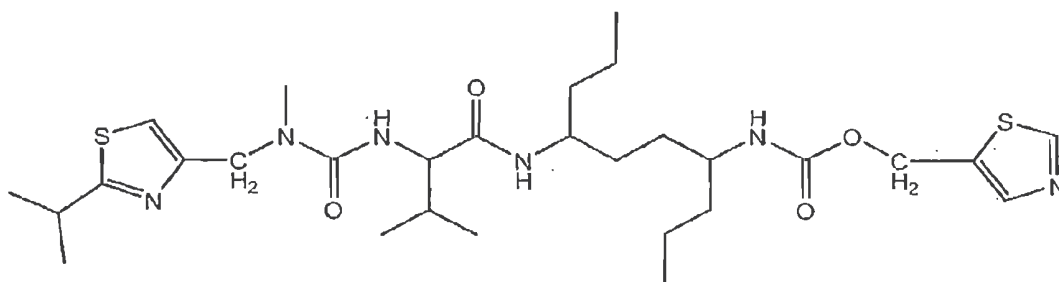


Table 7: "1" Structures

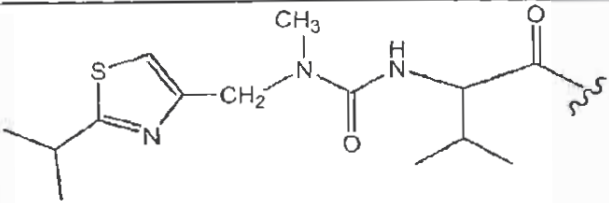
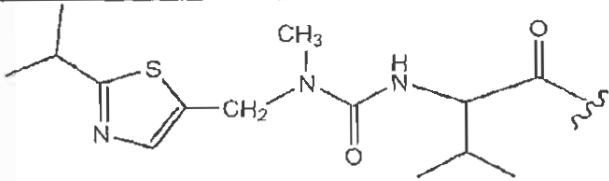
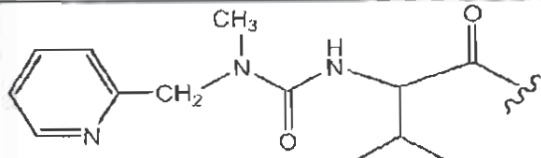
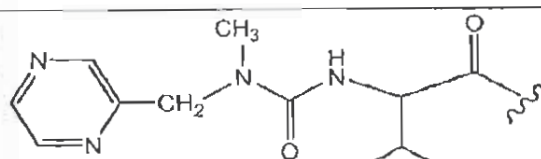
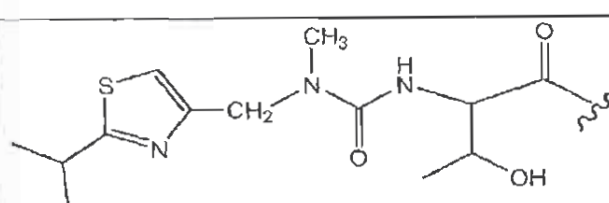
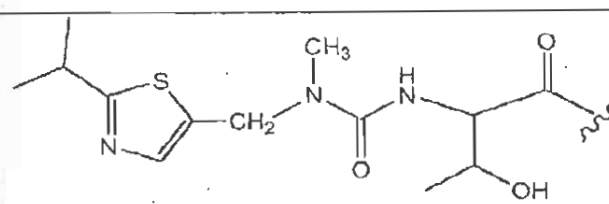
Code	"1" Structure
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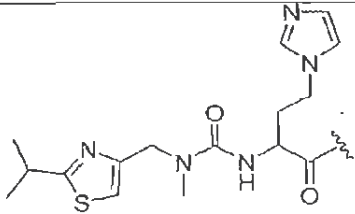
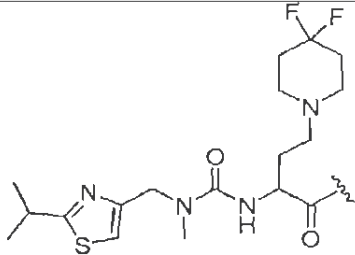
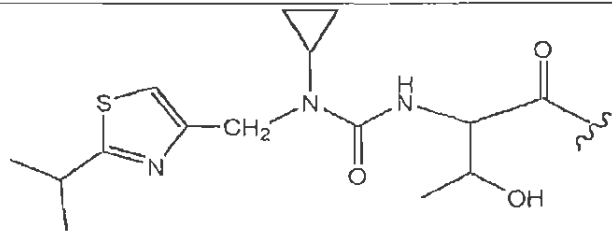
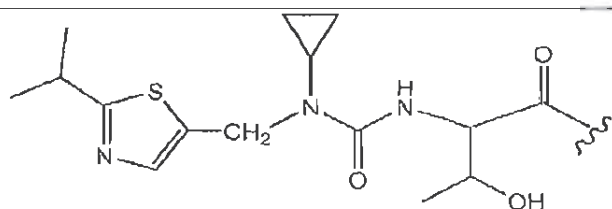
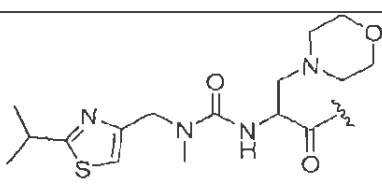
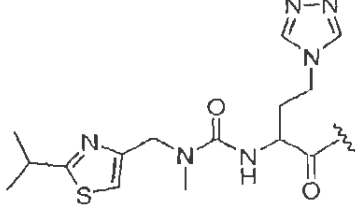
Code	"1" Structure
1a	
1b	
1c	
1d	
1e	
1f	
1g	

Code	"1" Structure
1h	 <chem>CC(=O)N[C@@H](C)CC[C@H](C)N</chem>
1i	 <chem>CC(=O)N[C@@H](C1CC1)CC[C@H](C)N</chem>
1j	 <chem>CC(=O)N[C@@H](C)C[C@H](C)[C@H](C)N(C)C</chem>
1k	 <chem>CC(=O)N[C@@H](C)C[C@H](CC)[C@H](C)N(C)C</chem>
1l	 <chem>CC(=O)N[C@@H](C)C[C@H](C1CC1)[C@H](C)N(C)C</chem>
1m	 <chem>CC(=O)N[C@@H](C)C[C@H](C)[C@H](C)N(C1CC1)C</chem>
1n	 <chem>CC(=O)N[C@@H](C)C[C@H](CC)[C@H](C)N(C1CC1)C</chem>

Code	"1" Structure
1o	 <chem>CC1(CCCC1C2CC2)C3CC3</chem>
1p	 <chem>CC(C)CC(C)C</chem>
1q	 <chem>CC(C)CC(C)C</chem>
1r	 <chem>CC(C)CC(C)C</chem>
1s	 <chem>CC(C)CC(C)C</chem>
1t	 <chem>CC(C)CC(C)C</chem>
1u	 <chem>CC(C)CC(C)C</chem>

Table 8: "2" Structures

Code	"2" Structure
2a	
2b	
2c	
2d	
2e	
2f	

Code	"2" Structure
2g	
2h	
2i	
2j	
2k	
2l	

Code	"2" Structure
2m	
2n	
2o	
2p	
2q	
2r	

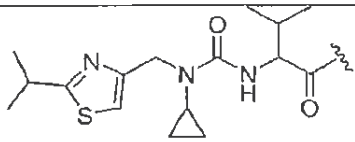
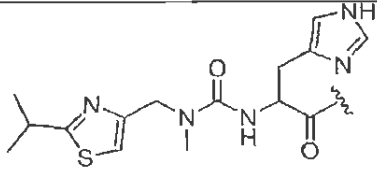
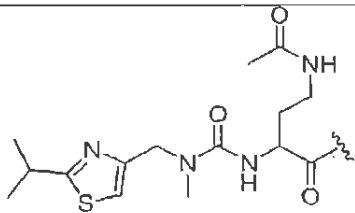
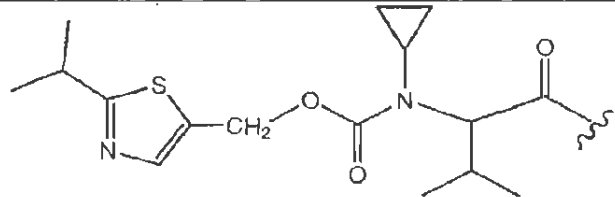
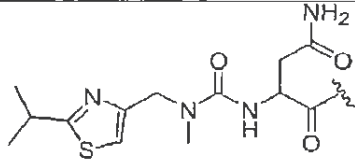
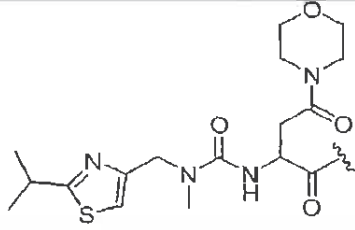
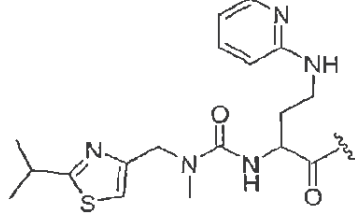
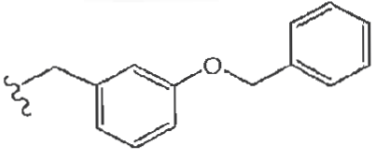
Code	"2" Structure
2s	
2t	
2u	
2v	
2w	
2x	
2y	

Table 9: "3" Structures

Code	"3" Structure
3a	-O-CH ₂ -(5-thiazolyl)
3b	-O-CH ₂ -(3-pyridyl)
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 ₂ CH ₂ -(4-morpholinyl)
4k	

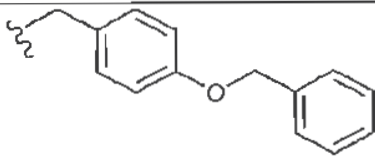
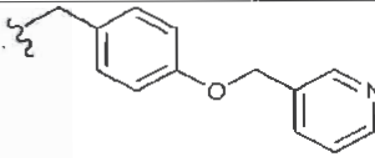
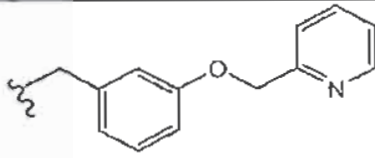
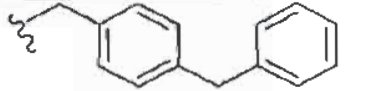
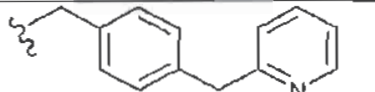
Code	"4" Structure
4l	
4m	
4n	
4o	
4p	

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)
5i	-CH ₂ -(2-pyridyl)

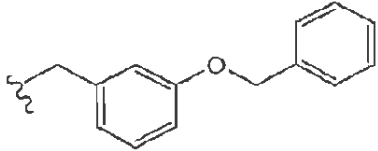
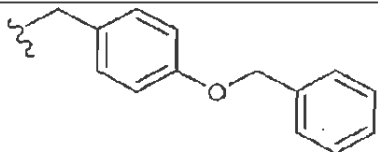
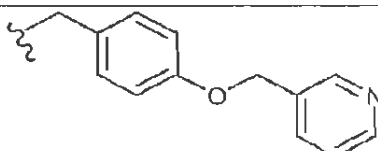
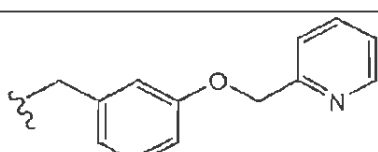
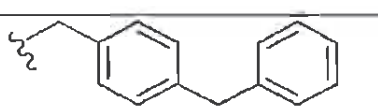
Code	"5" Structure
5j	-CH ₂ CH ₂ -(4-morpholiny)
5k	
5l	
5m	
5n	
5o	

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.,
 5 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.,
 10 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.,
 15 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.,

[illegible]

- 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.,
5 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.,
10 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.,
15 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.,
20 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.,
25 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.,
30 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.,
35 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.,
1j.2i.3a.4f.5a., 1p.2i.3a.4f.5a., 1a.2m.3a.4f.5a., 1b.2m.3a.4f.5a., 1f.2m.3a.4f.5a.,
40 1h.2m.3a.4f.5a., 1j.2m.3a.4f.5a., 1p.2m.3a.4f.5a., 1a.2o.3a.4f.5a., 1b.2o.3a.4f.5a.,
1f.2o.3a.4f.5a., 1h.2o.3a.4f.5a., 1j.2o.3a.4f.5a., 1p.2o.3a.4f.5a., 1a.2u.3a.4f.5a.,

- 1b.2u.3a.4f.5a., 1f.2u.3a.4f.5a., 1h.2u.3a.4f.5a., 1j.2u.3a.4f.5a., 1p.2u.3a.4f.5a.,
 1a.2y.3a.4f.5a., 1b.2y.3a.4f.5a., 1f.2y.3a.4f.5a., 1h.2y.3a.4f.5a., 1j.2y.3a.4f.5a.,
 1p.2y.3a.4f.5a., 1a.2a.3b.4f.5a., 1b.2a.3b.4f.5a., 1f.2a.3b.4f.5a., 1h.2a.3b.4f.5a.,
 1j.2a.3b.4f.5a., 1p.2a.3b.4f.5a., 1a.2b.3b.4f.5a., 1b.2b.3b.4f.5a., 1f.2b.3b.4f.5a.,
 5 1h.2b.3b.4f.5a., 1j.2b.3b.4f.5a., 1p.2b.3b.4f.5a., 1a.2e.3b.4f.5a., 1b.2e.3b.4f.5a.,
 1f.2e.3b.4f.5a., 1h.2e.3b.4f.5a., 1j.2e.3b.4f.5a., 1p.2e.3b.4f.5a., 1a.2f.3b.4f.5a.,
 1b.2f.3b.4f.5a., 1f.2f.3b.4f.5a., 1h.2f.3b.4f.5a., 1j.2f.3b.4f.5a., 1p.2f.3b.4f.5a.,
 1a.2i.3b.4f.5a., 1b.2i.3b.4f.5a., 1f.2i.3b.4f.5a., 1h.2i.3b.4f.5a., 1j.2i.3b.4f.5a.,
 1p.2i.3b.4f.5a., 1a.2m.3b.4f.5a., 1b.2m.3b.4f.5a., 1f.2m.3b.4f.5a., 1h.2m.3b.4f.5a.,
 10 1j.2m.3b.4f.5a., 1p.2m.3b.4f.5a., 1a.2o.3b.4f.5a., 1b.2o.3b.4f.5a., 1f.2o.3b.4f.5a.,
 1h.2o.3b.4f.5a., 1j.2o.3b.4f.5a., 1p.2o.3b.4f.5a., 1a.2u.3b.4f.5a., 1b.2u.3b.4f.5a.,
 1f.2u.3b.4f.5a., 1h.2u.3b.4f.5a., 1j.2u.3b.4f.5a., 1p.2u.3b.4f.5a., 1a.2y.3b.4f.5a.,
 1b.2y.3b.4f.5a., 1f.2y.3b.4f.5a., 1h.2y.3b.4f.5a., 1j.2y.3b.4f.5a., 1p.2y.3b.4f.5a.,
 1a.2a.3e.4f.5a., 1b.2a.3e.4f.5a., 1f.2a.3e.4f.5a., 1h.2a.3e.4f.5a., 1j.2a.3e.4f.5a.,
 15 1p.2a.3e.4f.5a., 1a.2b.3e.4f.5a., 1b.2b.3e.4f.5a., 1f.2b.3e.4f.5a., 1h.2b.3e.4f.5a.,
 1j.2b.3e.4f.5a., 1p.2b.3e.4f.5a., 1a.2e.3e.4f.5a., 1b.2e.3e.4f.5a., 1f.2e.3e.4f.5a.,
 1h.2e.3e.4f.5a., 1j.2e.3e.4f.5a., 1p.2e.3e.4f.5a., 1a.2f.3e.4f.5a., 1b.2f.3e.4f.5a.,
 1f.2f.3e.4f.5a., 1h.2f.3e.4f.5a., 1j.2f.3e.4f.5a., 1p.2f.3e.4f.5a., 1a.2i.3e.4f.5a.,
 1b.2i.3e.4f.5a., 1f.2i.3e.4f.5a., 1h.2i.3e.4f.5a., 1j.2i.3e.4f.5a., 1p.2i.3e.4f.5a.,
 20 1a.2m.3e.4f.5a., 1b.2m.3e.4f.5a., 1f.2m.3e.4f.5a., 1h.2m.3e.4f.5a., 1j.2m.3e.4f.5a.,
 1p.2m.3e.4f.5a., 1a.2o.3e.4f.5a., 1b.2o.3e.4f.5a., 1f.2o.3e.4f.5a., 1h.2o.3e.4f.5a.,
 1j.2o.3e.4f.5a., 1p.2o.3e.4f.5a., 1a.2u.3e.4f.5a., 1b.2u.3e.4f.5a., 1f.2u.3e.4f.5a.,
 1h.2u.3e.4f.5a., 1j.2u.3e.4f.5a., 1p.2u.3e.4f.5a., 1a.2y.3e.4f.5a., 1b.2y.3e.4f.5a.,
 1f.2y.3e.4f.5a., 1h.2y.3e.4f.5a., 1j.2y.3e.4f.5a., 1p.2y.3e.4f.5a., 1a.2a.3g.4f.5a.,
 25 1b.2a.3g.4f.5a., 1f.2a.3g.4f.5a., 1h.2a.3g.4f.5a., 1j.2a.3g.4f.5a., 1p.2a.3g.4f.5a.,
 1a.2b.3g.4f.5a., 1b.2b.3g.4f.5a., 1f.2b.3g.4f.5a., 1h.2b.3g.4f.5a., 1j.2b.3g.4f.5a.,
 1p.2b.3g.4f.5a., 1a.2e.3g.4f.5a., 1b.2e.3g.4f.5a., 1f.2e.3g.4f.5a., 1h.2e.3g.4f.5a.,
 1j.2e.3g.4f.5a., 1p.2e.3g.4f.5a., 1a.2f.3g.4f.5a., 1b.2f.3g.4f.5a., 1f.2f.3g.4f.5a.,
 1h.2f.3g.4f.5a., 1j.2f.3g.4f.5a., 1p.2f.3g.4f.5a., 1a.2i.3g.4f.5a., 1b.2i.3g.4f.5a.,
 30 1f.2i.3g.4f.5a., 1h.2i.3g.4f.5a., 1j.2i.3g.4f.5a., 1p.2i.3g.4f.5a., 1a.2m.3g.4f.5a.,
 1b.2m.3g.4f.5a., 1f.2m.3g.4f.5a., 1h.2m.3g.4f.5a., 1j.2m.3g.4f.5a., 1p.2m.3g.4f.5a.,
 1a.2o.3g.4f.5a., 1b.2o.3g.4f.5a., 1f.2o.3g.4f.5a., 1h.2o.3g.4f.5a., 1j.2o.3g.4f.5a.,
 1p.2o.3g.4f.5a., 1a.2u.3g.4f.5a., 1b.2u.3g.4f.5a., 1f.2u.3g.4f.5a., 1h.2u.3g.4f.5a.,
 1j.2u.3g.4f.5a., 1p.2u.3g.4f.5a., 1a.2y.3g.4f.5a., 1b.2y.3g.4f.5a., 1f.2y.3g.4f.5a.,
 35 1h.2y.3g.4f.5a., 1j.2y.3g.4f.5a., 1p.2y.3g.4f.5a., 1a.2a.3a.4g.5a., 1b.2a.3a.4g.5a.,
 1f.2a.3a.4g.5a., 1h.2a.3a.4g.5a., 1j.2a.3a.4g.5a., 1p.2a.3a.4g.5a., 1a.2b.3a.4g.5a.,
 1b.2b.3a.4g.5a., 1f.2b.3a.4g.5a., 1h.2b.3a.4g.5a., 1j.2b.3a.4g.5a., 1p.2b.3a.4g.5a.,
 1a.2e.3a.4g.5a., 1b.2e.3a.4g.5a., 1f.2e.3a.4g.5a., 1h.2e.3a.4g.5a., 1j.2e.3a.4g.5a.,
 1p.2e.3a.4g.5a., 1a.2f.3a.4g.5a., 1b.2f.3a.4g.5a., 1f.2f.3a.4g.5a., 1h.2f.3a.4g.5a.,
 40 1j.2f.3a.4g.5a., 1p.2f.3a.4g.5a., 1a.2i.3a.4g.5a., 1b.2i.3a.4g.5a., 1f.2i.3a.4g.5a.,
 1h.2i.3a.4g.5a., 1j.2i.3a.4g.5a., 1p.2i.3a.4g.5a., 1a.2m.3a.4g.5a., 1b.2m.3a.4g.5a.,

[illegible]

- 1h.2f.3a.4h.5a., 1j.2f.3a.4h.5a., 1p.2f.3a.4h.5a., 1a.2i.3a.4h.5a., 1b.2i.3a.4h.5a.,
 1f.2i.3a.4h.5a., 1h.2i.3a.4h.5a., 1j.2i.3a.4h.5a., 1p.2i.3a.4h.5a., 1a.2m.3a.4h.5a.,
 1b.2m.3a.4h.5a., 1f.2m.3a.4h.5a., 1h.2m.3a.4h.5a., 1j.2m.3a.4h.5a., 1p.2m.3a.4h.5a.,
 1a.2o.3a.4h.5a., 1b.2o.3a.4h.5a., 1f.2o.3a.4h.5a., 1h.2o.3a.4h.5a., 1j.2o.3a.4h.5a.,
 5 1p.2o.3a.4h.5a., 1a.2u.3a.4h.5a., 1b.2u.3a.4h.5a., 1f.2u.3a.4h.5a., 1h.2u.3a.4h.5a.,
 1j.2u.3a.4h.5a., 1p.2u.3a.4h.5a., 1a.2y.3a.4h.5a., 1b.2y.3a.4h.5a., 1f.2y.3a.4h.5a.,
 1h.2y.3a.4h.5a., 1j.2y.3a.4h.5a., 1p.2y.3a.4h.5a., 1a.2a.3b.4h.5a., 1b.2a.3b.4h.5a.,
 1f.2a.3b.4h.5a., 1h.2a.3b.4h.5a., 1j.2a.3b.4h.5a., 1p.2a.3b.4h.5a., 1a.2b.3b.4h.5a.,
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 1h.2f.3e.4a.5d., 1j.2f.3e.4a.5d., 1p.2f.3e.4a.5d., 1a.2i.3e.4a.5d., 1b.2i.3e.4a.5d.,
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 1p.2o.3e.4a.5d., 1a.2u.3e.4a.5d., 1b.2u.3e.4a.5d., 1f.2u.3e.4a.5d., 1h.2u.3e.4a.5d.,
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 5 1b.2y.3g.4d.5d., 1f.2y.3g.4d.5d., 1h.2y.3g.4d.5d., 1j.2y.3g.4d.5d., 1p.2y.3g.4d.5d.,
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 10 1f.2f.3a.4f.5d., 1h.2f.3a.4f.5d., 1j.2f.3a.4f.5d., 1p.2f.3a.4f.5d., 1a.2i.3a.4f.5d.,
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 20 1j.2e.3b.4f.5d., 1p.2e.3b.4f.5d., 1a.2f.3b.4f.5d., 1b.2f.3b.4f.5d., 1f.2f.3b.4f.5d.,
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 5 1f.2o.3g.4f.5d., 1h.2o.3g.4f.5d., 1j.2o.3g.4f.5d., 1p.2o.3g.4f.5d., 1a.2u.3g.4f.5d.,
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 5 1f.2i.3g.4g.5d., 1h.2i.3g.4g.5d., 1j.2i.3g.4g.5d., 1p.2i.3g.4g.5d., 1a.2m.3g.4g.5d.,
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 1a.2b.3a.4h.5d., 1b.2b.3a.4h.5d., 1f.2b.3a.4h.5d., 1h.2b.3a.4h.5d., 1j.2b.3a.4h.5d.,
 1p.2b.3a.4h.5d., 1a.2e.3a.4h.5d., 1b.2e.3a.4h.5d., 1f.2e.3a.4h.5d., 1h.2e.3a.4h.5d.,
 1j.2e.3a.4h.5d., 1p.2e.3a.4h.5d., 1a.2f.3a.4h.5d., 1b.2f.3a.4h.5d., 1f.2f.3a.4h.5d.,
 15 1h.2f.3a.4h.5d., 1j.2f.3a.4h.5d., 1p.2f.3a.4h.5d., 1a.2i.3a.4h.5d., 1b.2i.3a.4h.5d.,
 1f.2i.3a.4h.5d., 1h.2i.3a.4h.5d., 1j.2i.3a.4h.5d., 1p.2i.3a.4h.5d., 1a.2m.3a.4h.5d.,
 1b.2m.3a.4h.5d., 1f.2m.3a.4h.5d., 1h.2m.3a.4h.5d., 1j.2m.3a.4h.5d.,
 1p.2m.3a.4h.5d., 1a.2o.3a.4h.5d., 1b.2o.3a.4h.5d., 1f.2o.3a.4h.5d., 1h.2o.3a.4h.5d.,
 1j.2o.3a.4h.5d., 1p.2o.3a.4h.5d., 1a.2u.3a.4h.5d., 1b.2u.3a.4h.5d., 1f.2u.3a.4h.5d.,
 20 1h.2u.3a.4h.5d., 1j.2u.3a.4h.5d., 1p.2u.3a.4h.5d., 1a.2y.3a.4h.5d., 1b.2y.3a.4h.5d.,
 1f.2y.3a.4h.5d., 1h.2y.3a.4h.5d., 1j.2y.3a.4h.5d., 1p.2y.3a.4h.5d., 1a.2a.3b.4h.5d.,
 1b.2a.3b.4h.5d., 1f.2a.3b.4h.5d., 1h.2a.3b.4h.5d., 1j.2a.3b.4h.5d., 1p.2a.3b.4h.5d.,
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 1f.2i.3b.4h.5d., 1h.2i.3b.4h.5d., 1j.2i.3b.4h.5d., 1p.2i.3b.4h.5d., 1a.2m.3b.4h.5d.,
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 35 1p.2b.3e.4h.5d., 1a.2e.3e.4h.5d., 1b.2e.3e.4h.5d., 1f.2e.3e.4h.5d., 1h.2e.3e.4h.5d.,
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 40 1a.2o.3e.4h.5d., 1b.2o.3e.4h.5d., 1f.2o.3e.4h.5d., 1h.2o.3e.4h.5d., 1j.2o.3e.4h.5d.,
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- 1j.2u.3e.4h.5d., 1p.2u.3e.4h.5d., 1a.2y.3e.4h.5d., 1b.2y.3e.4h.5d., 1f.2y.3e.4h.5d.,
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 5 1a.2e.3g.4h.5d., 1b.2e.3g.4h.5d., 1f.2e.3g.4h.5d., 1h.2e.3g.4h.5d., 1j.2e.3g.4h.5d.,
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 10 1b.2o.3g.4h.5d., 1f.2o.3g.4h.5d., 1h.2o.3g.4h.5d., 1j.2o.3g.4h.5d., 1p.2o.3g.4h.5d.,
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 40 1b.2i.3e.4i.5d., 1f.2i.3e.4i.5d., 1h.2i.3e.4i.5d., 1j.2i.3e.4i.5d., 1p.2i.3e.4i.5d.,
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- 1p.2m.3e.4i.5d., 1a.2o.3e.4i.5d., 1b.2o.3e.4i.5d., 1f.2o.3e.4i.5d., 1h.2o.3e.4i.5d.,
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 5 1b.2a.3g.4i.5d., 1f.2a.3g.4i.5d., 1h.2a.3g.4i.5d., 1j.2a.3g.4i.5d., 1p.2a.3g.4i.5d.,
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 20 1j.2f.3a.4a.5f., 1p.2f.3a.4a.5f., 1a.2i.3a.4a.5f., 1b.2i.3a.4a.5f., 1f.2i.3a.4a.5f.,
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 1b.2o.3a.4a.5f., 1f.2o.3a.4a.5f., 1h.2o.3a.4a.5f., 1j.2o.3a.4a.5f., 1p.2o.3a.4a.5f.,
 1a.2u.3a.4a.5f., 1b.2u.3a.4a.5f., 1f.2u.3a.4a.5f., 1h.2u.3a.4a.5f., 1j.2u.3a.4a.5f.,
 25 1p.2u.3a.4a.5f., 1a.2y.3a.4a.5f., 1b.2y.3a.4a.5f., 1f.2y.3a.4a.5f., 1h.2y.3a.4a.5f.,
 1j.2y.3a.4a.5f., 1p.2y.3a.4a.5f., 1a.2a.3b.4a.5f., 1b.2a.3b.4a.5f., 1f.2a.3b.4a.5f.,
 1h.2a.3b.4a.5f., 1j.2a.3b.4a.5f., 1p.2a.3b.4a.5f., 1a.2b.3b.4a.5f., 1b.2b.3b.4a.5f.,
 1f.2b.3b.4a.5f., 1h.2b.3b.4a.5f., 1j.2b.3b.4a.5f., 1p.2b.3b.4a.5f., 1a.2e.3b.4a.5f.,
 1b.2e.3b.4a.5f., 1f.2e.3b.4a.5f., 1h.2e.3b.4a.5f., 1j.2e.3b.4a.5f., 1p.2e.3b.4a.5f.,
 30 1a.2f.3b.4a.5f., 1b.2f.3b.4a.5f., 1f.2f.3b.4a.5f., 1h.2f.3b.4a.5f., 1j.2f.3b.4a.5f.,
 1p.2f.3b.4a.5f., 1a.2i.3b.4a.5f., 1b.2i.3b.4a.5f., 1f.2i.3b.4a.5f., 1h.2i.3b.4a.5f.,
 1j.2i.3b.4a.5f., 1p.2i.3b.4a.5f., 1a.2m.3b.4a.5f., 1b.2m.3b.4a.5f., 1f.2m.3b.4a.5f.,
 1h.2m.3b.4a.5f., 1j.2m.3b.4a.5f., 1p.2m.3b.4a.5f., 1a.2o.3b.4a.5f., 1b.2o.3b.4a.5f.,
 1f.2o.3b.4a.5f., 1h.2o.3b.4a.5f., 1j.2o.3b.4a.5f., 1p.2o.3b.4a.5f., 1a.2u.3b.4a.5f.,
 35 1b.2u.3b.4a.5f., 1f.2u.3b.4a.5f., 1h.2u.3b.4a.5f., 1j.2u.3b.4a.5f., 1p.2u.3b.4a.5f.,
 1a.2y.3b.4a.5f., 1b.2y.3b.4a.5f., 1f.2y.3b.4a.5f., 1h.2y.3b.4a.5f., 1j.2y.3b.4a.5f.,
 1p.2y.3b.4a.5f., 1a.2a.3e.4a.5f., 1b.2a.3e.4a.5f., 1f.2a.3e.4a.5f., 1h.2a.3e.4a.5f.,
 1j.2a.3e.4a.5f., 1p.2a.3e.4a.5f., 1a.2b.3e.4a.5f., 1b.2b.3e.4a.5f., 1f.2b.3e.4a.5f.,
 1h.2b.3e.4a.5f., 1j.2b.3e.4a.5f., 1p.2b.3e.4a.5f., 1a.2e.3e.4a.5f., 1b.2e.3e.4a.5f.,
 40 1f.2e.3e.4a.5f., 1h.2e.3e.4a.5f., 1j.2e.3e.4a.5f., 1p.2e.3e.4a.5f., 1a.2f.3e.4a.5f.,
 1b.2f.3e.4a.5f., 1f.2f.3e.4a.5f., 1h.2f.3e.4a.5f., 1j.2f.3e.4a.5f., 1p.2f.3e.4a.5f.,

1a.2i.3e.4a.5f., 1b.2i.3e.4a.5f., 1f.2i.3e.4a.5f., 1h.2i.3e.4a.5f., 1j.2i.3e.4a.5f.,
 1p.2i.3e.4a.5f., 1a.2m.3e.4a.5f., 1b.2m.3e.4a.5f., 1f.2m.3e.4a.5f., 1h.2m.3e.4a.5f.,
 1j.2m.3e.4a.5f., 1p.2m.3e.4a.5f., 1a.2o.3e.4a.5f., 1b.2o.3e.4a.5f., 1f.2o.3e.4a.5f.,
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 5 1f.2u.3e.4a.5f., 1h.2u.3e.4a.5f., 1j.2u.3e.4a.5f., 1p.2u.3e.4a.5f., 1a.2y.3e.4a.5f.,
 1b.2y.3e.4a.5f., 1f.2y.3e.4a.5f., 1h.2y.3e.4a.5f., 1j.2y.3e.4a.5f., 1p.2y.3e.4a.5f.,
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 10 1h.2e.3g.4a.5f., 1j.2e.3g.4a.5f., 1p.2e.3g.4a.5f., 1a.2f.3g.4a.5f., 1b.2f.3g.4a.5f.,
 1f.2f.3g.4a.5f., 1h.2f.3g.4a.5f., 1j.2f.3g.4a.5f., 1p.2f.3g.4a.5f., 1a.2i.3g.4a.5f.,
 1b.2i.3g.4a.5f., 1f.2i.3g.4a.5f., 1h.2i.3g.4a.5f., 1j.2i.3g.4a.5f., 1p.2i.3g.4a.5f.,
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 15 1j.2o.3g.4a.5f., 1p.2o.3g.4a.5f., 1a.2u.3g.4a.5f., 1b.2u.3g.4a.5f., 1f.2u.3g.4a.5f.,
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 20 1p.2b.3a.4d.5f., 1a.2e.3a.4d.5f., 1b.2e.3a.4d.5f., 1f.2e.3a.4d.5f., 1h.2e.3a.4d.5f.,
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 1h.2f.3a.4d.5f., 1j.2f.3a.4d.5f., 1p.2f.3a.4d.5f., 1a.2i.3a.4d.5f., 1b.2i.3a.4d.5f.,
 1f.2i.3a.4d.5f., 1h.2i.3a.4d.5f., 1j.2i.3a.4d.5f., 1p.2i.3a.4d.5f., 1a.2m.3a.4d.5f.,
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 25 1a.2o.3a.4d.5f., 1b.2o.3a.4d.5f., 1f.2o.3a.4d.5f., 1h.2o.3a.4d.5f., 1j.2o.3a.4d.5f.,
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 35 1f.2m.3b.4d.5f., 1h.2m.3b.4d.5f., 1j.2m.3b.4d.5f., 1p.2m.3b.4d.5f., 1a.2o.3b.4d.5f.,
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 5 1h.2m.3e.4d.5f., 1j.2m.3e.4d.5f., 1p.2m.3e.4d.5f., 1a.2o.3e.4d.5f., 1b.2o.3e.4d.5f.,
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 10 1j.2a.3g.4d.5f., 1p.2a.3g.4d.5f., 1a.2b.3g.4d.5f., 1b.2b.3g.4d.5f., 1f.2b.3g.4d.5f.,
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 15 1p.2i.3g.4d.5f., 1a.2m.3g.4d.5f., 1b.2m.3g.4d.5f., 1f.2m.3g.4d.5f., 1h.2m.3g.4d.5f.,
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 35 1h.2f.3b.4f.5f., 1j.2f.3b.4f.5f., 1p.2f.3b.4f.5f., 1a.2i.3b.4f.5f., 1b.2i.3b.4f.5f.,
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 40 1j.2u.3b.4f.5f., 1p.2u.3b.4f.5f., 1a.2y.3b.4f.5f., 1b.2y.3b.4f.5f., 1f.2y.3b.4f.5f.,
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 1p.2e.3e.4f.5f., 1a.2f.3e.4f.5f., 1b.2f.3e.4f.5f., 1f.2f.3e.4f.5f., 1h.2f.3e.4f.5f.,
 5 1j.2f.3e.4f.5f., 1p.2f.3e.4f.5f., 1a.2i.3e.4f.5f., 1b.2i.3e.4f.5f., 1f.2i.3e.4f.5f.,
 1h.2i.3e.4f.5f., 1j.2i.3e.4f.5f., 1p.2i.3e.4f.5f., 1a.2m.3e.4f.5f., 1b.2m.3e.4f.5f.,
 1f.2m.3e.4f.5f., 1h.2m.3e.4f.5f., 1j.2m.3e.4f.5f., 1p.2m.3e.4f.5f., 1a.2o.3e.4f.5f.,
 1b.2o.3e.4f.5f., 1f.2o.3e.4f.5f., 1h.2o.3e.4f.5f., 1j.2o.3e.4f.5f., 1p.2o.3e.4f.5f.,
 1a.2u.3e.4f.5f., 1b.2u.3e.4f.5f., 1f.2u.3e.4f.5f., 1h.2u.3e.4f.5f., 1j.2u.3e.4f.5f.,
 10 1p.2u.3e.4f.5f., 1a.2y.3e.4f.5f., 1b.2y.3e.4f.5f., 1f.2y.3e.4f.5f., 1h.2y.3e.4f.5f.,
 1j.2y.3e.4f.5f., 1p.2y.3e.4f.5f., 1a.2a.3g.4f.5f., 1b.2a.3g.4f.5f., 1f.2a.3g.4f.5f.,
 1h.2a.3g.4f.5f., 1j.2a.3g.4f.5f., 1p.2a.3g.4f.5f., 1a.2b.3g.4f.5f., 1b.2b.3g.4f.5f.,
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 1b.2e.3g.4f.5f., 1f.2e.3g.4f.5f., 1h.2e.3g.4f.5f., 1j.2e.3g.4f.5f., 1p.2e.3g.4f.5f.,
 15 1a.2f.3g.4f.5f., 1b.2f.3g.4f.5f., 1f.2f.3g.4f.5f., 1h.2f.3g.4f.5f., 1j.2f.3g.4f.5f.,
 1p.2f.3g.4f.5f., 1a.2i.3g.4f.5f., 1b.2i.3g.4f.5f., 1f.2i.3g.4f.5f., 1h.2i.3g.4f.5f.,
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 1f.2o.3g.4f.5f., 1h.2o.3g.4f.5f., 1j.2o.3g.4f.5f., 1p.2o.3g.4f.5f., 1a.2u.3g.4f.5f.,
 20 1b.2u.3g.4f.5f., 1f.2u.3g.4f.5f., 1h.2u.3g.4f.5f., 1j.2u.3g.4f.5f., 1p.2u.3g.4f.5f.,
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 25 1f.2e.3a.4g.5f., 1h.2e.3a.4g.5f., 1j.2e.3a.4g.5f., 1p.2e.3a.4g.5f., 1a.2f.3a.4g.5f.,
 1b.2f.3a.4g.5f., 1f.2f.3a.4g.5f., 1h.2f.3a.4g.5f., 1j.2f.3a.4g.5f., 1p.2f.3a.4g.5f.,
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 30 1h.2o.3a.4g.5f., 1j.2o.3a.4g.5f., 1p.2o.3a.4g.5f., 1a.2u.3a.4g.5f., 1b.2u.3a.4g.5f.,
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 35 1j.2b.3b.4g.5f., 1p.2b.3b.4g.5f., 1a.2e.3b.4g.5f., 1b.2e.3b.4g.5f., 1f.2e.3b.4g.5f.,
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 1f.2f.3b.4g.5f., 1h.2f.3b.4g.5f., 1j.2f.3b.4g.5f., 1p.2f.3b.4g.5f., 1a.2i.3b.4g.5f.,
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 40 1p.2m.3b.4g.5f., 1a.2o.3b.4g.5f., 1b.2o.3b.4g.5f., 1f.2o.3b.4g.5f., 1h.2o.3b.4g.5f.,
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 5 1p.2b.3e.4g.5f., 1a.2e.3e.4g.5f., 1b.2e.3e.4g.5f., 1f.2e.3e.4g.5f., 1h.2e.3e.4g.5f.,
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 10 1a.2o.3e.4g.5f., 1b.2o.3e.4g.5f., 1f.2o.3e.4g.5f., 1h.2o.3e.4g.5f., 1j.2o.3e.4g.5f.,
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 15 1b.2b.3g.4g.5f., 1f.2b.3g.4g.5f., 1h.2b.3g.4g.5f., 1j.2b.3g.4g.5f., 1p.2b.3g.4g.5f.,
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 20 1f.2m.3g.4g.5f., 1h.2m.3g.4g.5f., 1j.2m.3g.4g.5f., 1p.2m.3g.4g.5f., 1a.2o.3g.4g.5f.,
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 35 1p.2y.3a.4h.5f., 1a.2a.3b.4h.5f., 1b.2a.3b.4h.5f., 1f.2a.3b.4h.5f., 1h.2a.3b.4h.5f.,
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 40 1a.2i.3b.4h.5f., 1b.2i.3b.4h.5f., 1f.2i.3b.4h.5f., 1h.2i.3b.4h.5f., 1j.2i.3b.4h.5f.,
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 5 1a.2a.3e.4h.5f., 1b.2a.3e.4h.5f., 1f.2a.3e.4h.5f., 1h.2a.3e.4h.5f., 1j.2a.3e.4h.5f.,
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 20 1h.2f.3g.4h.5f., 1j.2f.3g.4h.5f., 1p.2f.3g.4h.5f., 1a.2i.3g.4h.5f., 1b.2i.3g.4h.5f.,
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 25 1j.2u.3g.4h.5f., 1p.2u.3g.4h.5f., 1a.2y.3g.4h.5f., 1b.2y.3g.4h.5f., 1f.2y.3g.4h.5f.,
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 30 1p.2e.3a.4i.5f., 1a.2f.3a.4i.5f., 1b.2f.3a.4i.5f., 1f.2f.3a.4i.5f., 1h.2f.3a.4i.5f.,
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 1b.2o.3a.4i.5f., 1f.2o.3a.4i.5f., 1h.2o.3a.4i.5f., 1j.2o.3a.4i.5f., 1p.2o.3a.4i.5f.,
 35 1a.2u.3a.4i.5f., 1b.2u.3a.4i.5f., 1f.2u.3a.4i.5f., 1h.2u.3a.4i.5f., 1j.2u.3a.4i.5f.,
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 1j.2y.3a.4i.5f., 1p.2y.3a.4i.5f., 1a.2a.3b.4i.5f., 1b.2a.3b.4i.5f., 1f.2a.3b.4i.5f.,
 1h.2a.3b.4i.5f., 1j.2a.3b.4i.5f., 1p.2a.3b.4i.5f., 1a.2b.3b.4i.5f., 1b.2b.3b.4i.5f.,
 1f.2b.3b.4i.5f., 1h.2b.3b.4i.5f., 1j.2b.3b.4i.5f., 1p.2b.3b.4i.5f., 1a.2e.3b.4i.5f.,
 40 1b.2e.3b.4i.5f., 1f.2e.3b.4i.5f., 1h.2e.3b.4i.5f., 1j.2e.3b.4i.5f., 1p.2e.3b.4i.5f.,
 1a.2f.3b.4i.5f., 1b.2f.3b.4i.5f., 1f.2f.3b.4i.5f., 1h.2f.3b.4i.5f., 1j.2f.3b.4i.5f.,

- 1p.2f.3b.4i.5f., 1a.2i.3b.4i.5f., 1b.2i.3b.4i.5f., 1f.2i.3b.4i.5f., 1h.2i.3b.4i.5f.,
 1j.2i.3b.4i.5f., 1p.2i.3b.4i.5f., 1a.2m.3b.4i.5f., 1b.2m.3b.4i.5f., 1f.2m.3b.4i.5f.,
 1h.2m.3b.4i.5f., 1j.2m.3b.4i.5f., 1p.2m.3b.4i.5f., 1a.2o.3b.4i.5f., 1b.2o.3b.4i.5f.,
 1f.2o.3b.4i.5f., 1h.2o.3b.4i.5f., 1j.2o.3b.4i.5f., 1p.2o.3b.4i.5f., 1a.2u.3b.4i.5f.,
 5 1b.2u.3b.4i.5f., 1f.2u.3b.4i.5f., 1h.2u.3b.4i.5f., 1j.2u.3b.4i.5f., 1p.2u.3b.4i.5f.,
 1a.2y.3b.4i.5f., 1b.2y.3b.4i.5f., 1f.2y.3b.4i.5f., 1h.2y.3b.4i.5f., 1j.2y.3b.4i.5f.,
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 10 1f.2e.3e.4i.5f., 1h.2e.3e.4i.5f., 1j.2e.3e.4i.5f., 1p.2e.3e.4i.5f., 1a.2f.3e.4i.5f.,
 1b.2f.3e.4i.5f., 1f.2f.3e.4i.5f., 1h.2f.3e.4i.5f., 1j.2f.3e.4i.5f., 1p.2f.3e.4i.5f.,
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 15 1h.2o.3e.4i.5f., 1j.2o.3e.4i.5f., 1p.2o.3e.4i.5f., 1a.2u.3e.4i.5f., 1b.2u.3e.4i.5f.,
 1f.2u.3e.4i.5f., 1h.2u.3e.4i.5f., 1j.2u.3e.4i.5f., 1p.2u.3e.4i.5f., 1a.2y.3e.4i.5f.,
 1b.2y.3e.4i.5f., 1f.2y.3e.4i.5f., 1h.2y.3e.4i.5f., 1j.2y.3e.4i.5f., 1p.2y.3e.4i.5f.,
 1a.2a.3g.4i.5f., 1b.2a.3g.4i.5f., 1f.2a.3g.4i.5f., 1h.2a.3g.4i.5f., 1j.2a.3g.4i.5f.,
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 20 1j.2b.3g.4i.5f., 1p.2b.3g.4i.5f., 1a.2e.3g.4i.5f., 1b.2e.3g.4i.5f., 1f.2e.3g.4i.5f.,
 1h.2e.3g.4i.5f., 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.,
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 25 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.,
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 30 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.,
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 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.,
 35 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.,
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 5 1f.2m.3b.4a.5g., 1h.2m.3b.4a.5g., 1j.2m.3b.4a.5g., 1p.2m.3b.4a.5g., 1a.2o.3b.4a.5g.,
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 20 1p.2y.3e.4a.5g., 1a.2a.3g.4a.5g., 1b.2a.3g.4a.5g., 1f.2a.3g.4a.5g., 1h.2a.3g.4a.5g.,
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 25 1a.2i.3g.4a.5g., 1b.2i.3g.4a.5g., 1f.2i.3g.4a.5g., 1h.2i.3g.4a.5g., 1j.2i.3g.4a.5g.,
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 30 1b.2y.3g.4a.5g., 1f.2y.3g.4a.5g., 1h.2y.3g.4a.5g., 1j.2y.3g.4a.5g., 1p.2y.3g.4a.5g.,
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 5 1h.2f.3b.4d.5g., 1j.2f.3b.4d.5g., 1p.2f.3b.4d.5g., 1a.2i.3b.4d.5g., 1b.2i.3b.4d.5g.,
 1f.2i.3b.4d.5g., 1h.2i.3b.4d.5g., 1j.2i.3b.4d.5g., 1p.2i.3b.4d.5g., 1a.2m.3b.4d.5g.,
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 1j.2o.3b.4d.5g., 1p.2o.3b.4d.5g., 1a.2u.3b.4d.5g., 1b.2u.3b.4d.5g., 1f.2u.3b.4d.5g.,
 10 1h.2u.3b.4d.5g., 1j.2u.3b.4d.5g., 1p.2u.3b.4d.5g., 1a.2y.3b.4d.5g., 1b.2y.3b.4d.5g.,
 1f.2y.3b.4d.5g., 1h.2y.3b.4d.5g., 1j.2y.3b.4d.5g., 1p.2y.3b.4d.5g., 1a.2a.3e.4d.5g.,
 1b.2a.3e.4d.5g., 1f.2a.3e.4d.5g., 1h.2a.3e.4d.5g., 1j.2a.3e.4d.5g., 1p.2a.3e.4d.5g.,
 1a.2b.3e.4d.5g., 1b.2b.3e.4d.5g., 1f.2b.3e.4d.5g., 1h.2b.3e.4d.5g., 1j.2b.3e.4d.5g.,
 1p.2b.3e.4d.5g., 1a.2e.3e.4d.5g., 1b.2e.3e.4d.5g., 1f.2e.3e.4d.5g., 1h.2e.3e.4d.5g.,
 15 1j.2e.3e.4d.5g., 1p.2e.3e.4d.5g., 1a.2f.3e.4d.5g., 1b.2f.3e.4d.5g., 1f.2f.3e.4d.5g.,
 1h.2f.3e.4d.5g., 1j.2f.3e.4d.5g., 1p.2f.3e.4d.5g., 1a.2i.3e.4d.5g., 1b.2i.3e.4d.5g.,
 1f.2i.3e.4d.5g., 1h.2i.3e.4d.5g., 1j.2i.3e.4d.5g., 1p.2i.3e.4d.5g., 1a.2m.3e.4d.5g.,
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 20 1p.2o.3e.4d.5g., 1a.2u.3e.4d.5g., 1b.2u.3e.4d.5g., 1f.2u.3e.4d.5g., 1h.2u.3e.4d.5g.,
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 1f.2a.3g.4d.5g., 1h.2a.3g.4d.5g., 1j.2a.3g.4d.5g., 1p.2a.3g.4d.5g., 1a.2b.3g.4d.5g.,
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 25 1a.2e.3g.4d.5g., 1b.2e.3g.4d.5g., 1f.2e.3g.4d.5g., 1h.2e.3g.4d.5g., 1j.2e.3g.4d.5g.,
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 1j.2f.3g.4d.5g., 1p.2f.3g.4d.5g., 1a.2i.3g.4d.5g., 1b.2i.3g.4d.5g., 1f.2i.3g.4d.5g.,
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 30 1b.2o.3g.4d.5g., 1f.2o.3g.4d.5g., 1h.2o.3g.4d.5g., 1j.2o.3g.4d.5g., 1p.2o.3g.4d.5g.,
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 35 1f.2b.3a.4f.5g., 1h.2b.3a.4f.5g., 1j.2b.3a.4f.5g., 1p.2b.3a.4f.5g., 1a.2e.3a.4f.5g.,
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 40 1h.2m.3a.4f.5g., 1j.2m.3a.4f.5g., 1p.2m.3a.4f.5g., 1a.2o.3a.4f.5g., 1b.2o.3a.4f.5g.,
 1f.2o.3a.4f.5g., 1h.2o.3a.4f.5g., 1j.2o.3a.4f.5g., 1p.2o.3a.4f.5g., 1a.2u.3a.4f.5g.,

- 1b.2u.3a.4f.5g., 1f.2u.3a.4f.5g., 1h.2u.3a.4f.5g., 1j.2u.3a.4f.5g., 1p.2u.3a.4f.5g.,
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 5 1h.2b.3b.4f.5g., 1j.2b.3b.4f.5g., 1p.2b.3b.4f.5g., 1a.2e.3b.4f.5g., 1b.2e.3b.4f.5g.,
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 1a.2i.3b.4f.5g., 1b.2i.3b.4f.5g., 1f.2i.3b.4f.5g., 1h.2i.3b.4f.5g., 1j.2i.3b.4f.5g.,
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 10 1j.2m.3b.4f.5g., 1p.2m.3b.4f.5g., 1a.2o.3b.4f.5g., 1b.2o.3b.4f.5g., 1f.2o.3b.4f.5g.,
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 15 1p.2a.3e.4f.5g., 1a.2b.3e.4f.5g., 1b.2b.3e.4f.5g., 1f.2b.3e.4f.5g., 1h.2b.3e.4f.5g.,
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 1f.2f.3e.4f.5g., 1h.2f.3e.4f.5g., 1j.2f.3e.4f.5g., 1p.2f.3e.4f.5g., 1a.2i.3e.4f.5g.,
 1b.2i.3e.4f.5g., 1f.2i.3e.4f.5g., 1h.2i.3e.4f.5g., 1j.2i.3e.4f.5g., 1p.2i.3e.4f.5g.,
 20 1a.2m.3e.4f.5g., 1b.2m.3e.4f.5g., 1f.2m.3e.4f.5g., 1h.2m.3e.4f.5g., 1j.2m.3e.4f.5g.,
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 25 1b.2a.3g.4f.5g., 1f.2a.3g.4f.5g., 1h.2a.3g.4f.5g., 1j.2a.3g.4f.5g., 1p.2a.3g.4f.5g.,
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 30 1f.2i.3g.4f.5g., 1h.2i.3g.4f.5g., 1j.2i.3g.4f.5g., 1p.2i.3g.4f.5g., 1a.2m.3g.4f.5g.,
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 40 1j.2f.3a.4g.5g., 1p.2f.3a.4g.5g., 1a.2i.3a.4g.5g., 1b.2i.3a.4g.5g., 1f.2i.3a.4g.5g.,
 1h.2i.3a.4g.5g., 1j.2i.3a.4g.5g., 1p.2i.3a.4g.5g., 1a.2m.3a.4g.5g., 1b.2m.3a.4g.5g.,

[illegible]

- 1h.2f.3a.4h.5g., 1j.2f.3a.4h.5g., 1p.2f.3a.4h.5g., 1a.2i.3a.4h.5g., 1b.2i.3a.4h.5g.,
 1f.2i.3a.4h.5g., 1h.2i.3a.4h.5g., 1j.2i.3a.4h.5g., 1p.2i.3a.4h.5g., 1a.2m.3a.4h.5g.,
 1b.2m.3a.4h.5g., 1f.2m.3a.4h.5g., 1h.2m.3a.4h.5g., 1j.2m.3a.4h.5g., 1p.2m.3a.4h.5g.,
 1a.2o.3a.4h.5g., 1b.2o.3a.4h.5g., 1f.2o.3a.4h.5g., 1h.2o.3a.4h.5g., 1j.2o.3a.4h.5g.,
 5 1p.2o.3a.4h.5g., 1a.2u.3a.4h.5g., 1b.2u.3a.4h.5g., 1f.2u.3a.4h.5g., 1h.2u.3a.4h.5g.,
 1j.2u.3a.4h.5g., 1p.2u.3a.4h.5g., 1a.2y.3a.4h.5g., 1b.2y.3a.4h.5g., 1f.2y.3a.4h.5g.,
 1h.2y.3a.4h.5g., 1j.2y.3a.4h.5g., 1p.2y.3a.4h.5g., 1a.2a.3b.4h.5g., 1b.2a.3b.4h.5g.,
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 10 1a.2e.3b.4h.5g., 1b.2e.3b.4h.5g., 1f.2e.3b.4h.5g., 1h.2e.3b.4h.5g., 1j.2e.3b.4h.5g.,
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 1h.2i.3b.4h.5g., 1j.2i.3b.4h.5g., 1p.2i.3b.4h.5g., 1a.2m.3b.4h.5g., 1b.2m.3b.4h.5g.,
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 15 1b.2o.3b.4h.5g., 1f.2o.3b.4h.5g., 1h.2o.3b.4h.5g., 1j.2o.3b.4h.5g., 1p.2o.3b.4h.5g.,
 1a.2u.3b.4h.5g., 1b.2u.3b.4h.5g., 1f.2u.3b.4h.5g., 1h.2u.3b.4h.5g., 1j.2u.3b.4h.5g.,
 1p.2u.3b.4h.5g., 1a.2y.3b.4h.5g., 1b.2y.3b.4h.5g., 1f.2y.3b.4h.5g., 1h.2y.3b.4h.5g.,
 1j.2y.3b.4h.5g., 1p.2y.3b.4h.5g., 1a.2a.3e.4h.5g., 1b.2a.3e.4h.5g., 1f.2a.3e.4h.5g.,
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 20 1f.2b.3e.4h.5g., 1h.2b.3e.4h.5g., 1j.2b.3e.4h.5g., 1p.2b.3e.4h.5g., 1a.2e.3e.4h.5g.,
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 25 1h.2m.3e.4h.5g., 1j.2m.3e.4h.5g., 1p.2m.3e.4h.5g., 1a.2o.3e.4h.5g., 1b.2o.3e.4h.5g.,
 1f.2o.3e.4h.5g., 1h.2o.3e.4h.5g., 1j.2o.3e.4h.5g., 1p.2o.3e.4h.5g., 1a.2u.3e.4h.5g.,
 1b.2u.3e.4h.5g., 1f.2u.3e.4h.5g., 1h.2u.3e.4h.5g., 1j.2u.3e.4h.5g., 1p.2u.3e.4h.5g.,
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 1h.2b.3g.4h.5g., 1j.2b.3g.4h.5g., 1p.2b.3g.4h.5g., 1a.2e.3g.4h.5g., 1b.2e.3g.4h.5g.,
 1f.2e.3g.4h.5g., 1h.2e.3g.4h.5g., 1j.2e.3g.4h.5g., 1p.2e.3g.4h.5g., 1a.2f.3g.4h.5g.,
 1b.2f.3g.4h.5g., 1f.2f.3g.4h.5g., 1h.2f.3g.4h.5g., 1j.2f.3g.4h.5g., 1p.2f.3g.4h.5g.,
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 35 1p.2i.3g.4h.5g., 1a.2m.3g.4h.5g., 1b.2m.3g.4h.5g., 1f.2m.3g.4h.5g., 1h.2m.3g.4h.5g.,
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 1f.2u.3g.4h.5g., 1h.2u.3g.4h.5g., 1j.2u.3g.4h.5g., 1p.2u.3g.4h.5g., 1a.2y.3g.4h.5g.,
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 40 1a.2a.3a.4i.5g., 1b.2a.3a.4i.5g., 1f.2a.3a.4i.5g., 1h.2a.3a.4i.5g., 1j.2a.3a.4i.5g.,
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- 1j.2b.3a.4i.5g., 1p.2b.3a.4i.5g., 1a.2e.3a.4i.5g., 1b.2e.3a.4i.5g., 1f.2e.3a.4i.5g.,
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 1f.2f.3a.4i.5g., 1h.2f.3a.4i.5g., 1j.2f.3a.4i.5g., 1p.2f.3a.4i.5g., 1a.2i.3a.4i.5g.,
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 25 1j.2f.3e.4i.5g., 1p.2f.3e.4i.5g., 1a.2i.3e.4i.5g., 1b.2i.3e.4i.5g., 1f.2i.3e.4i.5g.,
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 1b.2o.3e.4i.5g., 1f.2o.3e.4i.5g., 1h.2o.3e.4i.5g., 1j.2o.3e.4i.5g., 1p.2o.3e.4i.5g.,
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 30 1p.2u.3e.4i.5g., 1a.2y.3e.4i.5g., 1b.2y.3e.4i.5g., 1f.2y.3e.4i.5g., 1h.2y.3e.4i.5g.,
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 1f.2b.3g.4i.5g., 1h.2b.3g.4i.5g., 1j.2b.3g.4i.5g., 1p.2b.3g.4i.5g., 1a.2e.3g.4i.5g.,
 1b.2e.3g.4i.5g., 1f.2e.3g.4i.5g., 1h.2e.3g.4i.5g., 1j.2e.3g.4i.5g., 1p.2e.3g.4i.5g.,
 35 1a.2f.3g.4i.5g., 1b.2f.3g.4i.5g., 1f.2f.3g.4i.5g., 1h.2f.3g.4i.5g., 1j.2f.3g.4i.5g.,
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 40 1b.2u.3g.4i.5g., 1f.2u.3g.4i.5g., 1h.2u.3g.4i.5g., 1j.2u.3g.4i.5g., 1p.2u.3g.4i.5g.,
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 5 1b.2f.3a.4a.5h., 1f.2f.3a.4a.5h., 1h.2f.3a.4a.5h., 1j.2f.3a.4a.5h., 1p.2f.3a.4a.5h.,
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 10 1f.2u.3a.4a.5h., 1h.2u.3a.4a.5h., 1j.2u.3a.4a.5h., 1p.2u.3a.4a.5h., 1a.2y.3a.4a.5h.,
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 20 1j.2o.3b.4a.5h., 1p.2o.3b.4a.5h., 1a.2u.3b.4a.5h., 1b.2u.3b.4a.5h., 1f.2u.3b.4a.5h.,
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 25 1p.2b.3e.4a.5h., 1a.2e.3e.4a.5h., 1b.2e.3e.4a.5h., 1f.2e.3e.4a.5h., 1h.2e.3e.4a.5h.,
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 35 1b.2b.3g.4a.5h., 1f.2b.3g.4a.5h., 1h.2b.3g.4a.5h., 1j.2b.3g.4a.5h., 1p.2b.3g.4a.5h.,
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 1j.2f.3g.4a.5h., 1p.2f.3g.4a.5h., 1a.2i.3g.4a.5h., 1b.2i.3g.4a.5h., 1f.2i.3g.4a.5h.,
 1h.2i.3g.4a.5h., 1j.2i.3g.4a.5h., 1p.2i.3g.4a.5h., 1a.2m.3g.4a.5h., 1b.2m.3g.4a.5h.,
 40 1f.2m.3g.4a.5h., 1h.2m.3g.4a.5h., 1j.2m.3g.4a.5h., 1p.2m.3g.4a.5h., 1a.2o.3g.4a.5h.,
 1b.2o.3g.4a.5h., 1f.2o.3g.4a.5h., 1h.2o.3g.4a.5h., 1j.2o.3g.4a.5h., 1p.2o.3g.4a.5h.,

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- 1a.2m.3g.4d.5h., 1b.2m.3g.4d.5h., 1f.2m.3g.4d.5h., 1h.2m.3g.4d.5h.,
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 5 1b.2y.3g.4d.5h., 1f.2y.3g.4d.5h., 1h.2y.3g.4d.5h., 1j.2y.3g.4d.5h., 1p.2y.3g.4d.5h.,
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 1h.2e.3a.4f.5h., 1j.2e.3a.4f.5h., 1p.2e.3a.4f.5h., 1a.2f.3a.4f.5h., 1b.2f.3a.4f.5h.,
 10 1f.2f.3a.4f.5h., 1h.2f.3a.4f.5h., 1j.2f.3a.4f.5h., 1p.2f.3a.4f.5h., 1a.2i.3a.4f.5h.,
 1b.2i.3a.4f.5h., 1f.2i.3a.4f.5h., 1h.2i.3a.4f.5h., 1j.2i.3a.4f.5h., 1p.2i.3a.4f.5h.,
 1a.2m.3a.4f.5h., 1b.2m.3a.4f.5h., 1f.2m.3a.4f.5h., 1h.2m.3a.4f.5h., 1j.2m.3a.4f.5h.,
 1p.2m.3a.4f.5h., 1a.2o.3a.4f.5h., 1b.2o.3a.4f.5h., 1f.2o.3a.4f.5h., 1h.2o.3a.4f.5h.,
 1j.2o.3a.4f.5h., 1p.2o.3a.4f.5h., 1a.2u.3a.4f.5h., 1b.2u.3a.4f.5h., 1f.2u.3a.4f.5h.,
 15 1h.2u.3a.4f.5h., 1j.2u.3a.4f.5h., 1p.2u.3a.4f.5h., 1a.2y.3a.4f.5h., 1b.2y.3a.4f.5h.,
 1f.2y.3a.4f.5h., 1h.2y.3a.4f.5h., 1j.2y.3a.4f.5h., 1p.2y.3a.4f.5h., 1a.2a.3b.4f.5h.,
 1b.2a.3b.4f.5h., 1f.2a.3b.4f.5h., 1h.2a.3b.4f.5h., 1j.2a.3b.4f.5h., 1p.2a.3b.4f.5h.,
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 20 1j.2e.3b.4f.5h., 1p.2e.3b.4f.5h., 1a.2f.3b.4f.5h., 1b.2f.3b.4f.5h., 1f.2f.3b.4f.5h.,
 1h.2f.3b.4f.5h., 1j.2f.3b.4f.5h., 1p.2f.3b.4f.5h., 1a.2i.3b.4f.5h., 1b.2i.3b.4f.5h.,
 1f.2i.3b.4f.5h., 1h.2i.3b.4f.5h., 1j.2i.3b.4f.5h., 1p.2i.3b.4f.5h., 1a.2m.3b.4f.5h.,
 1b.2m.3b.4f.5h., 1f.2m.3b.4f.5h., 1h.2m.3b.4f.5h., 1j.2m.3b.4f.5h., 1p.2m.3b.4f.5h.,
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 25 1p.2o.3b.4f.5h., 1a.2u.3b.4f.5h., 1b.2u.3b.4f.5h., 1f.2u.3b.4f.5h., 1h.2u.3b.4f.5h.,
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 1h.2y.3b.4f.5h., 1j.2y.3b.4f.5h., 1p.2y.3b.4f.5h., 1a.2a.3e.4f.5h., 1b.2a.3e.4f.5h.,
 1f.2a.3e.4f.5h., 1h.2a.3e.4f.5h., 1j.2a.3e.4f.5h., 1p.2a.3e.4f.5h., 1a.2b.3e.4f.5h.,
 1b.2b.3e.4f.5h., 1f.2b.3e.4f.5h., 1h.2b.3e.4f.5h., 1j.2b.3e.4f.5h., 1p.2b.3e.4f.5h.,
 30 1a.2e.3e.4f.5h., 1b.2e.3e.4f.5h., 1f.2e.3e.4f.5h., 1h.2e.3e.4f.5h., 1j.2e.3e.4f.5h.,
 1p.2e.3e.4f.5h., 1a.2f.3e.4f.5h., 1b.2f.3e.4f.5h., 1f.2f.3e.4f.5h., 1h.2f.3e.4f.5h.,
 1j.2f.3e.4f.5h., 1p.2f.3e.4f.5h., 1a.2i.3e.4f.5h., 1b.2i.3e.4f.5h., 1f.2i.3e.4f.5h.,
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 1f.2m.3e.4f.5h., 1h.2m.3e.4f.5h., 1j.2m.3e.4f.5h., 1p.2m.3e.4f.5h., 1a.2o.3e.4f.5h.,
 35 1b.2o.3e.4f.5h., 1f.2o.3e.4f.5h., 1h.2o.3e.4f.5h., 1j.2o.3e.4f.5h., 1p.2o.3e.4f.5h.,
 1a.2u.3e.4f.5h., 1b.2u.3e.4f.5h., 1f.2u.3e.4f.5h., 1h.2u.3e.4f.5h., 1j.2u.3e.4f.5h.,
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 1h.2a.3g.4f.5h., 1j.2a.3g.4f.5h., 1p.2a.3g.4f.5h., 1a.2b.3g.4f.5h., 1b.2b.3g.4f.5h.,
 40 1f.2b.3g.4f.5h., 1h.2b.3g.4f.5h., 1j.2b.3g.4f.5h., 1p.2b.3g.4f.5h., 1a.2e.3g.4f.5h.,
 1b.2e.3g.4f.5h., 1f.2e.3g.4f.5h., 1h.2e.3g.4f.5h., 1j.2e.3g.4f.5h., 1p.2e.3g.4f.5h.,

- 1a.2f.3g.4f.5h., 1b.2f.3g.4f.5h., 1f.2f.3g.4f.5h., 1h.2f.3g.4f.5h., 1j.2f.3g.4f.5h.,
 1p.2f.3g.4f.5h., 1a.2i.3g.4f.5h., 1b.2i.3g.4f.5h., 1f.2i.3g.4f.5h., 1h.2i.3g.4f.5h.,
 1j.2i.3g.4f.5h., 1p.2i.3g.4f.5h., 1a.2m.3g.4f.5h., 1b.2m.3g.4f.5h., 1f.2m.3g.4f.5h.,
 1h.2m.3g.4f.5h., 1j.2m.3g.4f.5h., 1p.2m.3g.4f.5h., 1a.2o.3g.4f.5h., 1b.2o.3g.4f.5h.,
 5 1f.2o.3g.4f.5h., 1h.2o.3g.4f.5h., 1j.2o.3g.4f.5h., 1p.2o.3g.4f.5h., 1a.2u.3g.4f.5h.,
 1b.2u.3g.4f.5h., 1f.2u.3g.4f.5h., 1h.2u.3g.4f.5h., 1j.2u.3g.4f.5h., 1p.2u.3g.4f.5h.,
 1a.2y.3g.4f.5h., 1b.2y.3g.4f.5h., 1f.2y.3g.4f.5h., 1h.2y.3g.4f.5h., 1j.2y.3g.4f.5h.,
 1p.2y.3g.4f.5h., 1a.2a.3a.4g.5h., 1b.2a.3a.4g.5h., 1f.2a.3a.4g.5h., 1h.2a.3a.4g.5h.,
 1j.2a.3a.4g.5h., 1p.2a.3a.4g.5h., 1a.2b.3a.4g.5h., 1b.2b.3a.4g.5h., 1f.2b.3a.4g.5h.,
 10 1h.2b.3a.4g.5h., 1j.2b.3a.4g.5h., 1p.2b.3a.4g.5h., 1a.2e.3a.4g.5h., 1b.2e.3a.4g.5h.,
 1f.2e.3a.4g.5h., 1h.2e.3a.4g.5h., 1j.2e.3a.4g.5h., 1p.2e.3a.4g.5h., 1a.2f.3a.4g.5h.,
 1b.2f.3a.4g.5h., 1f.2f.3a.4g.5h., 1h.2f.3a.4g.5h., 1j.2f.3a.4g.5h., 1p.2f.3a.4g.5h.,
 1a.2i.3a.4g.5h., 1b.2i.3a.4g.5h., 1f.2i.3a.4g.5h., 1h.2i.3a.4g.5h., 1j.2i.3a.4g.5h.,
 1p.2i.3a.4g.5h., 1a.2m.3a.4g.5h., 1b.2m.3a.4g.5h., 1f.2m.3a.4g.5h., 1h.2m.3a.4g.5h.,
 15 1j.2m.3a.4g.5h., 1p.2m.3a.4g.5h., 1a.2o.3a.4g.5h., 1b.2o.3a.4g.5h., 1f.2o.3a.4g.5h.,
 1h.2o.3a.4g.5h., 1j.2o.3a.4g.5h., 1p.2o.3a.4g.5h., 1a.2u.3a.4g.5h., 1b.2u.3a.4g.5h.,
 1f.2u.3a.4g.5h., 1h.2u.3a.4g.5h., 1j.2u.3a.4g.5h., 1p.2u.3a.4g.5h., 1a.2y.3a.4g.5h.,
 1b.2y.3a.4g.5h., 1f.2y.3a.4g.5h., 1h.2y.3a.4g.5h., 1j.2y.3a.4g.5h., 1p.2y.3a.4g.5h.,
 1a.2a.3b.4g.5h., 1b.2a.3b.4g.5h., 1f.2a.3b.4g.5h., 1h.2a.3b.4g.5h., 1j.2a.3b.4g.5h.,
 20 1p.2a.3b.4g.5h., 1a.2b.3b.4g.5h., 1b.2b.3b.4g.5h., 1f.2b.3b.4g.5h., 1h.2b.3b.4g.5h.,
 1j.2b.3b.4g.5h., 1p.2b.3b.4g.5h., 1a.2e.3b.4g.5h., 1b.2e.3b.4g.5h., 1f.2e.3b.4g.5h.,
 1h.2e.3b.4g.5h., 1j.2e.3b.4g.5h., 1p.2e.3b.4g.5h., 1a.2f.3b.4g.5h., 1b.2f.3b.4g.5h.,
 1f.2f.3b.4g.5h., 1h.2f.3b.4g.5h., 1j.2f.3b.4g.5h., 1p.2f.3b.4g.5h., 1a.2i.3b.4g.5h.,
 1b.2i.3b.4g.5h., 1f.2i.3b.4g.5h., 1h.2i.3b.4g.5h., 1j.2i.3b.4g.5h., 1p.2i.3b.4g.5h.,
 25 1a.2m.3b.4g.5h., 1b.2m.3b.4g.5h., 1f.2m.3b.4g.5h., 1h.2m.3b.4g.5h., 1j.2m.3b.4g.5h.,
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 1j.2o.3b.4g.5h., 1p.2o.3b.4g.5h., 1a.2u.3b.4g.5h., 1b.2u.3b.4g.5h., 1f.2u.3b.4g.5h.,
 1h.2u.3b.4g.5h., 1j.2u.3b.4g.5h., 1p.2u.3b.4g.5h., 1a.2y.3b.4g.5h., 1b.2y.3b.4g.5h.,
 1f.2y.3b.4g.5h., 1h.2y.3b.4g.5h., 1j.2y.3b.4g.5h., 1p.2y.3b.4g.5h., 1a.2a.3e.4g.5h.,
 30 1b.2a.3e.4g.5h., 1f.2a.3e.4g.5h., 1h.2a.3e.4g.5h., 1j.2a.3e.4g.5h., 1p.2a.3e.4g.5h.,
 1a.2b.3e.4g.5h., 1b.2b.3e.4g.5h., 1f.2b.3e.4g.5h., 1h.2b.3e.4g.5h., 1j.2b.3e.4g.5h.,
 1p.2b.3e.4g.5h., 1a.2e.3e.4g.5h., 1b.2e.3e.4g.5h., 1f.2e.3e.4g.5h., 1h.2e.3e.4g.5h.,
 1j.2e.3e.4g.5h., 1p.2e.3e.4g.5h., 1a.2f.3e.4g.5h., 1b.2f.3e.4g.5h., 1f.2f.3e.4g.5h.,
 1h.2f.3e.4g.5h., 1j.2f.3e.4g.5h., 1p.2f.3e.4g.5h., 1a.2i.3e.4g.5h., 1b.2i.3e.4g.5h.,
 35 1f.2i.3e.4g.5h., 1h.2i.3e.4g.5h., 1j.2i.3e.4g.5h., 1p.2i.3e.4g.5h., 1a.2m.3e.4g.5h.,
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 1p.2o.3e.4g.5h., 1a.2u.3e.4g.5h., 1b.2u.3e.4g.5h., 1f.2u.3e.4g.5h., 1h.2u.3e.4g.5h.,
 1j.2u.3e.4g.5h., 1p.2u.3e.4g.5h., 1a.2y.3e.4g.5h., 1b.2y.3e.4g.5h., 1f.2y.3e.4g.5h.,
 40 1h.2y.3e.4g.5h., 1j.2y.3e.4g.5h., 1p.2y.3e.4g.5h., 1a.2a.3g.4g.5h., 1b.2a.3g.4g.5h.,
 1f.2a.3g.4g.5h., 1h.2a.3g.4g.5h., 1j.2a.3g.4g.5h., 1p.2a.3g.4g.5h., 1a.2b.3g.4g.5h.,

[illegible]

- 1f.2y.3e.4h.5h., 1h.2y.3e.4h.5h., 1j.2y.3e.4h.5h., 1p.2y.3e.4h.5h., 1a.2a.3g.4h.5h.,
 1b.2a.3g.4h.5h., 1f.2a.3g.4h.5h., 1h.2a.3g.4h.5h., 1j.2a.3g.4h.5h., 1p.2a.3g.4h.5h.,
 1a.2b.3g.4h.5h., 1b.2b.3g.4h.5h., 1f.2b.3g.4h.5h., 1h.2b.3g.4h.5h., 1j.2b.3g.4h.5h.,
 1p.2b.3g.4h.5h., 1a.2e.3g.4h.5h., 1b.2e.3g.4h.5h., 1f.2e.3g.4h.5h., 1h.2e.3g.4h.5h.,
 5 1j.2e.3g.4h.5h., 1p.2e.3g.4h.5h., 1a.2f.3g.4h.5h., 1b.2f.3g.4h.5h., 1f.2f.3g.4h.5h.,
 1h.2f.3g.4h.5h., 1j.2f.3g.4h.5h., 1p.2f.3g.4h.5h., 1a.2i.3g.4h.5h., 1b.2i.3g.4h.5h.,
 1f.2i.3g.4h.5h., 1h.2i.3g.4h.5h., 1j.2i.3g.4h.5h., 1p.2i.3g.4h.5h., 1a.2m.3g.4h.5h.,
 1b.2m.3g.4h.5h., 1f.2m.3g.4h.5h., 1h.2m.3g.4h.5h., 1j.2m.3g.4h.5h.,
 1p.2m.3g.4h.5h., 1a.2o.3g.4h.5h., 1b.2o.3g.4h.5h., 1f.2o.3g.4h.5h., 1h.2o.3g.4h.5h.,
 10 1j.2o.3g.4h.5h., 1p.2o.3g.4h.5h., 1a.2u.3g.4h.5h., 1b.2u.3g.4h.5h., 1f.2u.3g.4h.5h.,
 1h.2u.3g.4h.5h., 1j.2u.3g.4h.5h., 1p.2u.3g.4h.5h., 1a.2y.3g.4h.5h., 1b.2y.3g.4h.5h.,
 1f.2y.3g.4h.5h., 1h.2y.3g.4h.5h., 1j.2y.3g.4h.5h., 1p.2y.3g.4h.5h., 1a.2a.3a.4i.5h.,
 1b.2a.3a.4i.5h., 1f.2a.3a.4i.5h., 1h.2a.3a.4i.5h., 1j.2a.3a.4i.5h., 1p.2a.3a.4i.5h.,
 1a.2b.3a.4i.5h., 1b.2b.3a.4i.5h., 1f.2b.3a.4i.5h., 1h.2b.3a.4i.5h., 1j.2b.3a.4i.5h.,
 15 1p.2b.3a.4i.5h., 1a.2e.3a.4i.5h., 1b.2e.3a.4i.5h., 1f.2e.3a.4i.5h., 1h.2e.3a.4i.5h.,
 1j.2e.3a.4i.5h., 1p.2e.3a.4i.5h., 1a.2f.3a.4i.5h., 1b.2f.3a.4i.5h., 1f.2f.3a.4i.5h.,
 1h.2f.3a.4i.5h., 1j.2f.3a.4i.5h., 1p.2f.3a.4i.5h., 1a.2i.3a.4i.5h., 1b.2i.3a.4i.5h.,
 1f.2i.3a.4i.5h., 1h.2i.3a.4i.5h., 1j.2i.3a.4i.5h., 1p.2i.3a.4i.5h., 1a.2m.3a.4i.5h.,
 1b.2m.3a.4i.5h., 1f.2m.3a.4i.5h., 1h.2m.3a.4i.5h., 1j.2m.3a.4i.5h., 1p.2m.3a.4i.5h.,
 20 1a.2o.3a.4i.5h., 1b.2o.3a.4i.5h., 1f.2o.3a.4i.5h., 1h.2o.3a.4i.5h., 1j.2o.3a.4i.5h.,
 1p.2o.3a.4i.5h., 1a.2u.3a.4i.5h., 1b.2u.3a.4i.5h., 1f.2u.3a.4i.5h., 1h.2u.3a.4i.5h.,
 1j.2u.3a.4i.5h., 1p.2u.3a.4i.5h., 1a.2y.3a.4i.5h., 1b.2y.3a.4i.5h., 1f.2y.3a.4i.5h.,
 1h.2y.3a.4i.5h., 1j.2y.3a.4i.5h., 1p.2y.3a.4i.5h., 1a.2a.3b.4i.5h., 1b.2a.3b.4i.5h.,
 1f.2a.3b.4i.5h., 1h.2a.3b.4i.5h., 1j.2a.3b.4i.5h., 1p.2a.3b.4i.5h., 1a.2b.3b.4i.5h.,
 25 1b.2b.3b.4i.5h., 1f.2b.3b.4i.5h., 1h.2b.3b.4i.5h., 1j.2b.3b.4i.5h., 1p.2b.3b.4i.5h.,
 1a.2e.3b.4i.5h., 1b.2e.3b.4i.5h., 1f.2e.3b.4i.5h., 1h.2e.3b.4i.5h., 1j.2e.3b.4i.5h.,
 1p.2e.3b.4i.5h., 1a.2f.3b.4i.5h., 1b.2f.3b.4i.5h., 1f.2f.3b.4i.5h., 1h.2f.3b.4i.5h.,
 1j.2f.3b.4i.5h., 1p.2f.3b.4i.5h., 1a.2i.3b.4i.5h., 1b.2i.3b.4i.5h., 1f.2i.3b.4i.5h.,
 1h.2i.3b.4i.5h., 1j.2i.3b.4i.5h., 1p.2i.3b.4i.5h., 1a.2m.3b.4i.5h., 1b.2m.3b.4i.5h.,
 30 1f.2m.3b.4i.5h., 1h.2m.3b.4i.5h., 1j.2m.3b.4i.5h., 1p.2m.3b.4i.5h., 1a.2o.3b.4i.5h.,
 1b.2o.3b.4i.5h., 1f.2o.3b.4i.5h., 1h.2o.3b.4i.5h., 1j.2o.3b.4i.5h., 1p.2o.3b.4i.5h.,
 1a.2u.3b.4i.5h., 1b.2u.3b.4i.5h., 1f.2u.3b.4i.5h., 1h.2u.3b.4i.5h., 1j.2u.3b.4i.5h.,
 1p.2u.3b.4i.5h., 1a.2y.3b.4i.5h., 1b.2y.3b.4i.5h., 1f.2y.3b.4i.5h., 1h.2y.3b.4i.5h.,
 1j.2y.3b.4i.5h., 1p.2y.3b.4i.5h., 1a.2a.3e.4i.5h., 1b.2a.3e.4i.5h., 1f.2a.3e.4i.5h.,
 35 1h.2a.3e.4i.5h., 1j.2a.3e.4i.5h., 1p.2a.3e.4i.5h., 1a.2b.3e.4i.5h., 1b.2b.3e.4i.5h.,
 1f.2b.3e.4i.5h., 1h.2b.3e.4i.5h., 1j.2b.3e.4i.5h., 1p.2b.3e.4i.5h., 1a.2e.3e.4i.5h.,
 1b.2e.3e.4i.5h., 1f.2e.3e.4i.5h., 1h.2e.3e.4i.5h., 1j.2e.3e.4i.5h., 1p.2e.3e.4i.5h.,
 1a.2f.3e.4i.5h., 1b.2f.3e.4i.5h., 1f.2f.3e.4i.5h., 1h.2f.3e.4i.5h., 1j.2f.3e.4i.5h.,
 1p.2f.3e.4i.5h., 1a.2i.3e.4i.5h., 1b.2i.3e.4i.5h., 1f.2i.3e.4i.5h., 1h.2i.3e.4i.5h.,
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- 1f.2o.3e.4i.5h., 1h.2o.3e.4i.5h., 1j.2o.3e.4i.5h., 1p.2o.3e.4i.5h., 1a.2u.3e.4i.5h.,
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 5 1b.2i.3e.4f.5i., 1f.2i.3e.4f.5i., 1h.2i.3e.4f.5i., 1j.2i.3e.4f.5i., 1p.2i.3e.4f.5i.,
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 15 1h.2f.3g.4f.5i., 1j.2f.3g.4f.5i., 1p.2f.3g.4f.5i., 1a.2i.3g.4f.5i., 1b.2i.3g.4f.5i.,
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 5 1f.2e.3e.4g.5i., 1h.2e.3e.4g.5i., 1j.2e.3e.4g.5i., 1p.2e.3e.4g.5i., 1a.2f.3e.4g.5i.,
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 5 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.,
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 10 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.,
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 10 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.,
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 1p.2y.3g.4i.5i..

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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
 35 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 IC₅₀ 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 IC₅₀ 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 EC₅₀ 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
5 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
10 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.

15 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
20 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,
25 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
5 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.
10 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
15 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
20 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
25 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,
5 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
10 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
15 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.
20 Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, 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.,
25 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
5 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
10 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
15 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
20 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
25 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
5 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
10 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
15 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
20 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.

25 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
5 (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
10 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.

15 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
20 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
25 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
5 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
10 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,
15 or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable carrier or excipient.

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
20 combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

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
25 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
5 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.

10 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
15 (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)
20 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 alfentanil, aprepitant, aripiprazole, buspirone, cafergot, caffeine, TMU, cilostazol, cocaine, codeine- N-demethylation, dapson, dextromethorphan, docetaxel, domperidone,
25 eplerenone, fentanyl, finasteride, gleeevec, 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
5 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
10 inhibitors of HCV, CCR5 inhibitors, and combinations thereof, and a pharmaceutically acceptable carrier or excipient.

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
15 with at least one additional therapeutic agent selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brexanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, capravirine, emivirine, delaviridine, efavirenz,
20 nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, Racivir ($\pm$ -FTC), D-d4FC, AVX754, tenofovir disoproxil fumarate, adefovir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-
25 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,

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, 5 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 excipient.

10 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
- 15 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, 20 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

25 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.

5

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
10 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
15 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
20 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.

25 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 alfentanil, 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,
5 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,
10 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-
15 083, 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 ($\pm$ -FTC), D-d4FC, emtricitabine,
20 phosphazide, fozivudine tidoxil, apricitibine (AVX754), GS-7340, KP-1461, and fosaltivudine tidoxil (formerly HDP 99.0003), 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.*, tenofovir and adefovir, 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,
25 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), elvitegravir, L-870812, and L-870810, MK-0518 (raltegravir), 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
5 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 --
10 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
15 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
20 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
25 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
5 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
10 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
15 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
20 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.

25 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
5 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
10 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
15 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
20 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.

25 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
5 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.

10 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.

15 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.

20 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.

25 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
5 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
10 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
15 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, brexanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147
20 (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,
25 zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir ($\pm$ -FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitabine (AVX754), amdoxovir, KP-1461, fosaltuvudine tidoxil (formerly HDP 99.0003), tenofovir, adefovir, 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,
 5 zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), 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),
 10 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
 15 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
 20 rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen),
 feron, reaféron, 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
 25 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

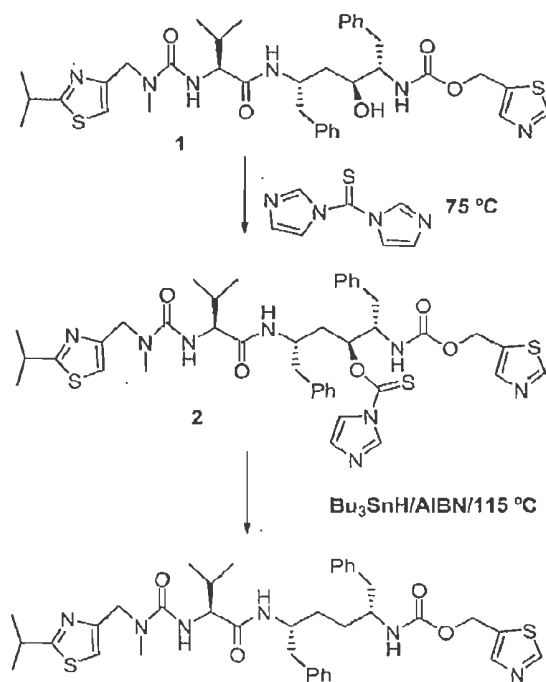
derivatives, A-831, A-689, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat),
PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005,
ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-
025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497
5 (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.

10 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
15 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
20 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.

ExamplesPreparation of Example A**Scheme 1****Example A****5** 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)⁺.

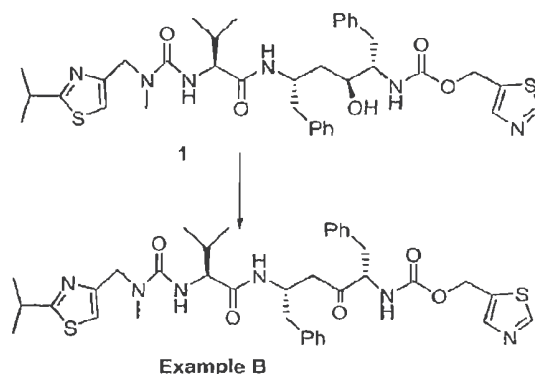
Example A

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)⁺. ¹H-NMR (CDCl₃) 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).

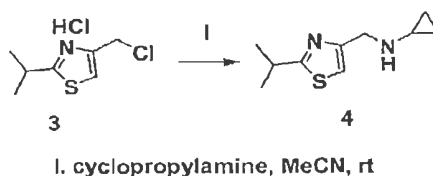
Preparation of Example B

10 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)⁺.

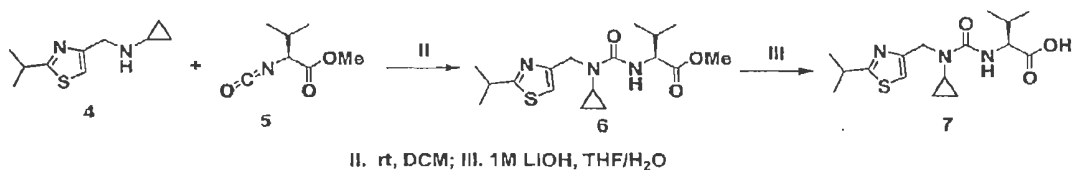
Preparation of Example CScheme 35 Compound 3

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

15 (LC/MS *m/z* 197 (M+H)⁺; 218 (M+Na)⁺).

Scheme 4Compound 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.

20

Compound 6

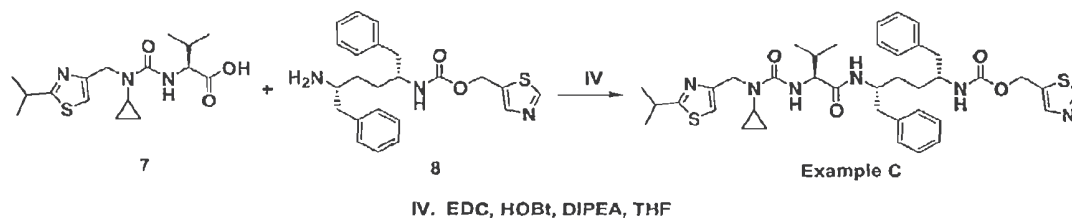
To a solution of Compound 4 in DCM (3 mL) at room temperature was added 5 (0.1 mL, 0.695 mmol). The resulting clear solution was allowed to stand

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.

5 Compound 7

Compound **6** was taken up in THF (5 mL) at room temperature, and LiOH (1 M in H₂O) 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
10 extracted several times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na₂SO₄, 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



15

Example C

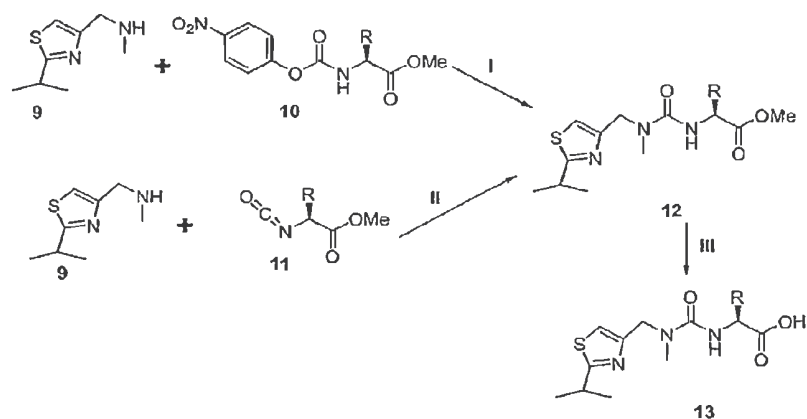
Compounds **7** (0.034 g, 0.100 mmol) and **8**, (0.034 g, 0.083 mmol) were diluted in THF (2 mL) at room temperature. To the resulting solution were added *N,N*-diisopropylethylamine (0.022 mL, 0.125 mmol), EDC (0.018 mL, 0.099
20 mmol) and HOBt (0.013 g, 0.099 mmol). The solution was then allowed to 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. (¹H-NMR (300 MHz, CDCl₃) δ 8.79 (s,
25 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);

5 LC/MS m/z 731 (M^+)).

Preparation of Examples D-I

Scheme 6



I. $\text{Et}_3\text{N}/\text{DMAP}/\text{THF}/65^\circ\text{C}$; II. $\text{CH}_2\text{Cl}_2/25^\circ\text{C}$; III. a. $\text{NaOH}/\text{dioxane}/\text{H}_2\text{O}$; b. HCl
 a: $\text{R} = \text{H}$
 b: $\text{R} = \text{CH}_3$
 c: $\text{R} = \text{CH}_2\text{CH}_3$
 d: $\text{R} = \text{CH}_2\text{OBn}$
 e: $\text{R} = \text{CH}(\text{O}-t\text{-Bu})\text{CH}_3$
 f: $\text{R} = \text{CH}(\text{OH})\text{CH}_3$

10

Compound 9

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

Compound 10

15

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

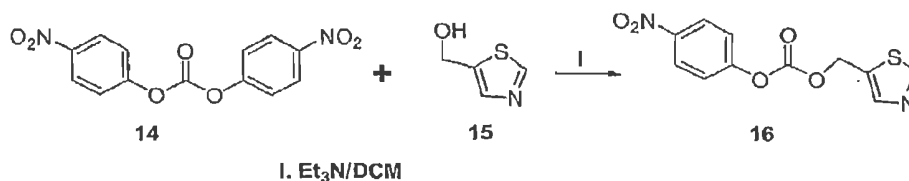
Method 1: To a solution of Compound 9 (0.8 mmol) in THF (2 mL) was
5 added a carbamate of Compound 10 (0.6 mmol), followed by DMAP (16 mg) and triethylamine (0.25 mL). The resulting mixture was heated at 70 °C for two hours and diluted with EtOAc. The organic phase was separated, and washed sequentially with saturated aqueous Na₂CO₃, water, and brine, then concentrated under reduced pressure. Purification of the residue by flash column
10 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 CH₂Cl₂ (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
15 chromatography (silica gel, hexane/EtOAc 1/1 – 1/3) gave structures of Compound 12.

Compound 13

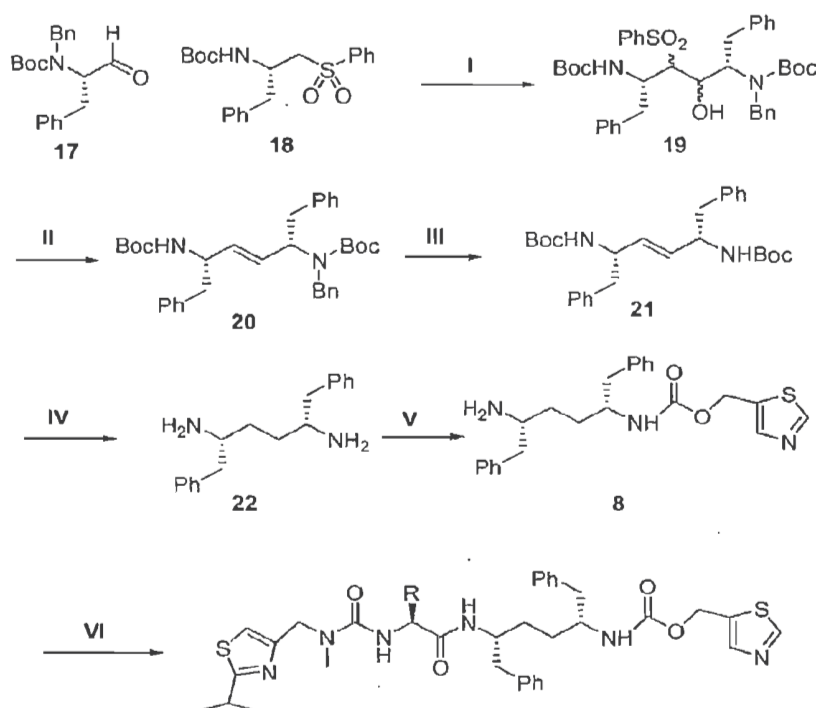
To a solution of structures of Compound 12 (1.8 mmol) in dioxane (8 mL) and water (8 mL) was added sodium hydroxide (3.6 mmol). The resulting
20 reaction mixture was stirred for 1 hour and acidified with HCl in dioxane (3.6 mmol). The reaction mixture was extracted with EtOAc and the organic phase was dried with anhydrous MgSO₄. 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 Na₂CO₃, 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).

10 **Scheme 8**

Examples:

D: R = H

E: R = CH₃F: R = CH₂CH₃G: R = CH₂OBnH: R = CH(O-t-Bu)CH₃I: R = CH(OH)CH₃

I. a. n-BuLi/-78 °C; b. I-Bu₂Al(OMe); II. a. Ac₂O/pyridine; b. Na-Hg/MeOH/THF; III. Na/NH₃/-33 °C; IV. a. H₂/10%Pd/C; b. TFA/DCM; V. 16/Et₃N; 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

5 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
10 °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
15 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 NH₄Cl, and warmed to 25 °C. The mixture was then extracted with EtOAc, and
20 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 Ac₂O (1.5 mL), followed by pyridine (3 mL). The resulting mixture was stirred for 12 hours and
25 concentrated. The concentrate was dissolved in MeOH (30 mL) and cooled to 0 °C. NaH₂PO₄ (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).

5 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 NH₄Cl (6 g) was then added slowly, the mixture was warmed to 25 °C, and the ammonia
10 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

15 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
20 for 4 hours, then concentrated under reduced pressure. The concentrated mixture was diluted with EtOAc, and washed sequentially with saturated aqueous Na₂CO₃, water, and brine. Concentration of the washed EtOAc mixture gave Compound 22 (420 mg).

Compound 8

25 To a solution of Compound 22 (1.57 mmol) in CH₃CN (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 Na₂CO₃, water and

brine. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH₃CN in water) gave Compound 8 (460 mg).

Example D

To the solution of Compound 13a (R= H; 0.08 mmol) and Compound 8
5 (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% CH₃CN in water) gave Example D (27
mg). m/z 663.1 (M+H)⁺. ¹H-NMR (CDCl₃) δ 8.79 (1 H, s), 7.83 (1 H, s), 7.25-7.04 (10
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),
15 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
20 (M+H)⁺. ¹H-NMR (CDCl₃) 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

25 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

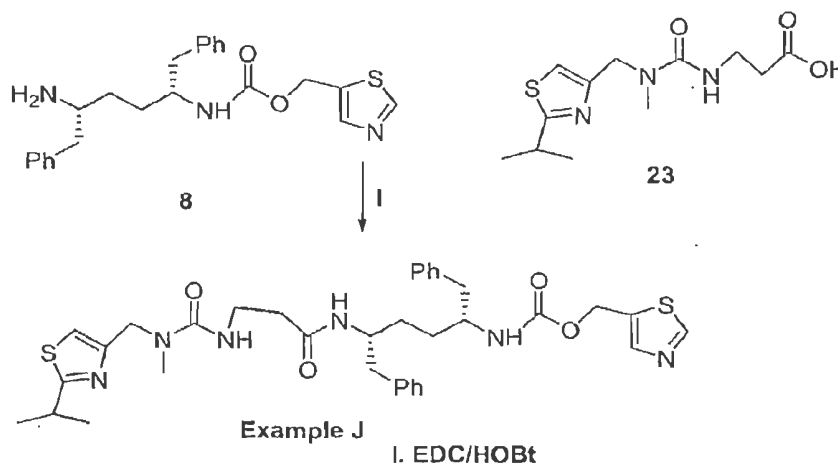
Example **H** was prepared following the procedure for Example **D** (90 mg), except that Compound **13e** was used instead of Compound **13a**. m/z 763.2 (M+H)⁺.

Example I

- 5 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% CH₃CN in water) gave Example I (14 mg). m/z 707.2 (M+H)⁺. ¹H-NMR (CDCl₃) 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),
 10 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 I

Scheme 9



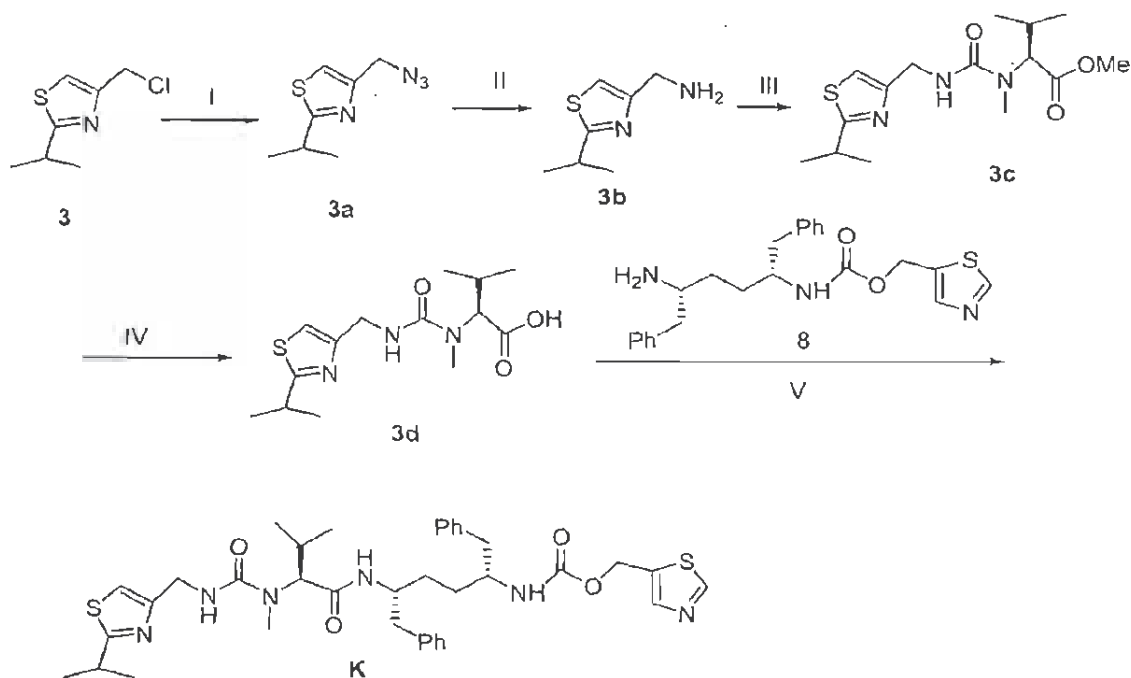
- 15 Example I

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

5 Scheme 10



1. NaN_3/DMF ; II. $\text{PPh}_3/\text{H}_2\text{O}$; III. a. $\text{Cl}_3\text{COCOCCl}_3$; b. $\text{HCl-NH}_2\text{CHiPrCO}_2\text{Et}$; IV. a. NaOH ; b. HCl ; V. $\text{EDC/HOBT/compound 8}$

Example K

Compound 5a

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

Compound 5b

To the solution of Compound **5a** (700 mg, 3.9 mmol) in THF (10 mL) was
15 added water (69 μ L, 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 **5b**, which was used for next step without further purification.

Compound 5c

5 To a solution of triphosgene (110 mg, 0.37 mmol) in CH₂Cl₂ (2 mL) at 0 °C was added a solution of Compound **5b** (1 mmol) and iPrNEt₂ (0.38 mL, 2.2 mmol) in CH₂Cl₂ (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 iPrNEt₂ (0.34 mL, 2.2 mmol) in CH₂Cl₂ (2 mL) was added. The
10 mixture was stirred for 12 hours, and diluted with EtOAc. The solution was washed with sat. Na₂CO₃ (2x), water (2x), and brine, and dried over Na₂SO₄. Concentration and purification with silica gel flash column gave Compound **5c** (300 mg).

Compound 5d

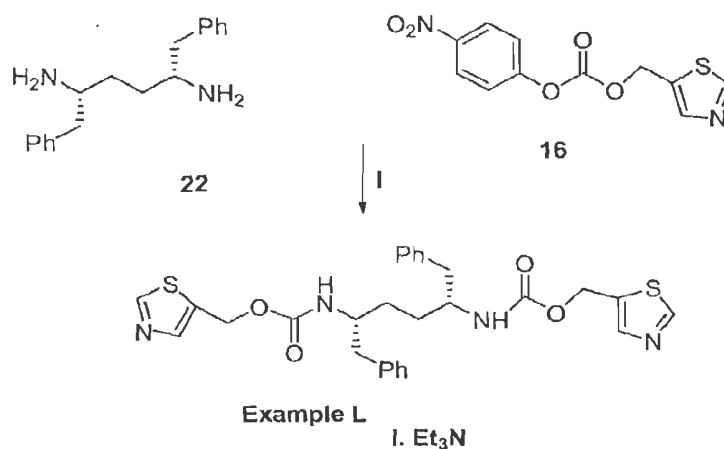
15 Compound **5d** was prepared following the procedure for Compound **13**, with the exception that Compound **5c** was used instead of Compound **12**.

Example K

Example **K** was prepared following the procedure for Example **D** (7 mg), except that Compound **5d** was used instead of Compound **13a**. m/z 705.2
20 (M+H)⁺. ¹H-NMR (CDCl₃) 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).

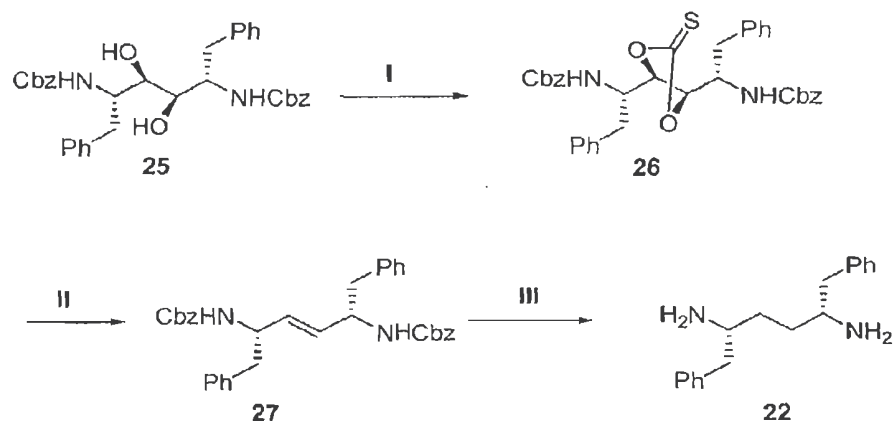
Preparation of Example L

Scheme 11



Example L

To a solution of Compound **22** (1.57 mmol) in CH₃CN (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 Na₂CO₃, 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)⁺. ¹H-NMR (CDCl₃) 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

5 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

10 A mixture of Compound 25 (7.4 g) and 1,1'-thiocarbonyldiimidazole (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

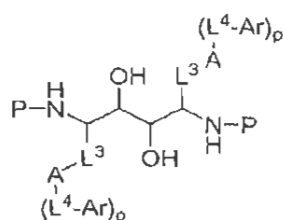
15 The mixture of Compound 26 (7.3 g) and triethylphosphite (100 mL) was heated at 160°C for 4 hours. Excess reagents were removed under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 3/1) gave Compound 27 (5 g).

Compound 22

20 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

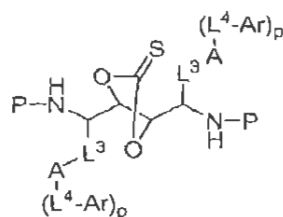
added to the mixture, and the mixture was stirred for 5 minutes. Filtration and evaporation of solvents gave Compound 22 (116 mg).

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:



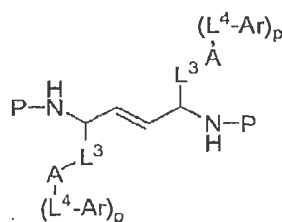
Analogs of Compound 25

wherein L^3 , A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group described in 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:

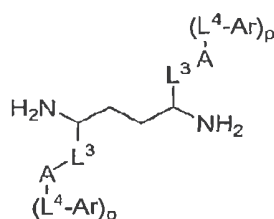


Analogs of Compound 26;

analog of Compound 27:



Analogs of Compound 27; and
analogs of Compound 22:

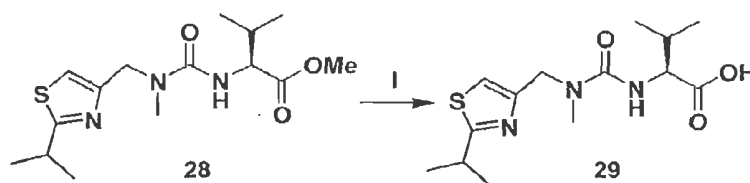


5

Analogs of Compound 22.

Preparation of Examples M and N

Scheme 13



I. a. LiOH, THF/H₂O, 25 °C; b. HCl

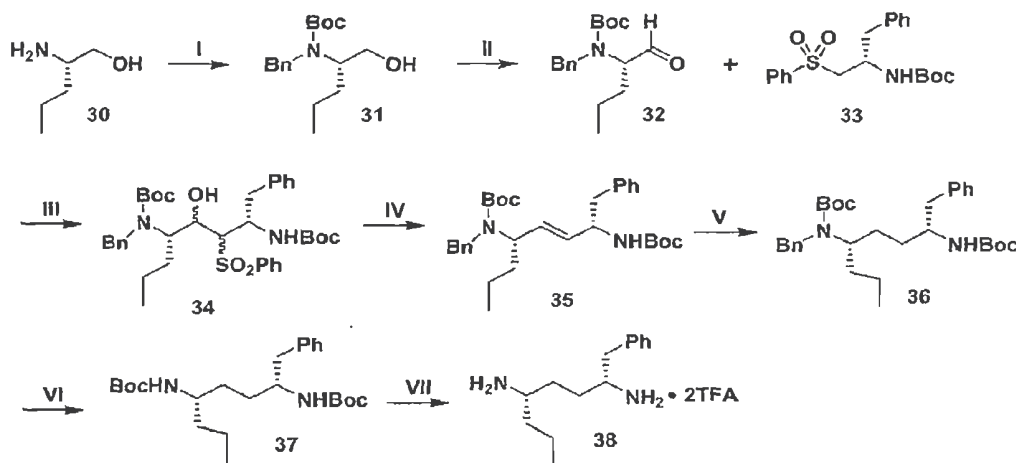
10 Compound 29

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 ($\text{M}+\text{H}$)⁺) that was used in the following procedures without further purification.

Scheme 14



I. a. PhCHO , MeOH ; b. NaBH_4 ; c. Boc_2O , $\text{THF}/\text{H}_2\text{O}$. II. $\text{Pyr}\cdot\text{SO}_3$, Et_3N , DMSO 0°C . III. $n\text{-BuLi}$, $\text{MeOI}(\text{i-Bu})_2$, 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

H₂O (25 mL) at room temperature and Boc₂O (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 MgSO₄ and concentrated *in vacuo*. Chromatography on SiO₂ (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 Et₃N (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•SO₃ 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 NaHCO₃, H₂O, and dried over anhydrous MgSO₄ 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. ¹H-NMR (CDCl₃, 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 NH₄Cl (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.

10 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 Na₂SO₄. 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

15 used in the following procedures without further purification.

Compound 35

Crude Compound **34** was suspended in CH₂Cl₂ (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.

20 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 CH₂Cl₂. The combined organic layers were dried over anhydrous MgSO₄ and concentrated *in vacuo* to produce 8.95 g (88%) of a white solid that was immediately taken up in MeOH (100 mL). Na₂HPO₄ (11.4 g,

25 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, H₂O (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 ($\text{M}+\text{Na}$)⁺).

5 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
10 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 ($\text{M}+\text{Na}$)⁺) that was used in the following procedures without further purification.

Compound 37

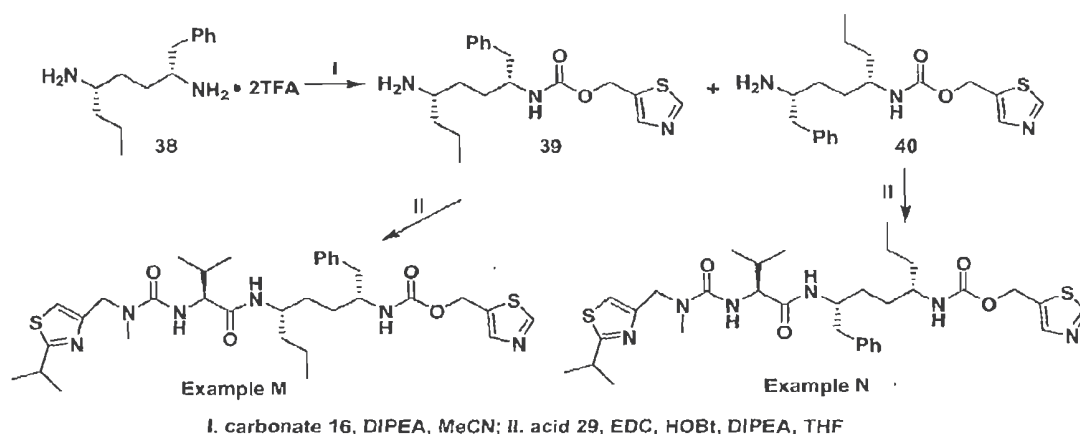
Compound 36 (0.528 g, 1.03 mmol) was diluted in THF (3 mL) and added
15 to liquefied ammonia (approx. 20 mL) at -35 °C. Small pieces of Na were added until a blue color persisted. After 1.5 h, solid NH_4Cl was added in portions until the remaining Na was destroyed and the ammonia was allowed to escape at ambient temperature. Water and EtOAc (20 mL each) were added, and the aqueous layer was extracted with EtOAc. The combined organic layers were
20 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 ($\text{M}+\text{H}$)⁺; 443.2 ($\text{M}+\text{Na}$)⁺).

Compound 38

25 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



5 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 CHCl₃/IPA (v/v, 13 mL) and treated with saturated Na₂CO₃ (3 mL). The resulting suspension was diluted with H₂O (3 mL), and the aqueous phase thoroughly extracted with 3/1 CHCl₃/IPA. The combined organic layers were dried over a 3/2 (w/w) mixture of anhydrous Na₂SO₄/anhydrous Na₂CO₃ and concentrated *in vacuo*. Chromatography on SiO₂ (0-20% MeOH/CH₂Cl₂) 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

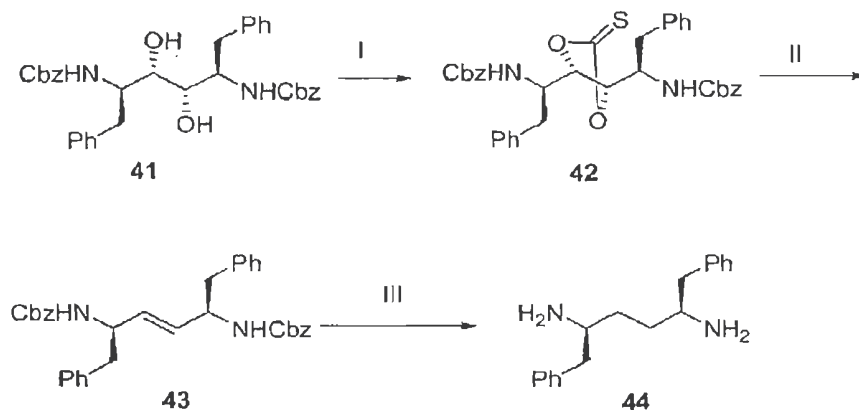
A flask was charged with Compound **39** (0.048 g, 0.133 mmol) and Compound **29** was added as a 0.2 M solution in THF (0.8 mL, 0.160 mmol). THF (1 mL) was added, followed by DIPEA (0.026 mL, 0.145 mmol), HOBT (0.022 g,

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 SiO₂ (0-20% MeOH/CH₂Cl₂). Fractions containing the desired compound were concentrated *in vacuo* and submitted to preparatory

- 5 LC/MS purification to afford 0.018 g (20%) of Example **M** as a colorless film
LC/MS *m/z*: 657.2 (M+H)⁺; ¹H-NMR (CDCl₃, 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* = 6.9 Hz, 6H); 0.96 (m, 6H);
10 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);
15 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)⁺; ¹H-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,
20 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. H₂, 10% Pd/C.

Compound 41

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

Compound 42

- 10 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 MgSO₄. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 1/1) gave Compound **42** (980 mg). *m/z*: 611.1 (M+H)⁺.

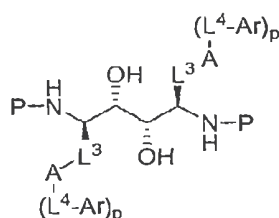
Compound 43

- 15 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

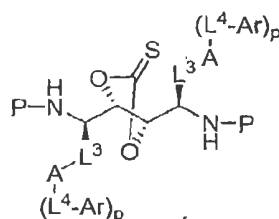
A mixture of Compound **43** (580 mg) in i-PrOH/EtOAc (12 mL/12 mL) was hydrogenated under high pressure (100 psi) for 24 hours in the presence of 10%Pd/C (200 mg). Celite was added and the mixture was stirred for 5 minutes. Filtration and evaporation gave Compound **44** (285 mg). m/z: 269.1 (M+H)⁺.

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:



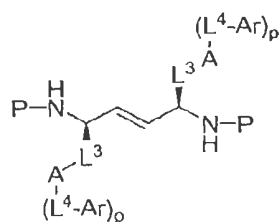
Analogs of Compound **41**

wherein L³, A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group 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**:

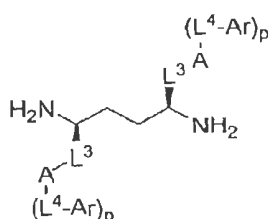


Analogs of Compound **42**;

analogs of Compound **43**:



Analogs of Compound **43**; and
analogs of Compound **44**:

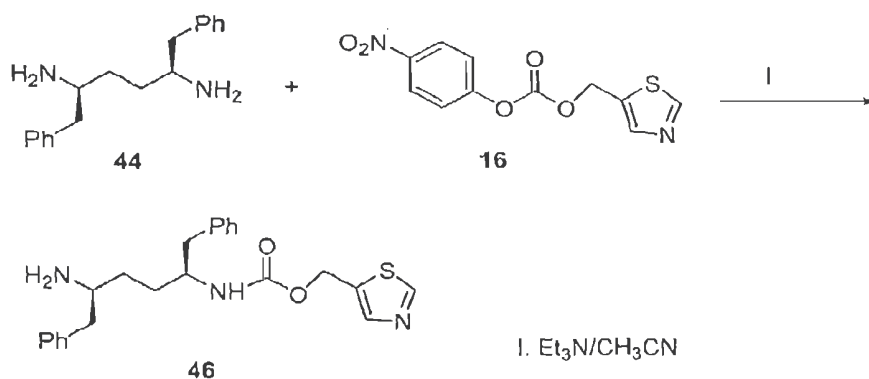


5

Analogs of Compound **44**.

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

10 Scheme 17

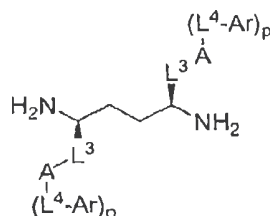


Compound 46

To the solution of Compound **45** (950 mg, 3.5 mmol) in CH₃CN (36 mL) at 0 °C was added Compound **16** (892 mg, 3.2 mmol), followed by
15 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 Na₂CO₃, water, and brine. Purification by flash column chromatography (silica gel, 100% EtOAc to CH₂Cl₂/MeOH = 4/1) gave Compound 46 (770 mg). m/z: 410.1 (M+H)⁺.

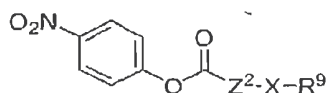
5 The skilled practitioner will recognize that the procedure outlined in Scheme 17 can be used to prepare a variety of compounds analogous to Compound 46. For example, 1,4-diamines analogous to Compound 44 can be prepared as discussed above:



10

Analogous of Compound 44.

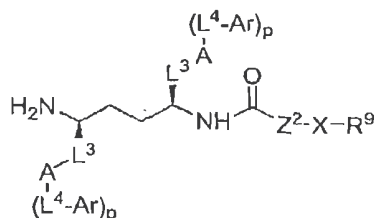
The analogs of Compound 44 can then be reacted with analogs of Compound 16:



15

Analogous of Compound 16,

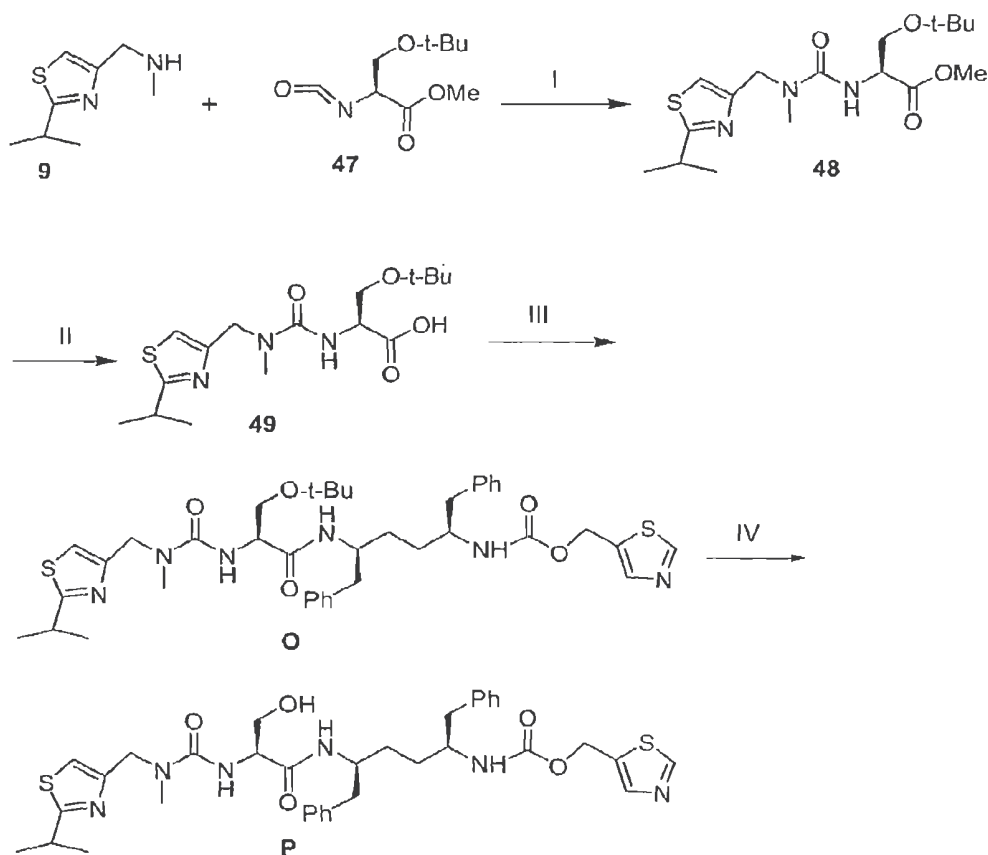
(wherein Z², X, and R⁹ are as defined herein) to form analogs of Compound 46:



20 It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diastereomers) can be prepared by the selection

of analogs of Compound 44 having the appropriate stereochemical configuration at the chiral centers.

Scheme 18



I. $\text{CH}_2\text{Cl}_2/25^\circ\text{C}$; II. a. $\text{NaOH}/\text{dioxane}/\text{H}_2\text{O}$; b. HCl ; III. amine 46/EDC/HOBt; IV. a. TFA; b. NaOH

5 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.

- 10 Purification by flash column chromatography (hexanes/EtOAc = 1/1.5) gave Compound 48 (242 mg). m/z : 372.1 ($\text{M}+\text{H}$)⁺.

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 MgSO₄.

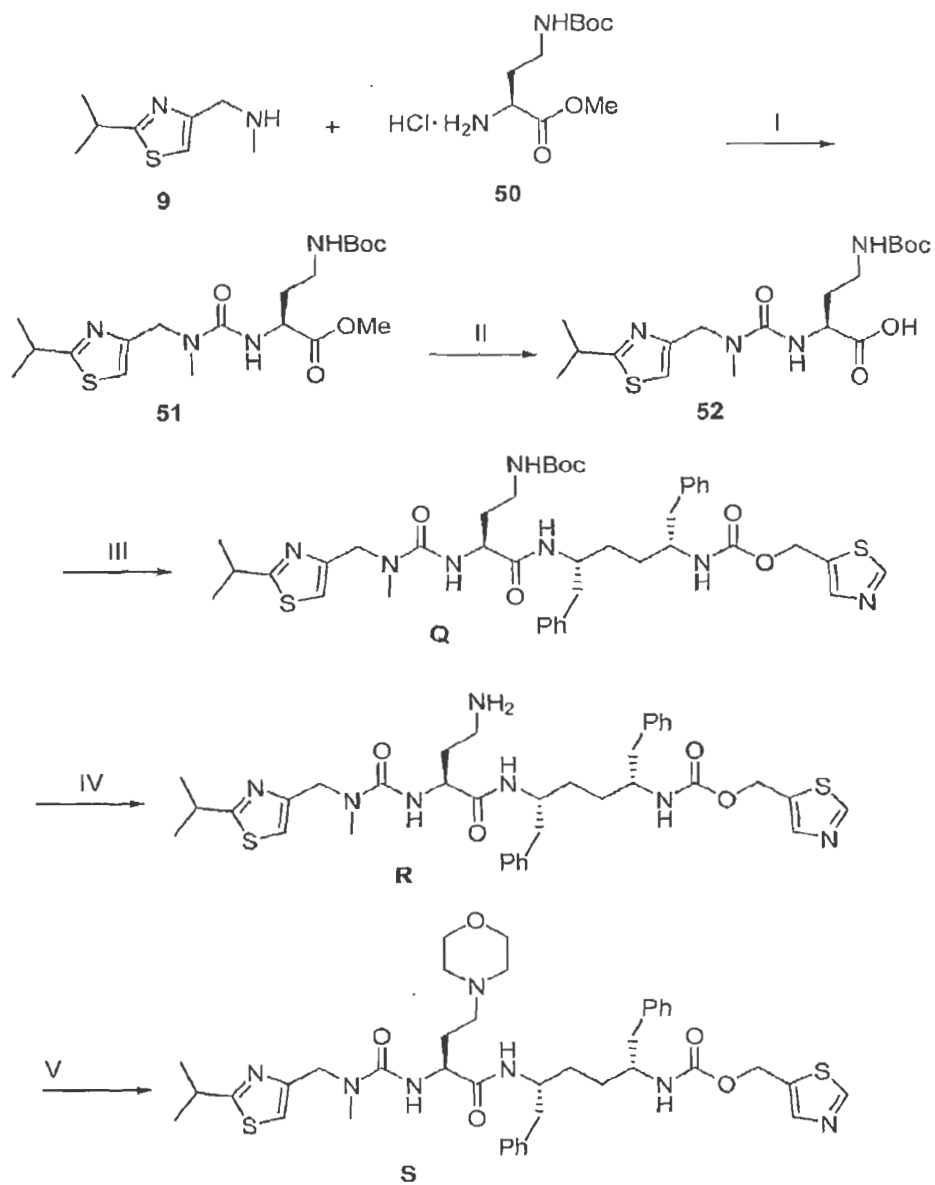
5 Concentration gave Compound 49 (200 mg). m/z: 356.2 (M-H)⁺.

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 diisopropylethylamine (0.2 mL). The mixture was stirred
10 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
15 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). ¹H-NMR (CDCl₃) 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),
20 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, CH₂Cl₂; II. LiOH, THF/H₂O;
 III. Compd. 8, DIPEA, EDC, HOBT, THF;
 IV.a. HCl/dioxane; b. Na₂CO₃; V.
 (BrCH₂CH₂)₂O, NaHCO₃, DMF

Compound 50

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

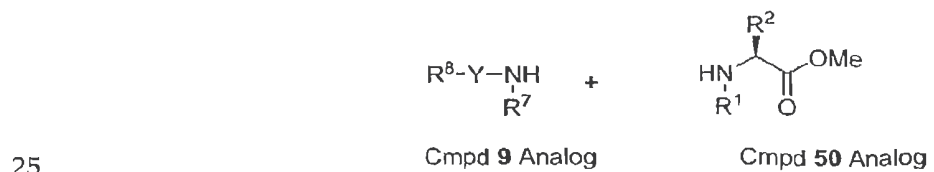
Compound 51

Compound 50 (7.0 g, 26.0 mmol) was dissolved in CH₂Cl₂ (330 mL) and 1,1-carbonyldiimidazole (4.22 g, 26.0 mmol) was added, followed by i-Pr₂NEt (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 CH₂Cl₂ 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 (Na₂SO₄), 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 Na₂SO₄, 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:



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



wherein R¹, R², R⁷, R⁸ and Y are as defined herein.

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

Example Q

- 10 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-Pr₂NEt (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
- 15 sequentially with saturated aqueous Na₂CO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5% iPrOH/CH₂Cl₂) gave Example Q (3.02 g). m/z: 806.2 (M+H)⁺.

Example R

- 20 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 Et₂O 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 Et₂O was
- 25 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)⁺.

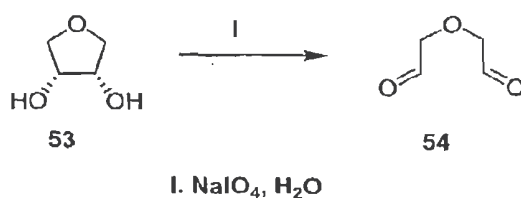
Example S

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:

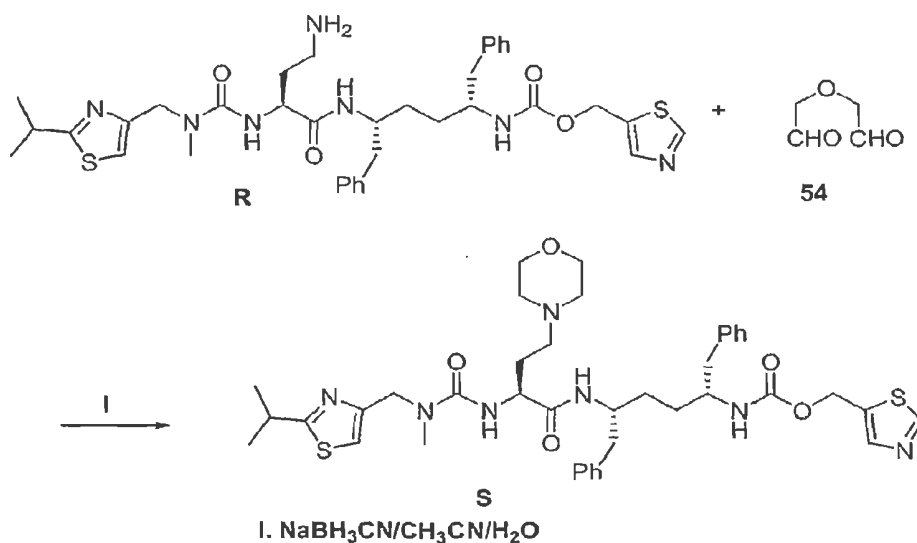
Scheme 20



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).

- 5 To solution of Compound 53 (0.550 g, 5.28 mmol) (Sigma-Aldrich) in H₂O (8.8 mL) at 0 °C was added NaIO₄ (1.016 g, 4.75 mmol). The mixture was allowed to slowly warm to 25 °C and stirred for 12 hours. Solid NaHCO₃ was added to the reaction mixture until pH 7. CHCl₃ (16 mL) was added and the mixture was allowed to stir for 5 minutes. The mixture was filtered and the solid was washed with CHCl₃ (6 mL). The combined H₂O/CHCl₃ solution was used directly in the next step without further purification.

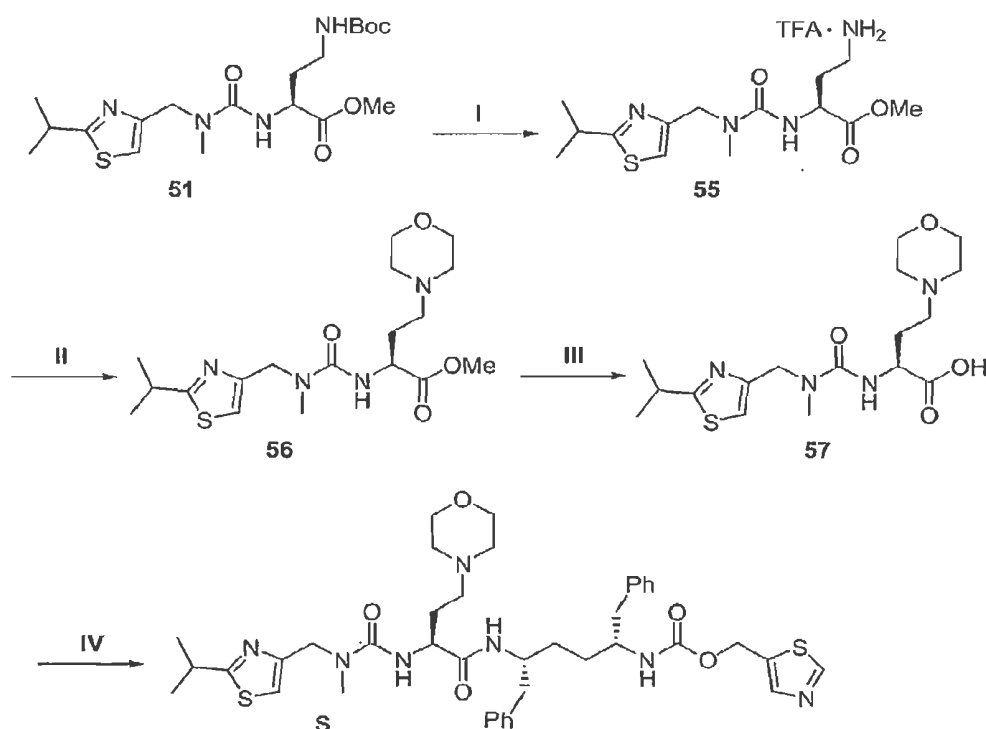
Scheme 21Example S

- 15 To a solution of Example R (70 mg, 0.1 mmol) in CH₃CN (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 CHCl₃/H₂O (4 mL/ 1 mL). The mixture was stirred for 12 hours, and basified with saturated Na₂CO₃ 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

5 Scheme 22



I. TFA, CH_2Cl_2 ; II. Cmpd 54, NaBH_3CN , $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; III. LiOH , $\text{THF}/\text{H}_2\text{O}$; 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 ($\text{M}+\text{H}$)⁺.

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 $\text{CHCl}_3/\text{H}_2\text{O}$ (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
5 H_2O and brine, dried over Na_2SO_4 , filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% $\text{MeOH}/\text{CH}_2\text{Cl}_2$ gradient) gave Compound 56 (0.17 g). m/z : 399.1 ($\text{M}+\text{H}$)⁺.

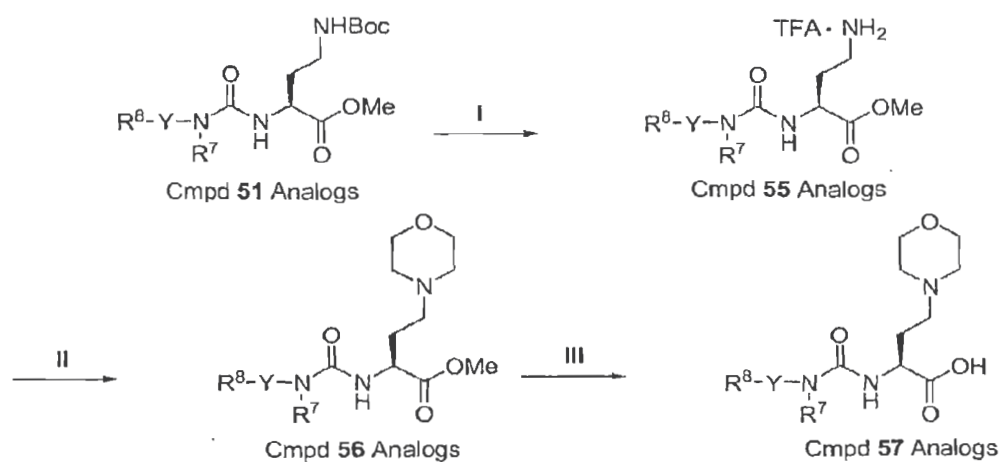
Compound 57

Compound 56 (377 mg, 0.95 mmol) was dissolved in THF (4 mL) and 1M
10 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 ($\text{M}+\text{H}$)⁺.

15 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 ($\text{M}+\text{H}$)⁺.

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



I. TFA, CH₂Cl₂; II. Ex. R, NaBH₃CN, H₂O/CH₃CN; III. LiOH, THF/H₂O

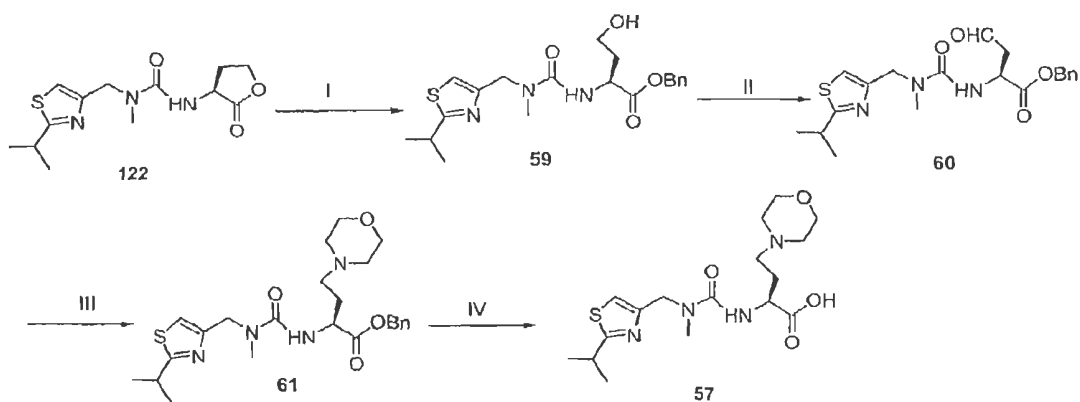
where

in R⁷, R⁸ and Y are as defined herein.

It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diastereomers) 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 Na₂SO₄. 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 Et₃N (36 mL) was stirred for 30 minutes. The mixture was cooled to 0-10 °C, SO₃-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. Na₂CO₃ 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 Na₂CO₃ (2x), water (3x), and brine. The mixture was dried over Na₂SO₄ and concentrated to give Compound 60 (32 g), which was used directly in next step without further purification.

Compound 61

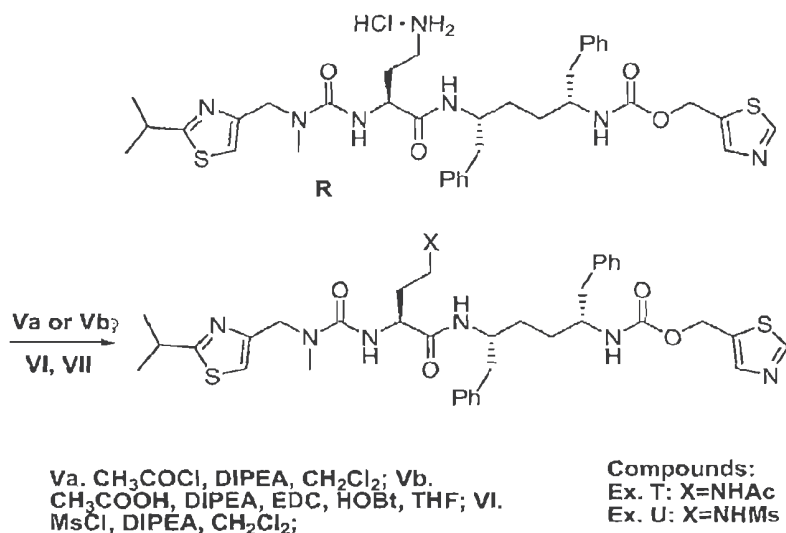
To a solution of Compound 60 (32 g) in CH₃CN (325 mL) was added morpholine (12.9 mL, 148 mmol), with a water bath around the reaction vessel, followed by HOAc (8.9 mL, 148 mmol), and NaBH(OAc)₃ (47 g, 222 mmol). The mixture was stirred for 12 hours. CH₃CN was removed under reduced pressure, and the mixture was diluted with EtOAc (300 mL). Sat. Na₂CO₃ 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 Na₂CO₃ (2x), water (1x), and brine (1x). The mixture was dried over Na₂SO₄. 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 CH₂Cl₂ (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 T5 Method I

The hydrochloride salt of Example **R** (100 mg, 0.13 mmol) was suspended in CH₂Cl₂ (2 mL) and dissolved by addition of iPr₂NEt (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/CH₂Cl₂) gave Example **T** (39 mg, 40%). *m/z*: 748.2 (M+H)⁺. ¹H NMR (CDCl₃) 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).

15 Method II

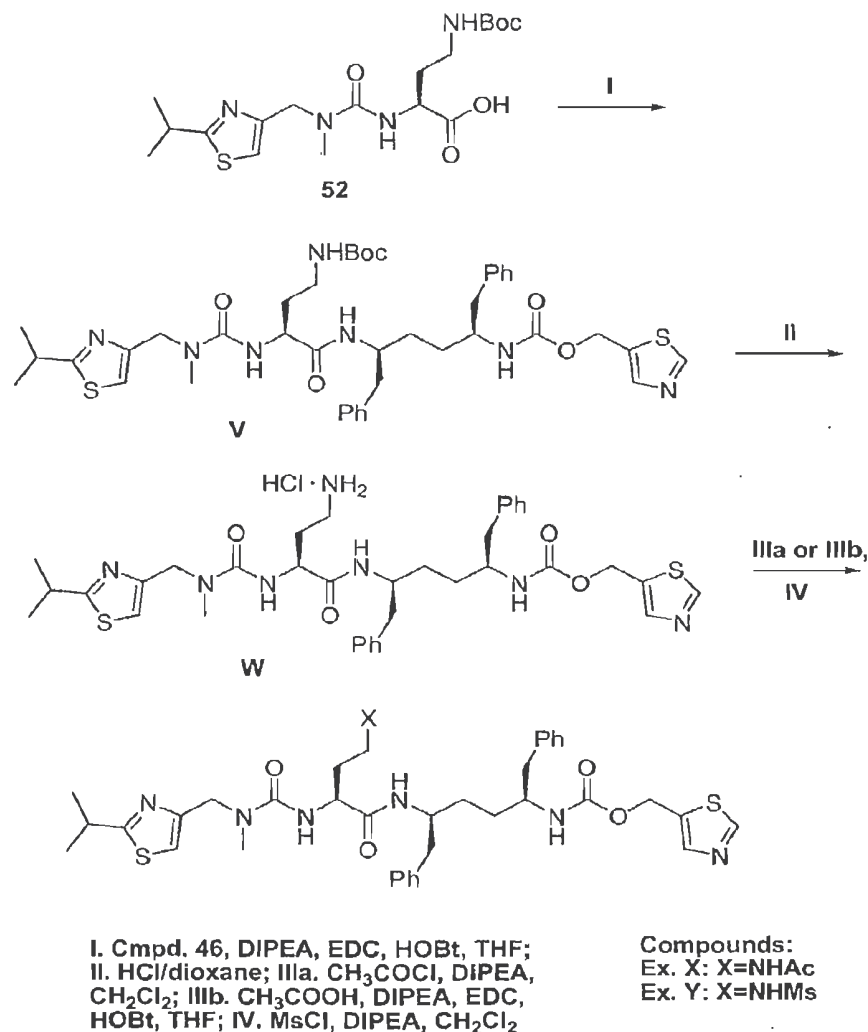
Saturated aqueous Na₂CO₃ solution was added to the hydrochloride salt of Example **R** (3.18 g, 3.46 mmol) while stirring until the solid disappeared. The aqueous solution was extracted with ethyl acetate. The organic phases were dried over Na₂SO₄, filtered, and evaporated to afford Example **R** as 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 μ L, 0.64 mmol) was added, followed by HOBt (85 mg, 0.64 mmol),
5 iPr₂NEt (304 μ L, 1.70 mmol), and EDC (151 μ L, 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 Na₂CO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and evaporated. Purification by Combiflash® (stationary
10 phase: silica gel; eluent: 10% MeOH/CH₂Cl₂) gave Example T (249 mg, 77%). m/z: 748.2 (M+H)⁺.

Example U

Example R (100 mg, 0.13 mmol) was suspended in CH₂Cl₂ (2 mL) and dissolved by addition of iPr₂NEt (69 μ L). Methanesulfonyl chloride (12 μ L) was
15 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/CH₂Cl₂) gave Example U (55 mg, 54%). m/z: 784.2 (M+H)⁺. ¹H NMR (CDCl₃) 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);
20 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**Example V

- 5 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

- 10 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 (CD₃OD) 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).

5 Compound 59

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 (CDCl₃) 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

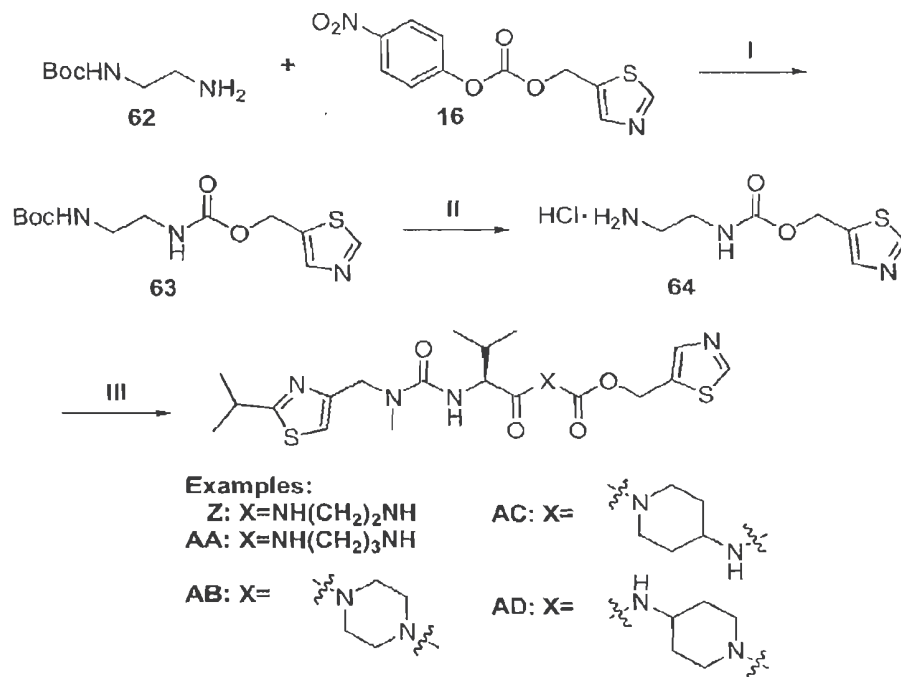
Example X (205 mg, 65%) was prepared following the Method II procedure for Example T except that Example W was used instead of Example R. m/z: 748.2 (M+H)⁺.

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 (CDCl₃) 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, CH₃CN; II. HCl/dioxane, EtOAc; III. acid 29, DIPEA, EDC, HOBT, THF

5

Compound 62

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

Compound 63

10 To a solution of Compound **62** (2.0 mmol) in CH₃CN (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 Na₂CO₃, water, and brine. The
 15 organic layers were dried with Na₂SO₄, 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
5 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

10 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 μ L, 1.16 mmol), and EDC (103 μ L, 0.58 mmol). The reaction was allowed to stir for 12 hours at 25 °C and concentrated under
15 reduced pressure. The residue was diluted with EtOAc and washed sequentially with saturated aqueous Na₂CO₃, water, and brine. The organic layers were dried with Na₂SO₄, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% MeOH/CH₂Cl₂ gradient) gave Example Z (54 mg, 38%). m/z : 497.1 (M+H)⁺. ¹H NMR (CDCl₃) δ 8.78 (s, 1H); 7.83 (s, 1H); 6.99 (s, 1H);
20 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
25 (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 (CDCl₃) 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

5 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 (CDCl₃) δ 8.82 (s, 1H); 7.89 (s, 1H); 6.96
10 (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
15 (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 (CDCl₃) 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,
20 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).

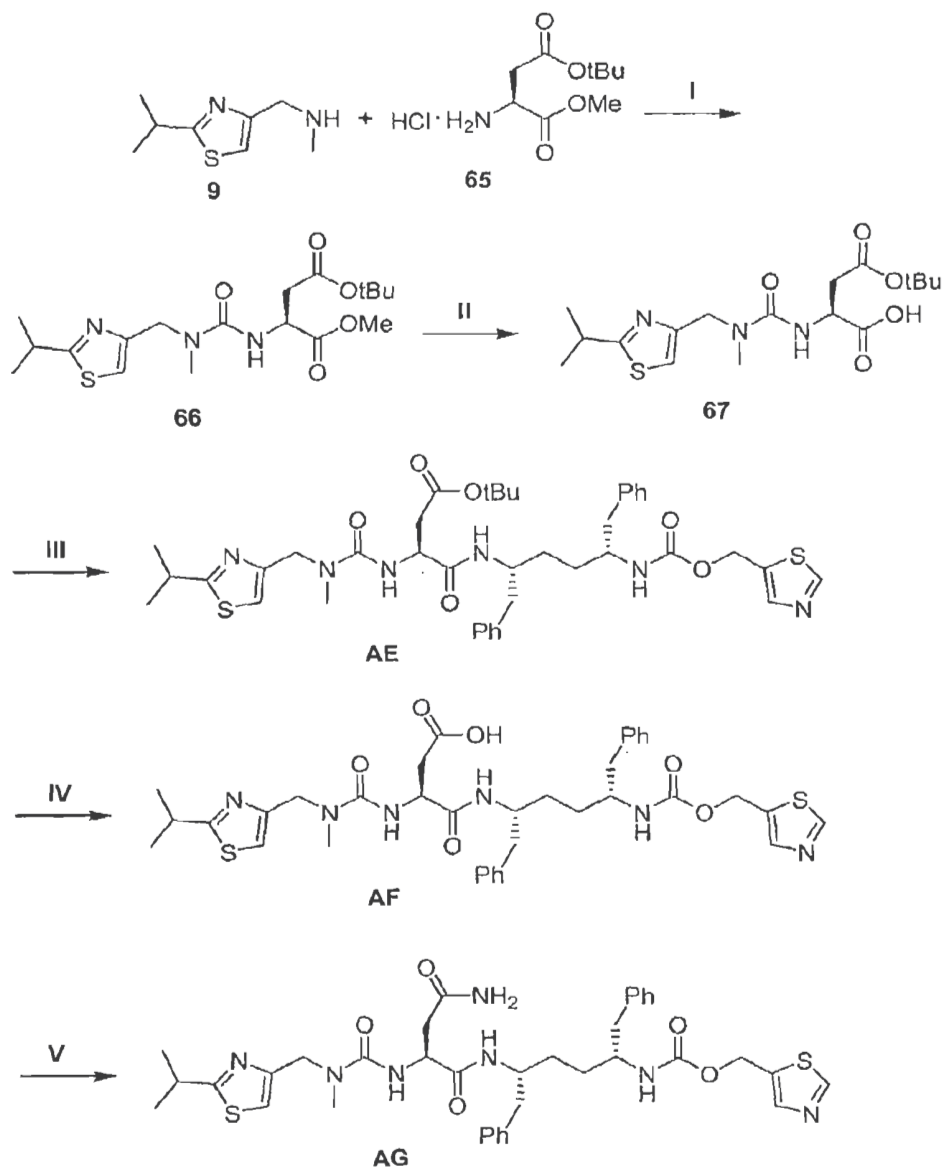
Example AD

 Example **AD** was prepared following the procedures I-III for Example **Z**, with the exception that tert-butyl 4-piperidinylcarbamate was used instead of
25 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 (CDCl₃) 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, CH₂Cl₂; II. NaOH, THF/H₂O; III. Compd. 8, DIPEA, EDC, HOBT, THF; IV. neat TFA; V. (Boc)₂O, NH₄HCO₃, pyridine, dioxane, DMF

5

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 CH₂Cl₂ (45 mL) and
5 1,1-carbonyldiimidazole (648 mg, 4.0 mmol) was added, followed by i-Pr₂NEt (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 CH₂Cl₂ (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
10 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
15 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 Na₂SO₄, filtered, and evaporated. Compound 67 (772 mg) was used directly in the next step without further purification. m/z: 386.0 (M+H)⁺.

20 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-Pr₂NEt (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
25 reduced pressure. The resulting residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na₂CO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and evaporated. Purification by

flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH₂Cl₂) gave Example AE (3.02 g). m/z: 777.2 (M+H)⁺.

Example AF

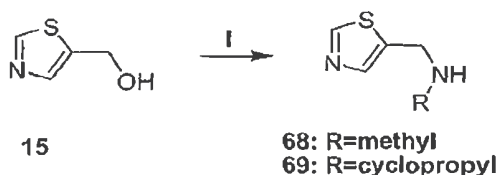
Example AE (100 mg, 0.13 mmol) was dissolved in neat TFA (3 mL). The mixture was stirred at 25 °C for 2 hours. The solvent was removed under reduced pressure. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH₃CN/H₂O gradient) gave Example AF (20 mg, 21%). m/z: 721.2 (M+H)⁺. ¹H NMR (CDCl₃) 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 Na₂SO₄, filtered, and evaporated. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH₃CN/H₂O gradient) gave Example AG (35 mg, 50%). ¹H NMR (CDCl₃) 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



I. a. MsCl, TEA, CH₃CN; b. MeNH₂/H₂O; c. cyclopropyl amine

Compound 15

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

5 Compound 68

Compound 15 (6.81 g, 59.1 mmol) was dissolved in CH₃CN (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 Na₂CO₃ and CH₂Cl₂. The organic phase was separated, dried over Na₂SO₄, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-10% MeOH/CH₂Cl₂ gradient) gave Compound 68 (5.07 g). m/z: 128.9 (M+H)⁺.

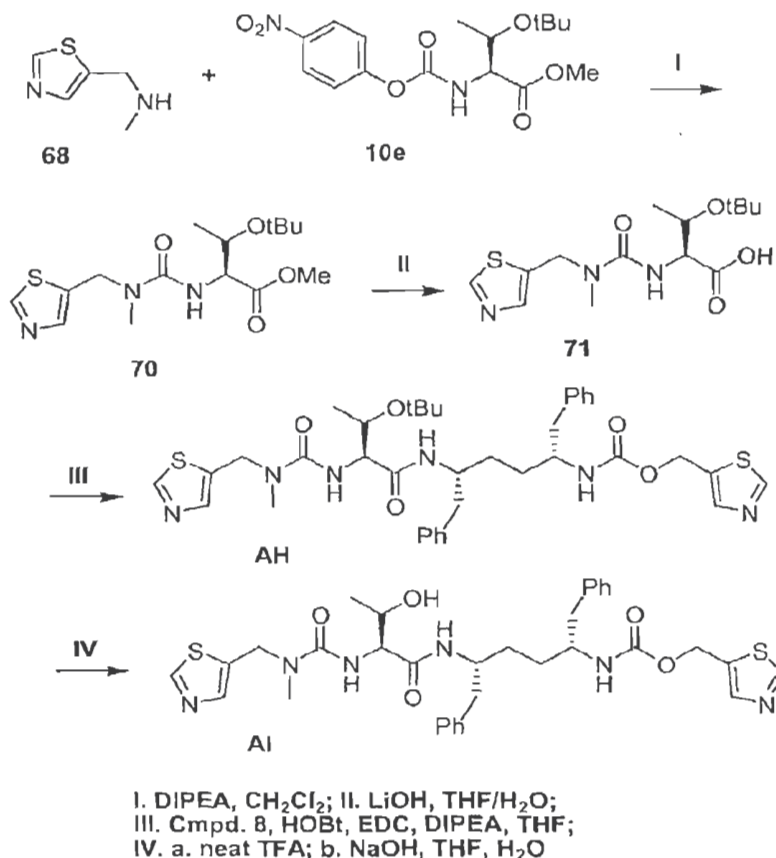
Compound 69

Compound 15 (10.0 g, 80 mmol) was dissolved in CH₃CN (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 CH₃CN (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 Na₂CO₃ and 3:1 CH₂Cl₂: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 ($\text{M}+\text{H}$)⁺.

Preparation of Examples AH and AI

Scheme 29



5

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
5 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 Na₂SO₄, 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
10 (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), iPr₃NEt (86 µL, 0.48 mmol), and EDC (42 µL, 0.24 mmol). The mixture
15 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 Na₂CO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 1-10%
20 MeOH/CH₂Cl₂ gradient) gave Example **AH** (66 mg). m/z: 721.2 (M+H)⁺.

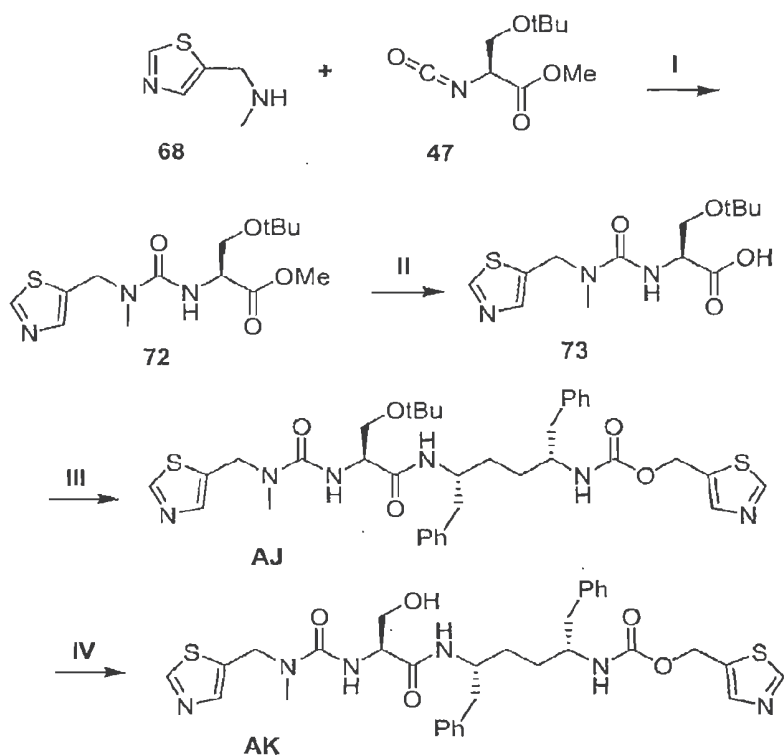
Compound AI

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
25 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 Na₂SO₄, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-20% i-PrOH/CH₂Cl₂ gradient) gave Example

AI (71 mg, 97%). m/z: 665.2 (M+H)⁺. ¹H NMR (CDCl₃) 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 AI and AK

Scheme 30



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**,
5 except that Compound **72** was used instead of Compound **48**.

Example AI

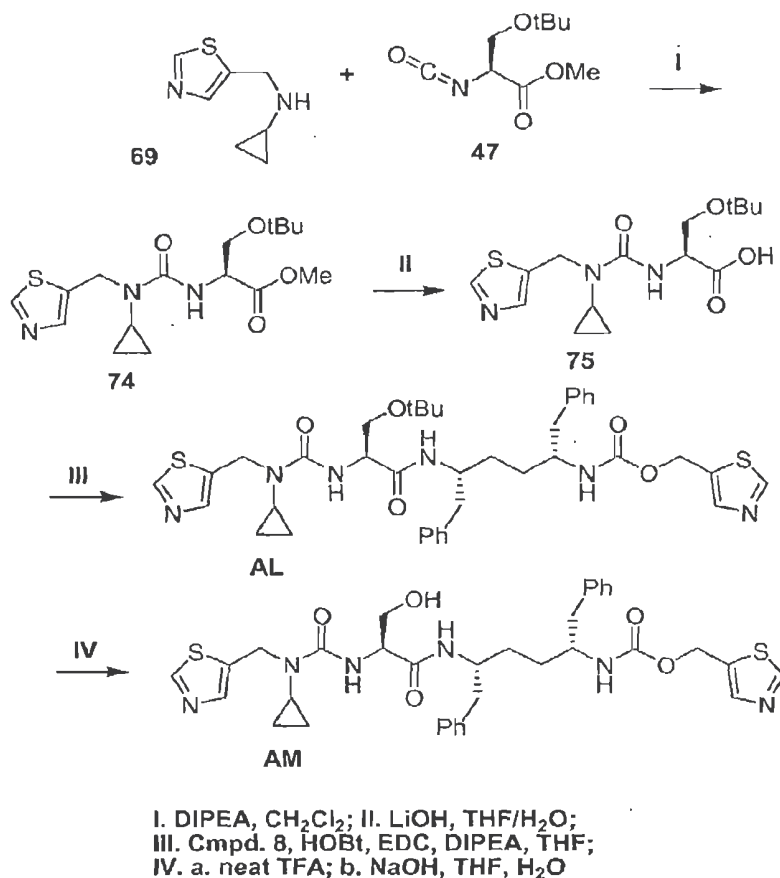
Example **AJ** (70 mg) was prepared following the same procedure used to prepare Example **AH**, with the exception that Compound **73** (41 mg, 0.13 mmol) was used instead of Compound **71**. m/z: 707.2 (M+H)⁺.

10 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 g, 0.10 mmol) was used instead of Example **AH**. m/z: 651.2 (M+H)⁺. ¹H NMR (CDCl₃) 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,
15 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

Compound 74

- 5 Compound 69 (1.56 g, 10.1 mmol) was dissolved in CH₂Cl₂ (10 mL).
 Compound 47 (1.7 g, 8.5 mmol) in CH₂Cl₂ (20 mL) was added, followed by
 iPr₂NEt (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 Na₂SO₄,
 10 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
 5 Na_2SO_4 and concentrated *in vacuo* to produce 0.331 g (quant) of Compound **75** as a colorless film (m/z 342.0 ($\text{M}+\text{H}$)⁺).

Example AL

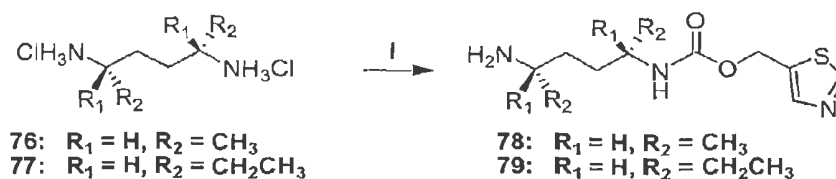
Example **AL** (2.20 g) was prepared following the same procedure used to prepare Example **AH**, with the exception that Compound **75** (2.00 g, 4.88 mmol)
 10 was used instead of Compound **71**. m/z : 733.2 ($\text{M}+\text{H}$)⁺.

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 ($\text{M}+\text{H}$)⁺. ^1H NMR (CDCl_3) δ
 15 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

20



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 **25** (described in Scheme 7) except that CBZ-L-alininol was used instead of CBZ-D-phenylalininol and Step
5 **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-D-phenylalininol.

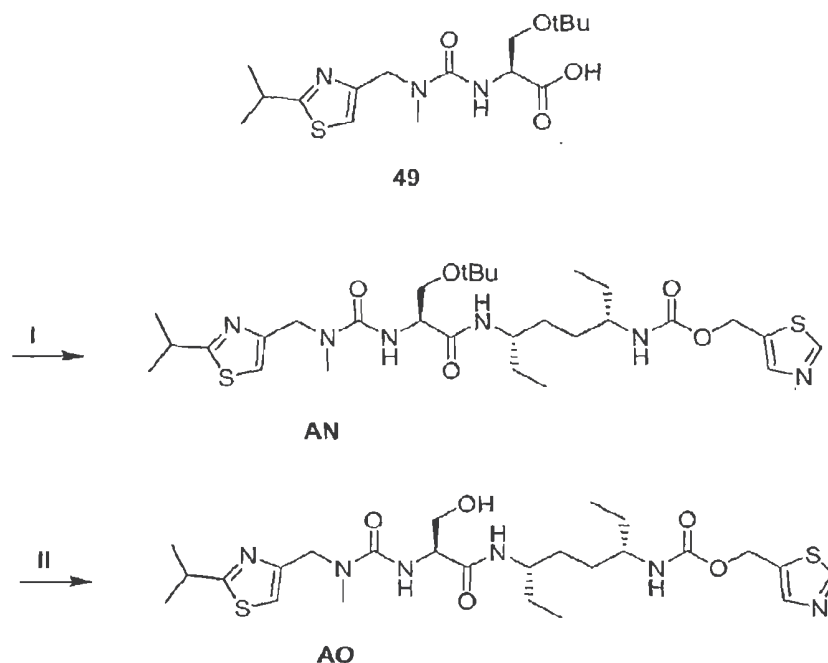
10 Compound 78

Compound **76** (7.93 mmol) is added to a solution of NaOH (16.7 mmol) in H₂O (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.
15 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 CHCl₃/IPA (50 mL). The resulting solution is washed with sat. Na₂CO₃ (50 mL) and water is added until the aqueous layer is homogeneous. The aqueous layer is extracted with 3/1 CHCl₃/IPA (3 X 25 mL). The combined organics are washed with saturated
20 Na₂CO₃ (50 mL), water (50 mL) and brine (50 mL) and are dried over anhydrous Na₂SO₄. The solvent is removed *in vacuo* and the residue purified by column chromatography on SiO₂ (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

25 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. **Compd. 79**, HOBT, EDC, DIPEA, THF;
 II. a. neat TFA; b. NaOH, THF, H₂O

Example AN

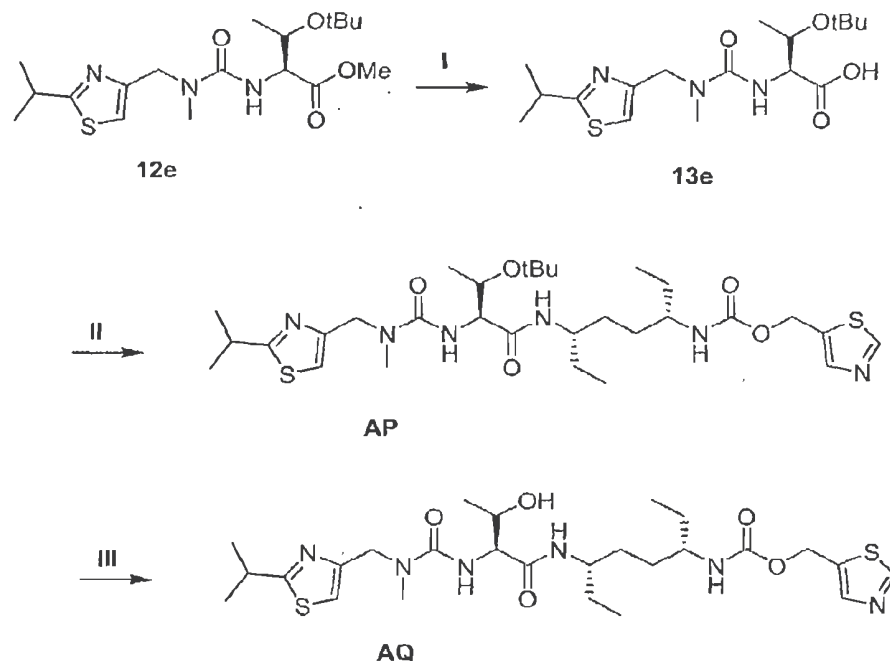
Example **AN** (68 mg) was prepared following the same procedure used to
 5 prepare Example **AH**, with the exceptions that Compound **49** (68 mg, 0.19 mmol)
 was used instead of Compound **71**, and Compound **79** (50 mg, 0.18 mmol) was
 used instead of Compound **8**. *m/z*: 625.2 (M+H)⁺.

Example AO

Example **AO** (66 mg, 76%) was prepared following the same procedure
 10 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 (CDCl₃) 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).

15 Preparation of Examples AP and AQ

Scheme 34



I. LiOH, THF/H₂O; II. Compd. 79, HOBt, EDC, DIPEA, THF;
 III. a. neat TFA; b. NaOH, THF, H₂O

Compound 13d

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)⁺.

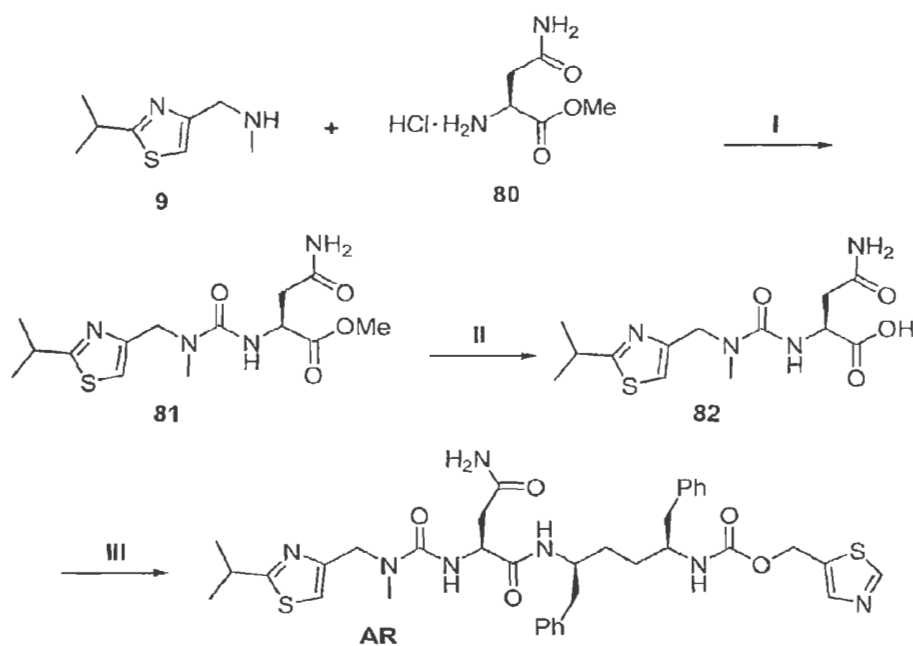
Compound AQ

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 (CDCl₃) 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).

5 Preparation of Example AR

Scheme 35



I. CDI, DIPEA, CH₂Cl₂; II. LiOH, THF/H₂O;
III. Cmpd. 46, DIPEA, EDC, HOBT, THF

Compound 80

10 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 CH₂Cl₂ (170 mL) and 1,1-carbonyldiimidazole (1.78 g, 11.0 mmol) was added, followed by iPr₂NEt (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 CH₂Cl₂ 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 with water and brine. The organic layers were dried over Na₂SO₄, filtered, and

5 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.

10 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 Na₂SO₄, 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

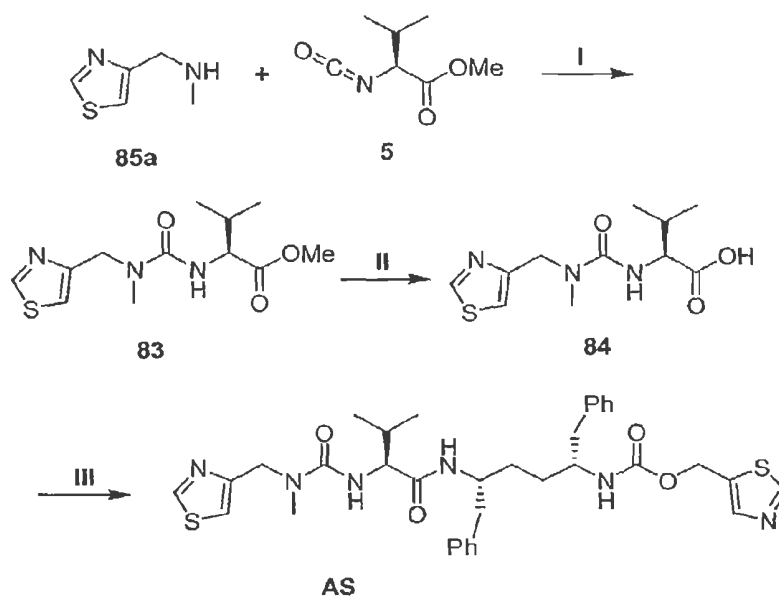
(M+H)⁺.

15 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), iPr₂NEt (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

20 pressure. The residue was diluted ethyl acetate and washed sequentially with saturated aqueous Na₂CO₃, water, and brine. The organic phase was dried over Na₂SO₄, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5-10% MeOH/CH₂Cl₂ gradient) gave Example **AR** (208 mg, 53%). m/z: 720.2 (M+H)⁺. ¹H NMR (CDCl₃) δ 8.80 (s, 1H); 7.84 (s, 1H);
25 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 ASScheme 36

I. DIPEA, CH_2Cl_2 ; II. LiOH, THF/ H_2O ; III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 85a

- 5 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

- 10 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 $^\circ\text{C}$. 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).
- 15 m/z: 286.0 ($\text{M}+\text{H}$) $^+$.

Compound 84

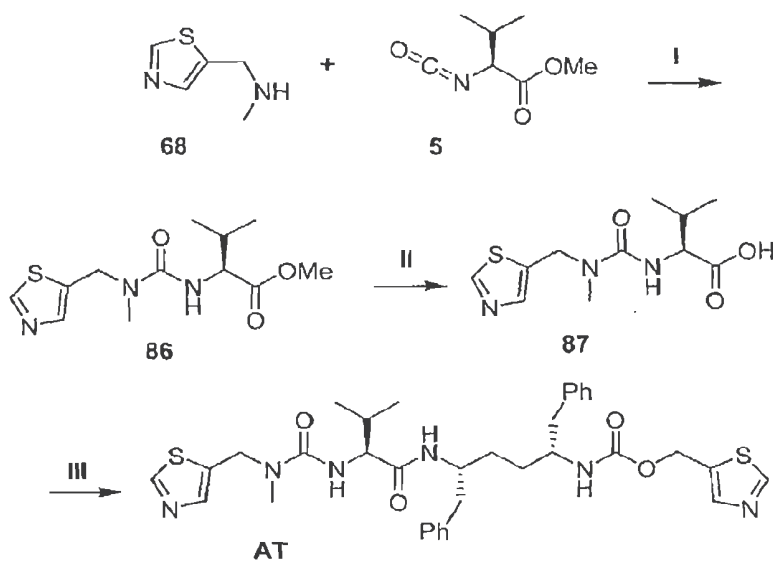
Compound **83** (0.51 g, 1.77 mmol) was dissolved in THF (10 mL) and 1M aqueous LiOH (3.54 mL) was added. The mixture was stirred at 25°C for 2 hours. The reaction was quenched with 1M HCl (4.8 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were
5 dried over Na₂SO₄, 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).
10 Compound **8** (225 mg, 0.55 mmol) was added, followed by HOBt (112 mg, 0.83 mmol), iPr₂NEt (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 Na₂CO₃, water, and brine. The organic phase was dried over
15 Na₂SO₄, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 7% i-PrOH/CH₂Cl₂) gave Example **AS** (219 mg, 60%). m/z: 663.1 (M+H)⁺. ¹H NMR (CDCl₃) 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,
20 1H); 2.31 (m, 1H); 1.60-1.30 (m, 4H); 1.00-0.80 (m, 6H).

Preparation of Example AT

Scheme 37



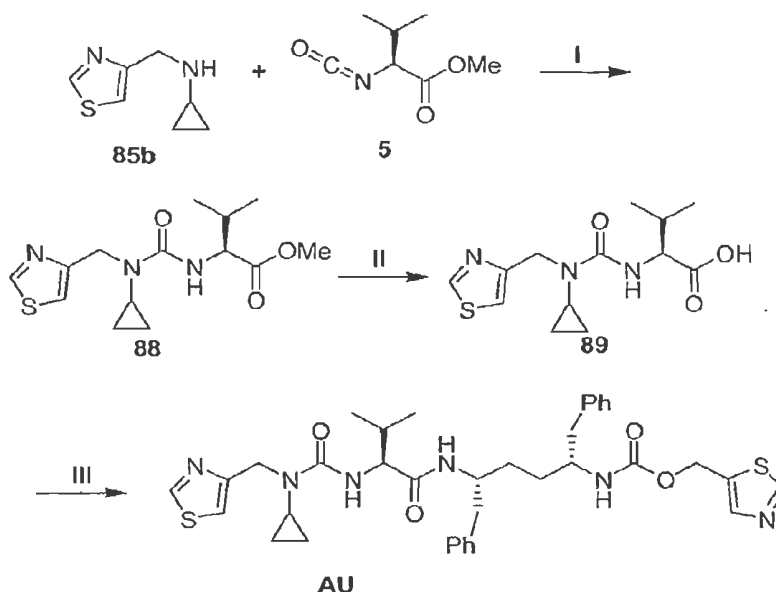
I. DIPEA, CH_2Cl_2 ; II. LiOH, THF/ H_2O ;
 III. Cmpd 8, HOBt, EDC, DIPEA, THF

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 instead of Compound 4. m/z 286.0 ($\text{M}+\text{H}^+$)

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 68. m/z : 312.0 ($\text{M}+\text{H}$) $^+$.

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 ($\text{M}+\text{H}$) $^+$.

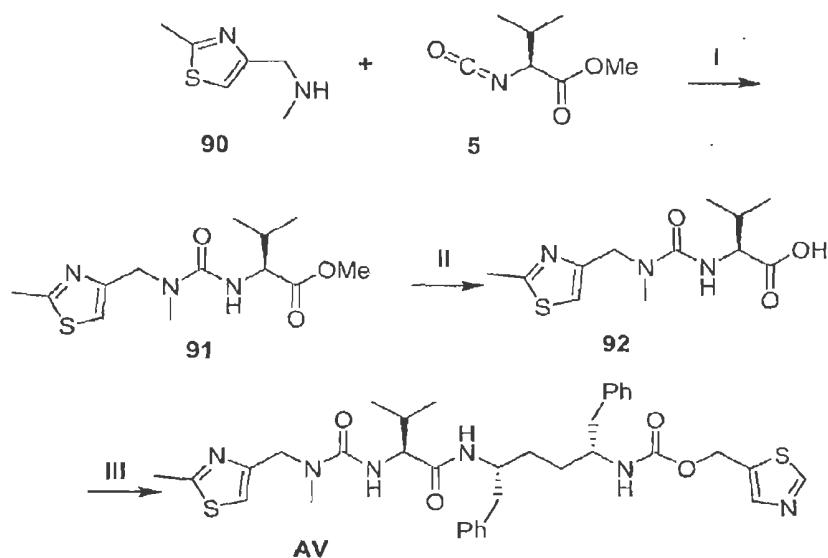
Example AU

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 (CDCl₃) 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, CH₂Cl₂; II. LiOH, THF/H₂O;
III. Compd. 8, HOBt, EDC, DIPEA, THF

10

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)

15 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

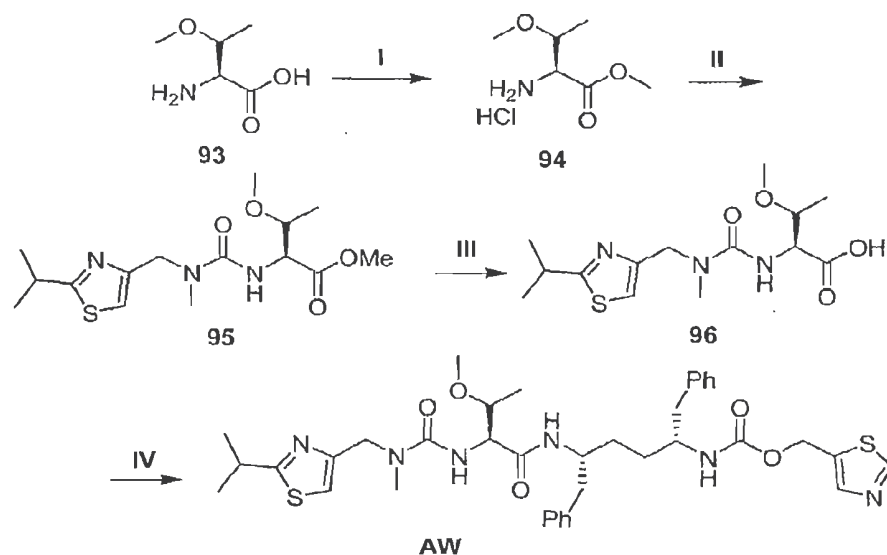
- 5 Compound **92** (188 mg) was prepared following the same procedure as Compound **7** except that Compound **91** was used instead of Compound **6**. m/z 284.0 ($M-H$)⁻

Example AV

- 10 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 (CDCl₃) 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, 6H): m/z 677.2 ($M+H$)⁺

- 15 Preparation of Example AW

Scheme 40



I. SOCl₂/MeOH; II. DIPEA, CH₂Cl₂; III. LiOH, THF/H₂O;
IV. Cmpd 8, HOBt, EDC, IPEA, THF

Compound 93

Compound 93 is commercially available from TCI, and was used without further purification.

Compound 94

- 5 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 °C for 20 minutes, and concentrated *in vacuo* to gave Compound 94.

Compound 95

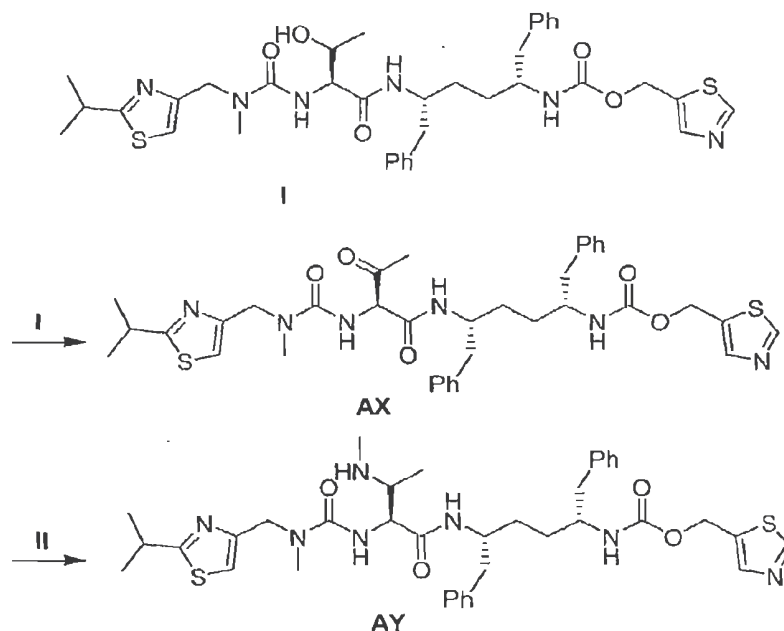
- To a stirred solution of Compound 94 (3.7 mmol) and
10 diisopropylethylamine (1.4 mL, 8.3 mmol) in dichloromethane (50 mL) was added CDI (609 mg, 3.7 mmol). The mixture was stirred for 12 hours. Compound 9 was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (0-100%: EtOAc/hexane) gave Compound 95 (100 mg). m/z 344.3 (M+H)⁺

15 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

- 20 Example AW (107 mg) was prepared following the procedure for Example C, except that Compound 96 was used instead of Compound 7. ¹H NMR (CDCl₃) 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
25 (m,4H): m/z 721.3 (M+H)⁺

Preparation of Examples AX and AY**Scheme 41**I. DMSO, Et₃N, SO₃ pyridine:II. NaBH(OAc)₃, AcOH, Methylamine/MeOHExample AX

5 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 SO₃ 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. NaHCO₃, and brine. Concentration gave

10 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,

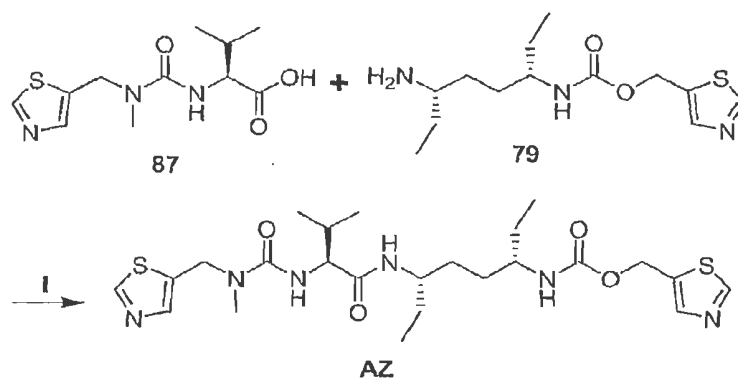
15 and the mixture was stirred for 2 hours. Concentration and purification by prep.

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

5 (M+H)⁺

Preparation of Example AZ

Scheme 42

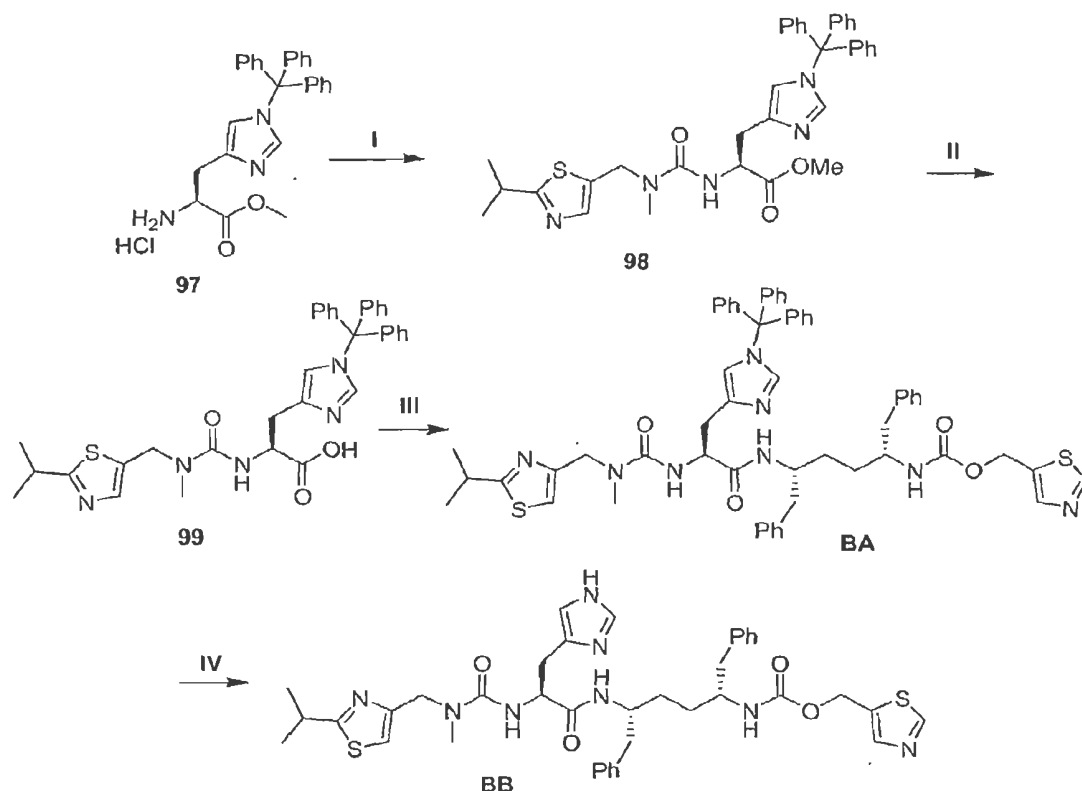


I. HOBT, EDC, DIPEA, THF

Example AZ

10 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. ^1H 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

15 (M+H)⁺

Preparation of Examples BA and BB**Scheme 43**

I. a. CDI/*i*Pr₂NEt; b. Compound 9; II. a. NaOH/THF/H₂O; b. HCl;
 III. Cmpd 8/EDC/HOBt, IPEA, THF; IV. Et₃SiH, TFA

Compound 97

5 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
 10 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)⁻

5 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

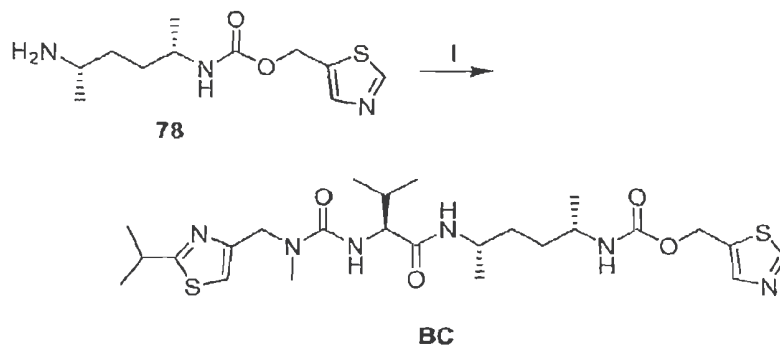
10 To a stirred solution of Example **BA** (111 mg, 0.113 mmol) and TFA (1.4 mL) was added Et₃SiH (0.1 mL). The mixture was stirred for 60 minutes, then concentrated and partitioned with EtOAc and sat. NaHCO₃, followed by extraction with EtOAc (2X) and drying over Na₂SO₄. Concentration and purification by flash column chromatography (0-15%: MeOH/DCM) gave

15 Example **BB** (50 mg).

¹H-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

20 (M+H)⁺

Preparation of Example BC**Scheme 44**



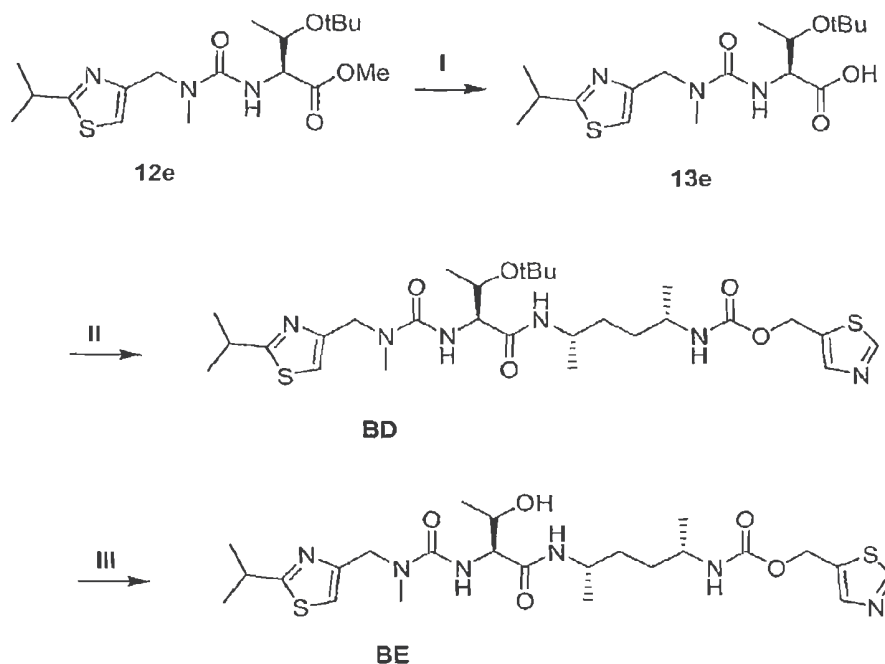
I. HOBt, EDC, DIPEA, THF, Cmpd 29

Example BC

- Example **BC** (95 mg) was prepared following the procedure used to
- 5 prepare Example **C**, except that Compound **29** was used instead of Compound **7**, and Compound **78** was used instead of Compound **8**. ^1H 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,
- 10 6 H): m/z 553.1 ($\text{M}+\text{H}$) $^+$

Preparation of Examples BD and BE

Scheme 45



I. LiOH, THF/H₂O; II. Cmpd. 78, HOBt, EDC, DIPEA, THF;
 III. a. neat TFA; b. NaOH, THF, H₂O

Example BD

Example BD (148 mg) was prepared following the procedure used to
 5 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)⁺

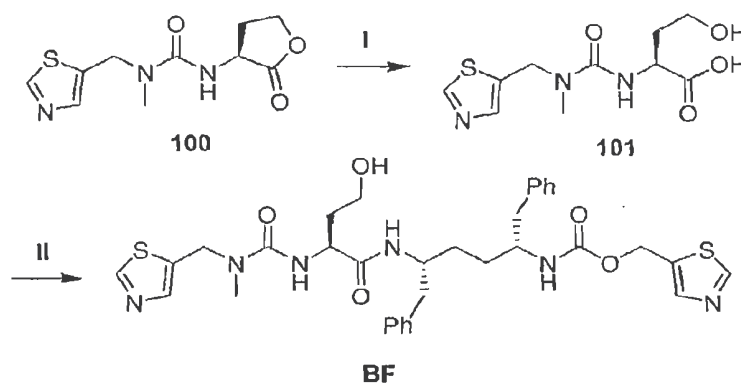
Example BE

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
 10 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 Na₂SO₄, filtered, and evaporated. Purification by flash
 chromatography (0-10% MeOH/CH₂Cl₂) gave Example BE (109 mg). ¹H NMR
 15 (CDCl₃) 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

5 Scheme 46



I. LiOH, THF/H₂O; II. Compd. 8, HOBt, EDC, DIPEA, THF

Compound 100

Compound 100 was prepared using the same method used to prepare
 10 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 μ l of 1 M LiOH/H₂O was added. After stirring overnight, 843 μ l of 1 N HCl
 15 was added. Concentration gave Compound 101.

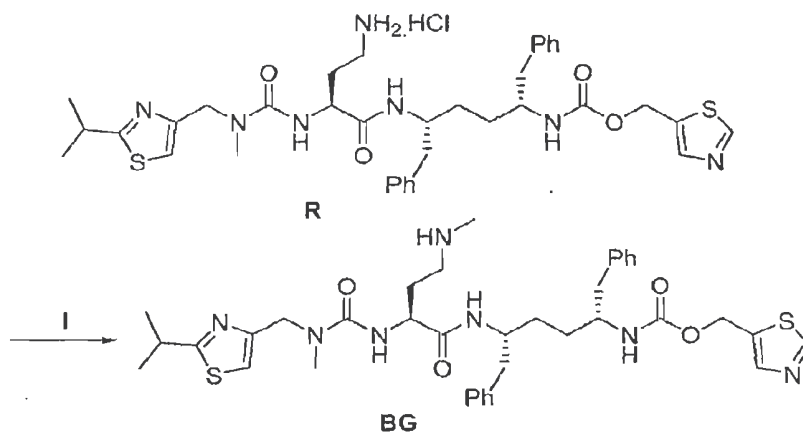
Example BF

Example BF (24 mg) was prepared following the procedure used to
 prepare Example C, except that Compound 101 was used instead of Compound
 7. ¹H NMR (CDCl₃) δ 8.77 (s, 1H), 8.73 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.27-7.10
 20 (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, Cs₂CO₃, THF

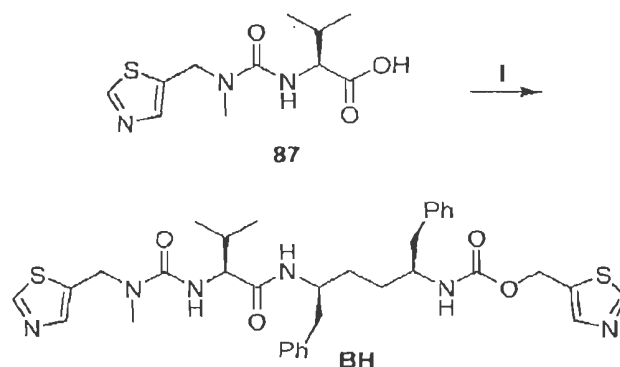
5

Example BG

Example R (102 mg, 0.137 mmol) was dissolved in THF (2 mL), then 2 mL of ethyltrifluoroacetate was added. Then 1.3 eq of MeI and excess Cs₂CO₃ were added. After stirring for 1 day, the mixture was partitioned with EtOAc and sat. Na₂CO₃, extracted with EtOAc (2X), and dried over Na₂SO₄. Purification by flash chromatography (0-20% MeOH/CH₂Cl₂) gave Example BG (6.5 mg). ¹H NMR (CD₃OD) 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)⁺.

10

15

Preparation of Example BH**Scheme 48**

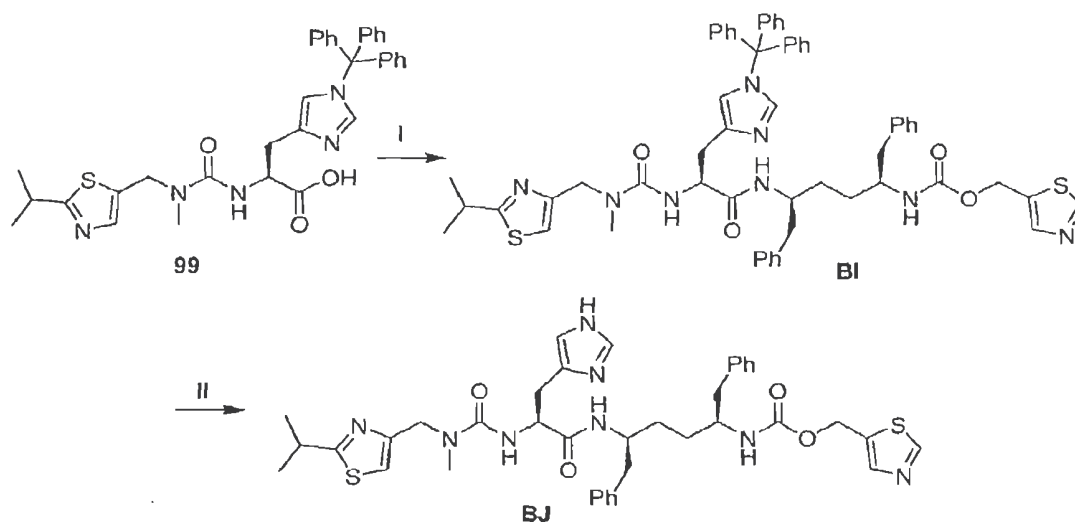
I. amine 59, HOBT, EDC, DIPEA, THF

5 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. ¹H NMR (CDCl₃) 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



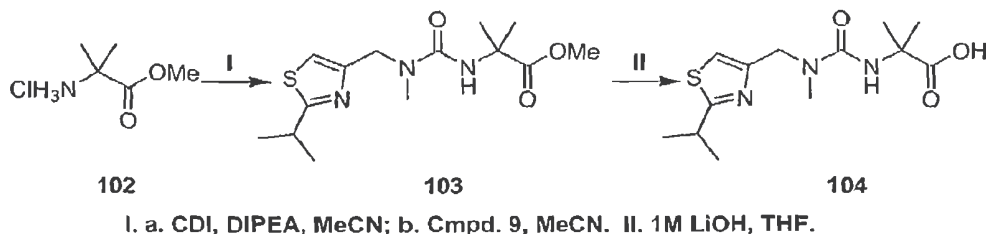
I. Compd. 46/EDC/HOBt, IPEA, THF; II. Et₃SiH, TFA

Example BI

- 5 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

- 10 Example BJ (728 mg) was prepared following the procedure used to prepare Example BB, except that Example BI was used instead of Example BA.
- ¹H-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
- 15 (M+H)⁺

Preparation of Compounds 104-115**Scheme 50**Compound 102

5 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. Na₂CO₃ until the pH of the washes was ~ pH 8. A brine wash (30 mL) was followed by drying over anhydrous MgSO₄. Following concentration *in vacuo*, the residue was purified on SiO₂ (0-65% EtOAc/hex) to provide 0.340 g (20%) of Compound **103** as an amorphous white solid (*m/z* 314.0 (M+H)⁺).

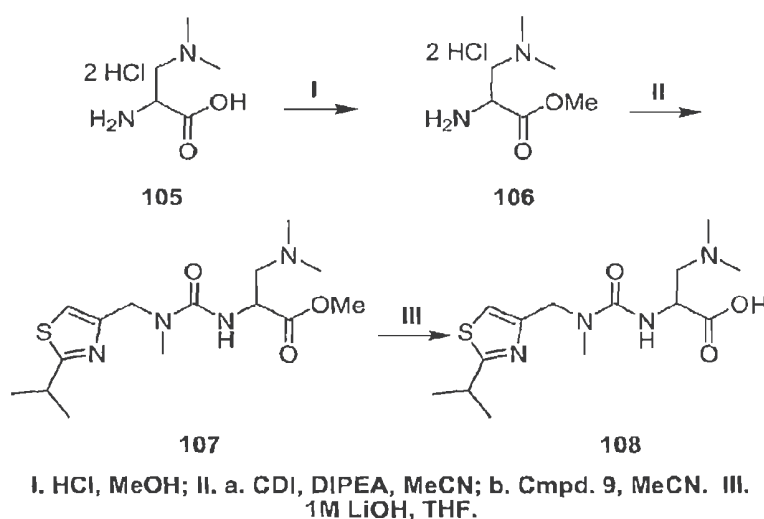
Compound 104

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 Na₂SO₄ and concentrated to provide 0.282 g (86%) of Compound **104** as an amorphous white powder that was used

5 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



Compound 105

Compound **105** is commercially available from Aldrich Chemical Co., and
10 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
15 Compound **106** as a racemic mixture. The foamy white solid was used without further purification (*m/z* 147.0 (M+H)⁺).

Compound 107

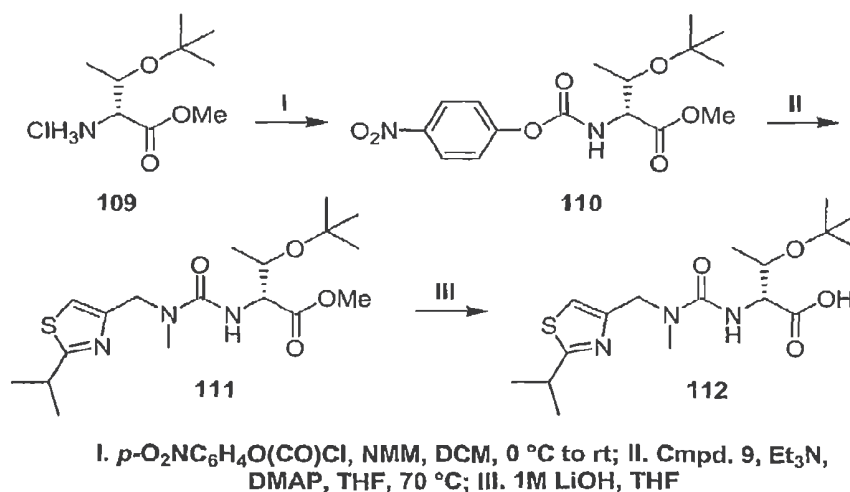
Compound **106** (5 mmol) was diluted in MeCN (65 mL) and treated with DIPEA (25 mmol). The resulting solution was added slowly via addition funnel

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. Na₂CO₃ (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 MgSO₄. Following concentration *in vacuo*, purification by column chromatography on SiO₂ (0-10% MeOH/DCM) provided 0.36 g (21%) of racemic Compound **107** as a yellow oil (*m/z* 343.1 (M+H)⁺).

10 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



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
5 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. Na₂CO₃. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined organics
10 were washed with brine (30 mL) prior to being dried over anhydrous Na₂SO₄. Following concentration *in vacuo*, the residue was purified by column chromatography on SiO₂ (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

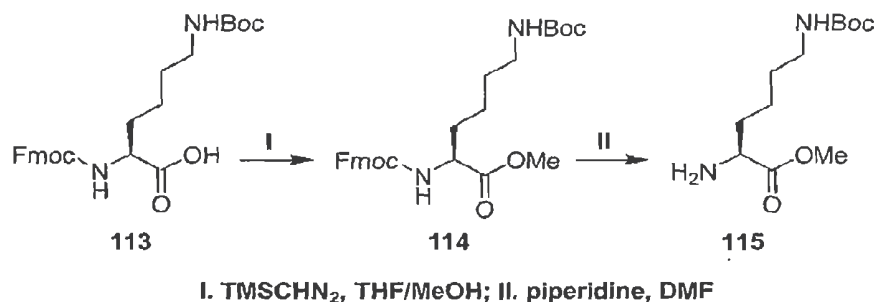
15 Compound **110** (1.1 mmol) was diluted in THF (3.5 mL). Compound **9** (1.4 mmol) was diluted in THF (3 mL), treated with Et₃N (2.8 mmol) and transferred to the reaction solution. DMAP (0.11 mmol) was added and the reaction was heated to 70 °C for 2 h. After cooling to room temperature, EtOAc (10 mL) and sat. Na₂CO₃ were added. The aqueous phase was extracted with EtOAc (3 X 10
20 mL) and the combined organics were washed with sat. Na₂CO₃, H₂O, and brine (15 mL each). After drying over anhydrous MgSO₄, volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO₂ (0-50% EA/hex) to produce 0.346 g (82%) of Compound **111** (*m/z* 386.0 (M+H)⁺).

Compound 112

25 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 ($\text{M}+\text{H}^+$)).

Scheme 53



Compound 113

Compound **113** is commercially available from Chem-Impex, and was used without further purification.

Compound 114

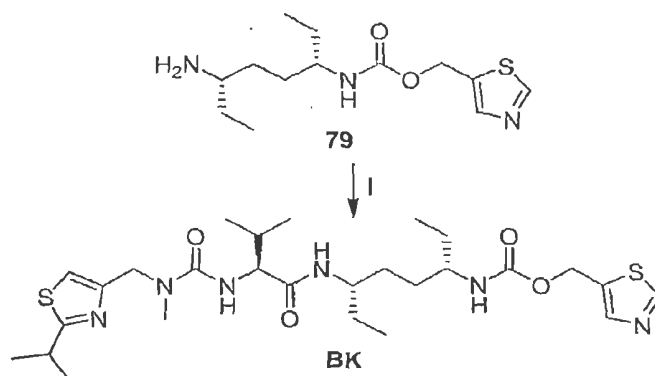
Compound **113** (3.2 mmol) was diluted in THF (15 mL). TMSCHN_2 (3.2 mmol) was added slowly, followed by MeOH (5 mL). The solution rapidly became colorless, and heavy evolution of gas was observed. After aging overnight, the volatiles were removed *in vacuo* and the residue purified by column chromatography on SiO_2 (0-50% EtOAc/hex) to produce 0.805 g (52%) of Compound **114** (m/z 505.2 ($\text{M}+\text{Na}^+$)).

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 g (94%) of Compound **115** as an amorphous white solid (m/z 261.0 ($\text{M}+\text{H}^+$)).

Preparation of Example BK

Scheme 54



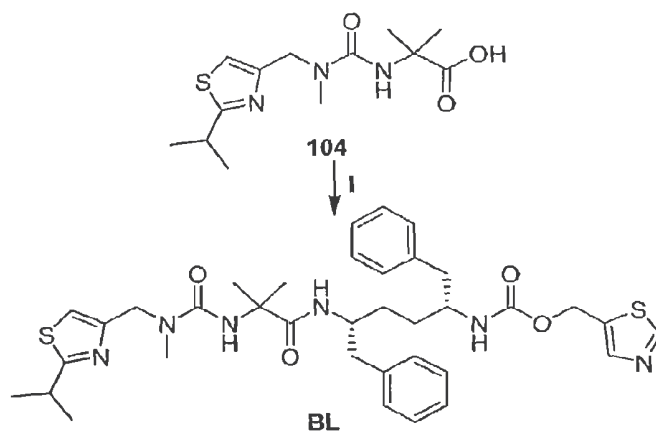
I. Cmpd. 29/EDC/HOBt/DIPEA/THF.

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 CHCl₃/IPA and sat. Na₂CO₃ (15 mL each). The aqueous layer was extracted with 3/1 CHCl₃/IPA (3 X 10 mL) and the combined organics were washed with sat. Na₂CO₃, water, and brine (15 mL each). Following drying over anhydrous MgSO₄, the volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO₂ (0-10% MeOH/DCM) to produce 8.5 mg (2%) of Compound BK *m/z* 581.2 (M+H)⁺; ¹H-NMR (CDCl₃, 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

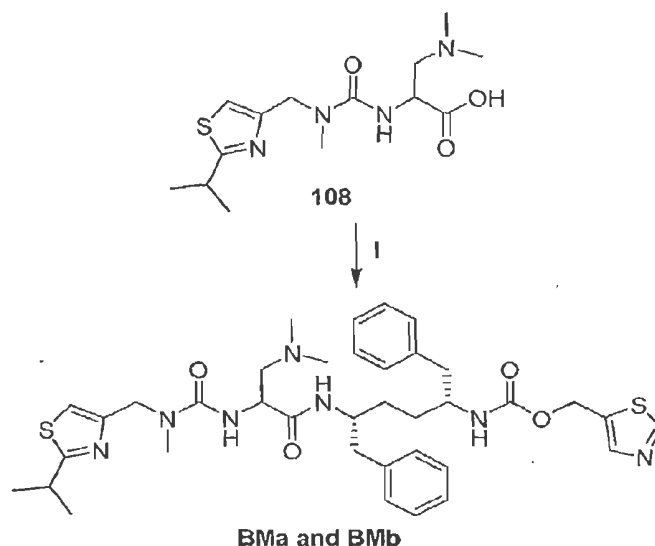
Scheme 55



I. Cmpd. 8/EDC/HOBt/DIPEA/THF.

Example BL

- Example **BL** was prepared in a similar fashion to Example **BK** using
- 5 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 ($M+H$)⁺; ¹H-NMR (CDCl₃, 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);
 - 10 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.

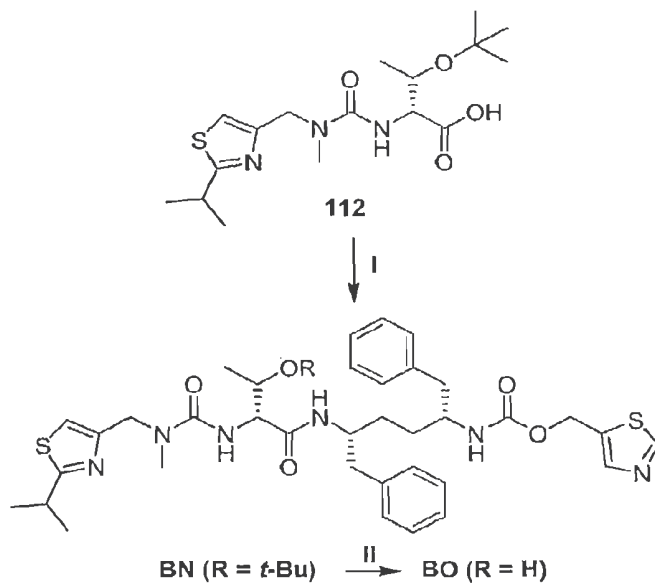
Examples BMa and BMb

- 5 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)⁺; ¹H-NMR (CDCl₃, 300
- 10 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).
- 15 (m/z 720.3 (M+H)⁺; ¹H-NMR (CDCl₃, 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.

5

Example BP

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 ($M+H$)⁺).

10 Example BO

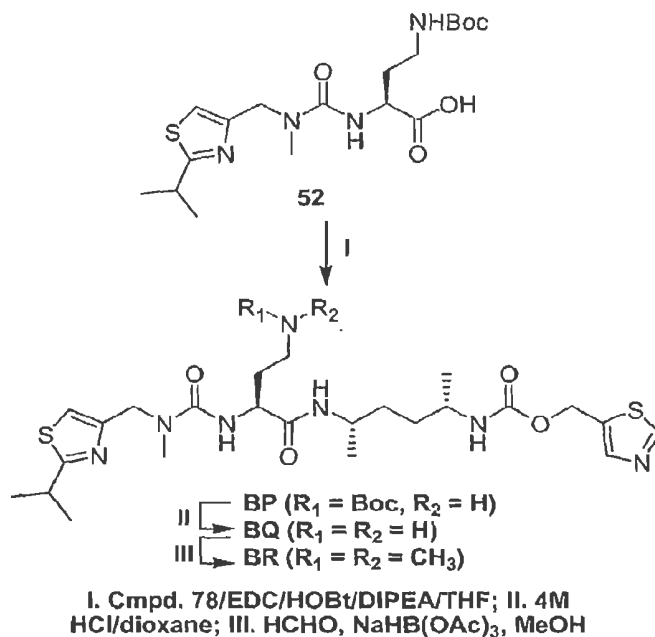
Example **BO** was prepared in a similar fashion to Example **AM** using Example **BN** (0.29 mmol) to produce 0.149 g (72%) of Example **BO** as an amorphous white solid. (m/z 707.3 ($M+H$)⁺; ¹H-NMR (CDCl₃, 300 MHz): 8.82 (s, 1H); 7.84 (s, 1H); 7.26-7.03 (m, 11H); 6.99 (s, 1H); 6.69 (d, $J = 9.6$, 1H); 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,

15

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



5

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 ($M+H$)⁺).

10 Example BQ

Example **BQ** (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 ($M+H$)⁺; ¹H-NMR (CD₃OD, 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);

15

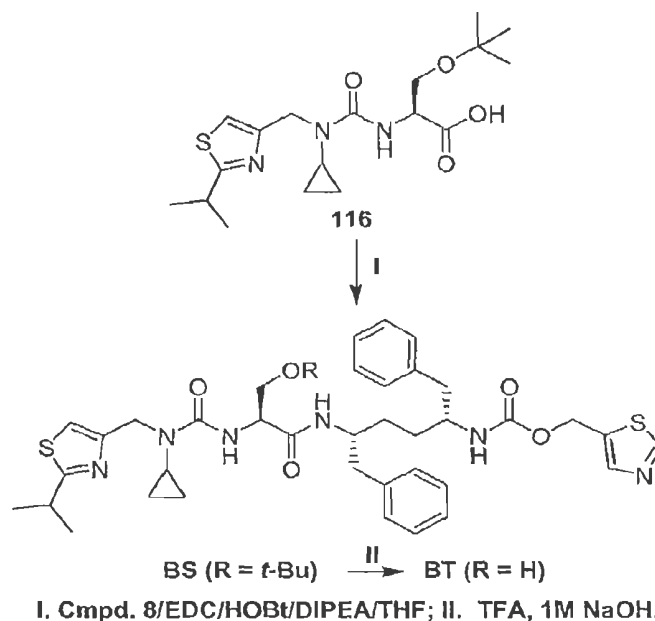
3.78-3.54 (m, 2H); 3.20-2.98 (m, 5H); 2.20 (br s, 1H); 2.07 (br s, 1H); 1.60-1.4 (m, 10H); 1.12 (m, 6H).

Example BR

Example BQ (0.11 mmol) was taken up in MeOH (1.5 mL). Formaldehyde
5 (37% in H₂O, 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
10 produce 0.058 g (77%) of the TFA salt of Example BR as an amorphous solid. *m/z*
582.3 (M+H)⁺; ¹H-NMR (CD₃OD, 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);
15 1.44 (m, 4H); 1.37 (d, *J* = 7 Hz, 6H); 1.10 (m, 6H).

Preparation of Examples BS and BT

Scheme 59



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 ($M+H$)⁺).

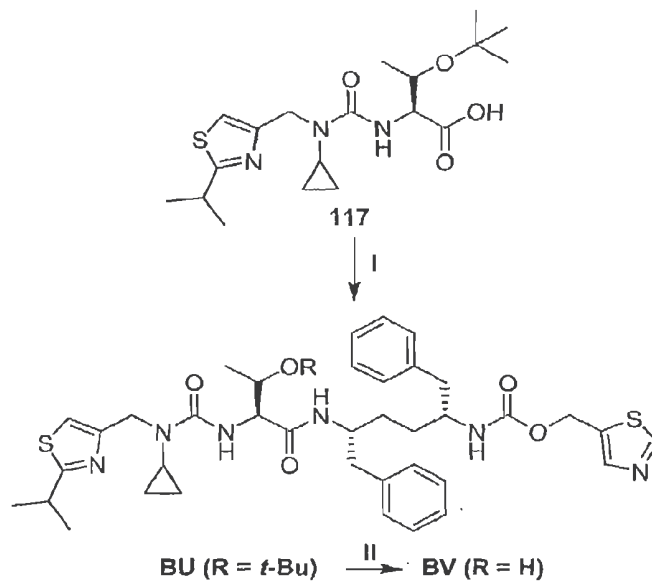
Example BT

Example BT was prepared in a similar fashion to Example AM using Example BU (0.18 mmol) to produce 0.080 g (62%) of Example BT as an amorphous white solid. m/z 719.3 ($M+H$)⁺; ¹H-NMR (CDCl₃, 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 ($M+H$)⁺).

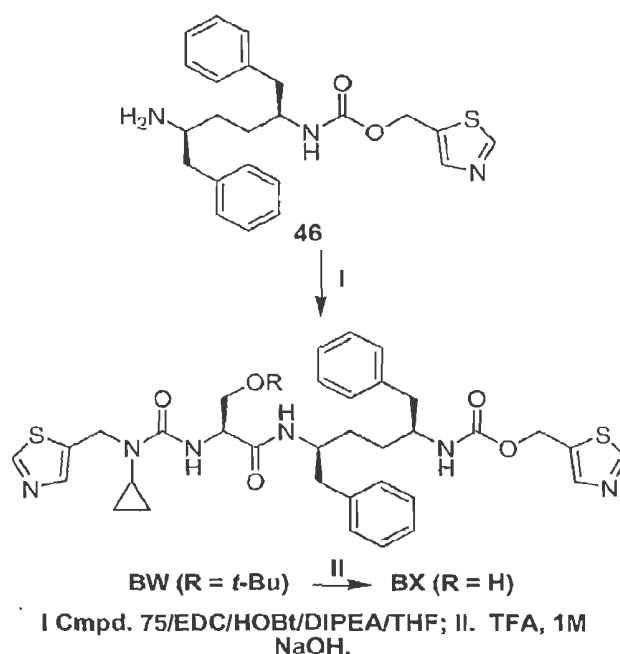
Example BV

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)⁺; ¹H-NMR (CDCl₃, 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



10 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)⁺).

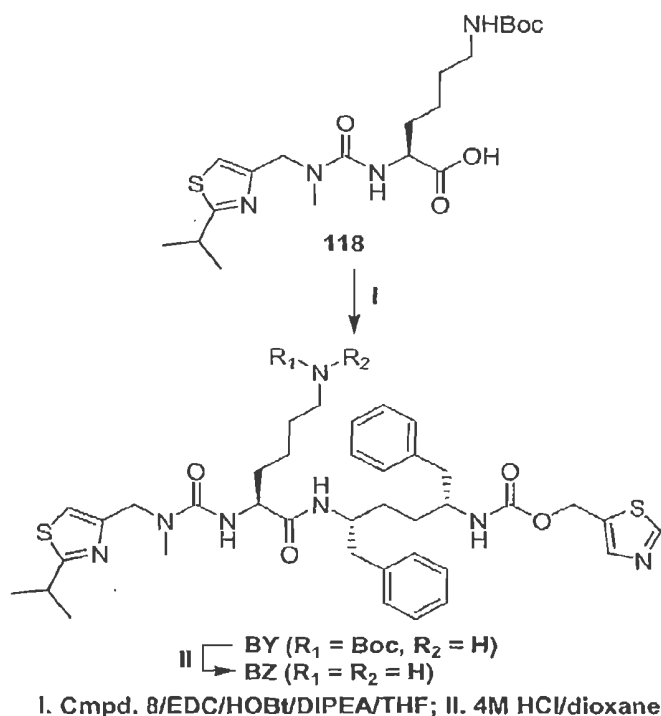
Example BX

15 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)⁺; ¹H-NMR (CDCl₃, 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);
- 5 1.20-0.88 (m, 2H); 0.88-0.54 (m, 2H).

Preparation of Examples BY and BZ

Scheme 62



Compound 118

- 10 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

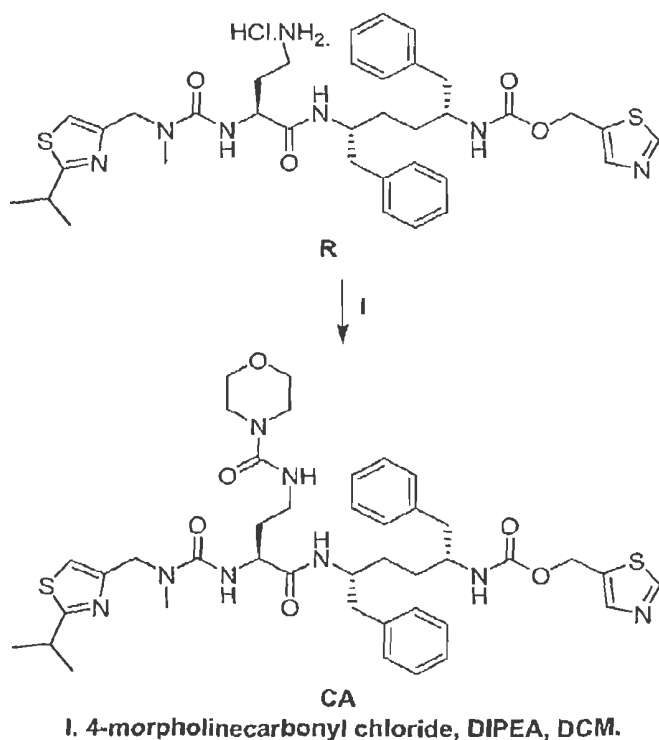
Example **BY** was prepared in a similar fashion to Example **BM** using Compound **118** (0.17 mmol) and Compound **8** (0.15 mmol) to produce 0.079 g (62%) of Example **BY** as an amorphous white solid (m/z 834.3 ($M+H$)⁺).

Example **BZ**

- 5 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 ($M+H$)⁺; ¹H-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);
- 10 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

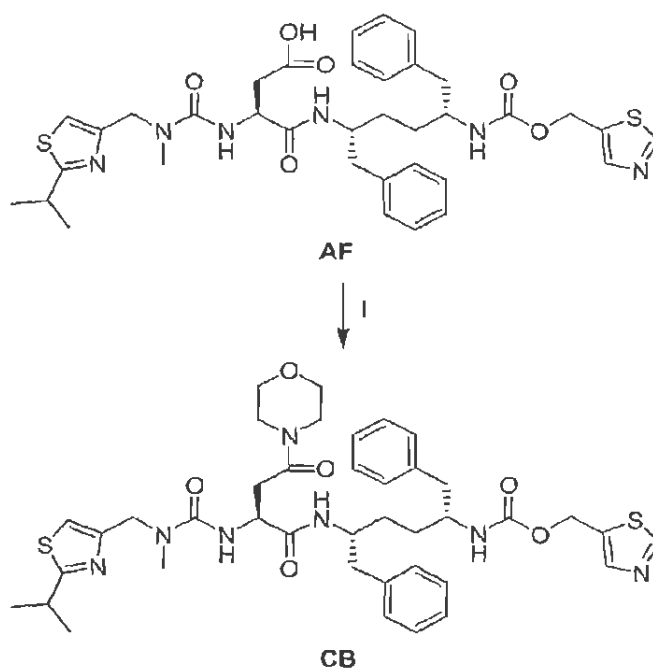


- 15 Example **CA**

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 SiO₂ (0-20% MeOH/DCM) to afford 0.068 g (76%) of Example CA as an amorphous white solid m/z 819.1 (M+H)⁺; ¹H-NMR (CDCl₃, 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



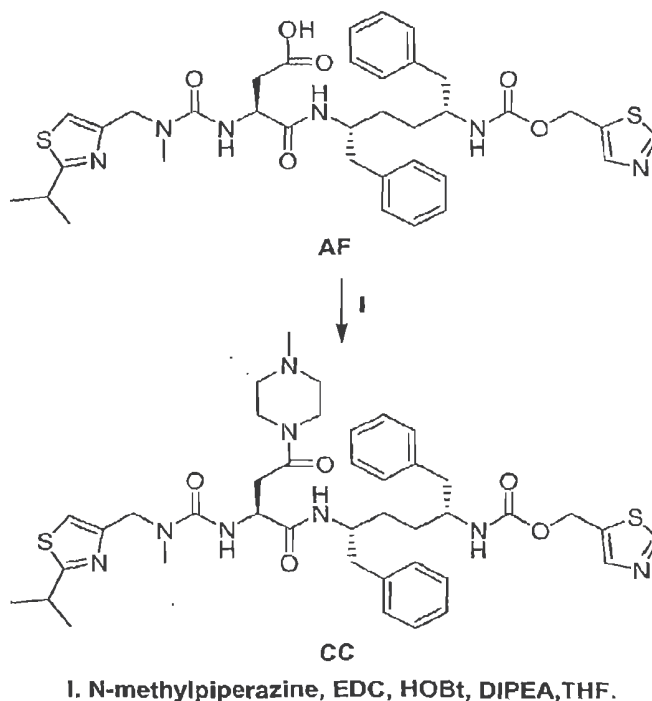
1. morpholine, EDC, HOBT, THF.

15 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. Na₂CO₃. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous MgSO₄ 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)⁺; ¹H-NMR (CDCl₃, 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

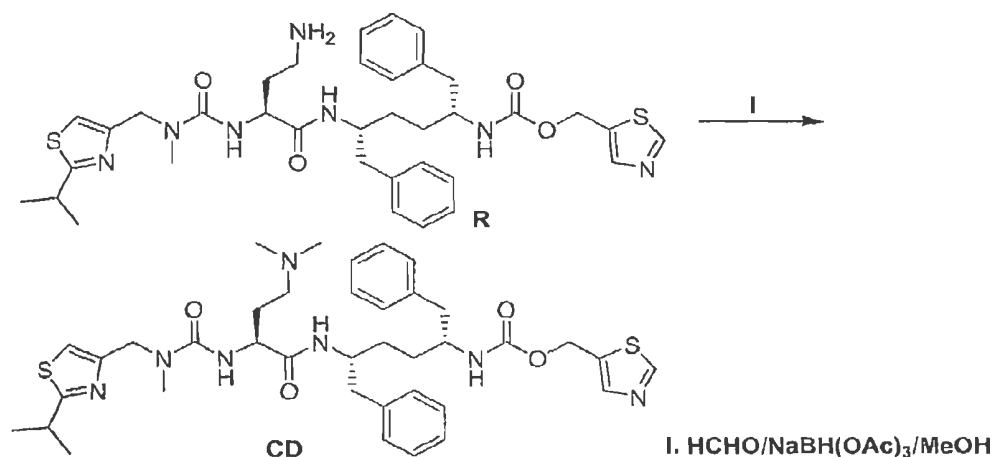


Example CC

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)⁺; ¹H-NMR (CDCl₃, 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).

10 Preparation of Example CD

Scheme 66



Example CD

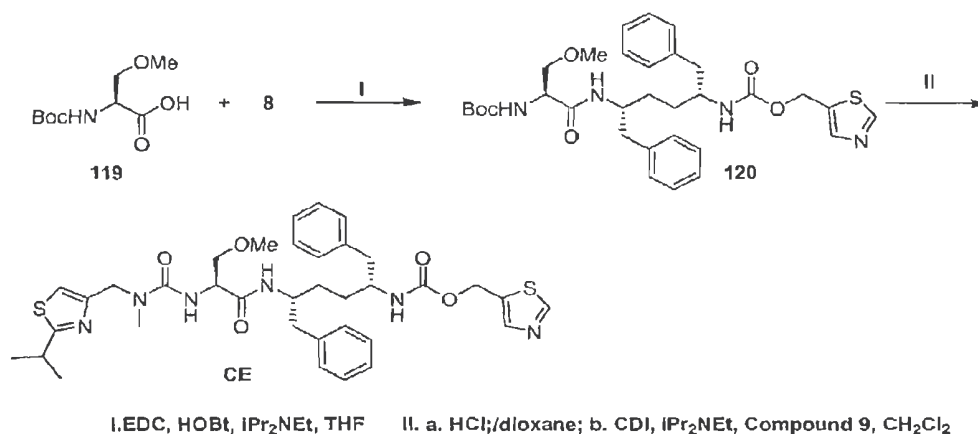
15 To a solution of Example R (30.5 mg, 0.043 mmol) in methanol (1.5 mL) was added formaldehyde (1 mL, 37% in H₂O). After stirring for 10 minutes, NaBH(OAc)₃ (49 mg, 0.23 mmol) was added and the resulting mixture was stirred for 10 h. The reaction was monitored with LC/MS. When LC/MS indicated the absence of starting material Example R, the reaction mixture was

20 evaporated to dryness, and filtered through a cotton plug. The crude product

was then purified through CombiFlash (10% MeOH/CH₂Cl₂) to give 29.7 mg of Example CD ¹H-NMR (CDCl₃, 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



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 iPr₂NEt (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/CH₂Cl₂). 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)⁺).

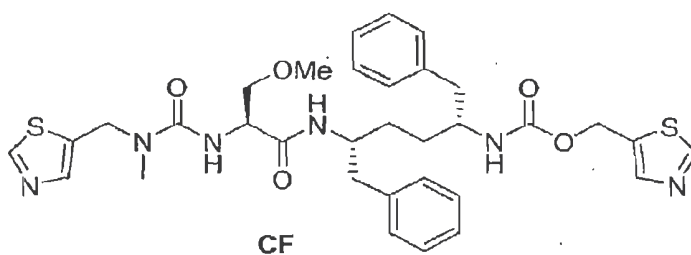
Example CE

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.

5 To a solution of the above white compound (52.5 mg, 0.096 mmol) in CH₂Cl₂ (10 mL) was added Compound **9** (19.8 mg, 0.096 mmol), CDI (15.6 mg, 0.096 mmol) followed by iPr₂NEt (33.4 μ L, 0.192 mmol). The mixture was stirred for 20 h before it was evaporated to dryness. The mixture was added CH₂Cl₂, then filtered through a cotton plug. The filtrate was evaporated to dryness and
10 purified with CombiFlash. The fractions with Example **CE** was collected and re-purified on the TLC to give 15.1 mg of Example **CE**. ¹H-NMR (CDCl₃, 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,
15 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



20

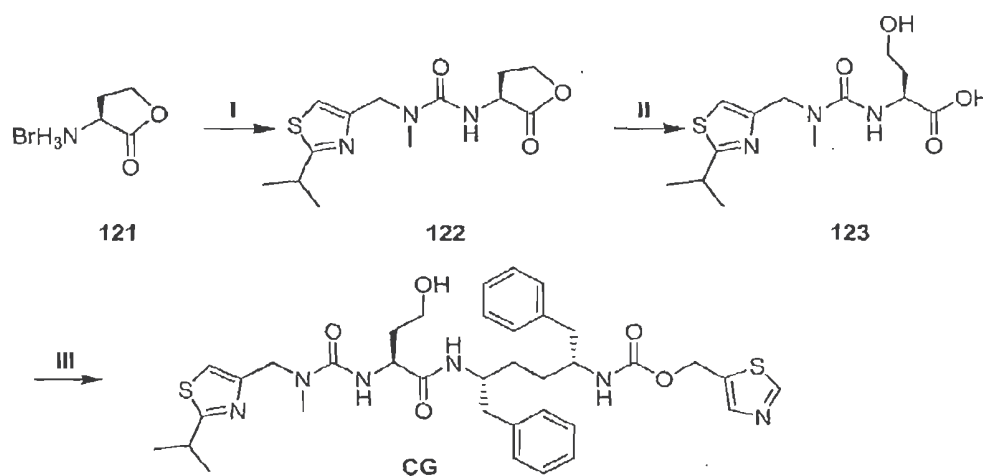
Example CF

Example **CF** was prepared using the same method as Example **CE**, except that Compound **9** was replaced with Compound **68**. ¹H-NMR (CDCl₃, 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 ($M+Na$)⁺).

5 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 CH₂Cl₂ (40 mL) was added. iPr₂NEt (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 CH₂Cl₂ 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

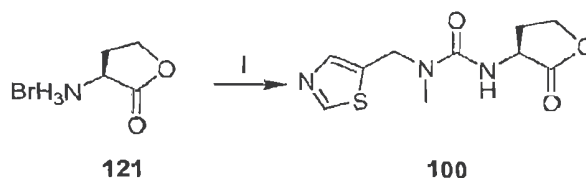
To a solution of Compound 122 (3.2g, 10.8 mmol) in THF (100 mL) was added freshly prepared 1M LiOH (10.8 mmol). The biphasic reaction was stirred vigorously at room temperature for 16 h before being quenched with 1M HCl. The pH of the mixture was adjusted to 2.5-3, and then evaporated to a small volume. The mixture was partitioned between CH₂Cl₂ and brine (50 mL), the aqueous layer was separated and extracted with CH₂Cl₂ twice. The combined CH₂Cl₂ layers were dried over anhydrous Na₂SO₄ 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. ¹H-NMR (CDCl₃, 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

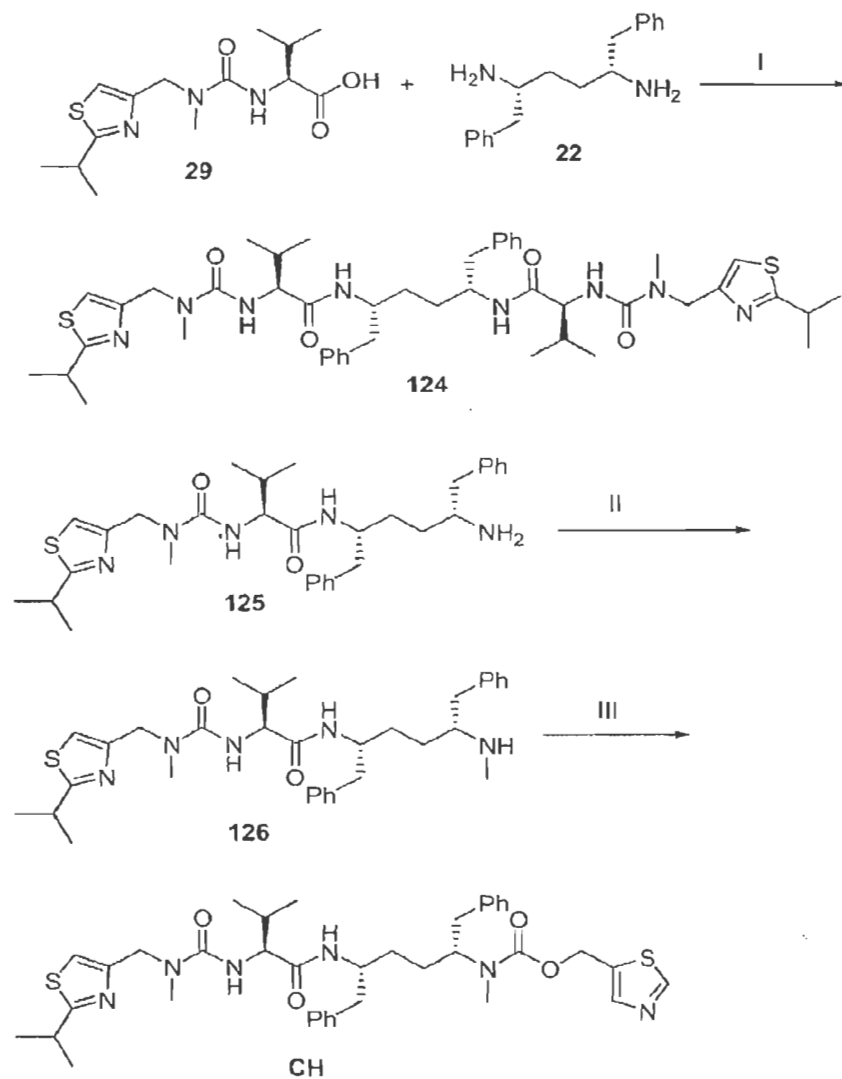


I. a. CDI, DIPEA, MeCN;

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/ $i\text{Pr}_2\text{NEt}$ /THF; II. $\text{HCHO}/\text{NaBH}(\text{OAc})_3/\text{HOAc}/\text{CH}_3\text{CN}$;
 III. Compd. 16/ $i\text{Pr}_2\text{NEt}$ / 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 μ L, 0.52 mmol), and diisopropylethylamine (150 μ L, 0.83 mmol). The mixture was stirred for 12 hours and concentrated. Purification by reverse HPLC gave
5 Compound **124** (70 mg) and Compound **125** (120 mg). Compound **124**: $^1\text{H-NMR}$ (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 ($\text{M}+\text{H}$) $^+$; Compound **125**: m/z 564.3 ($\text{M}+\text{H}$) $^+$

10 Compound 126

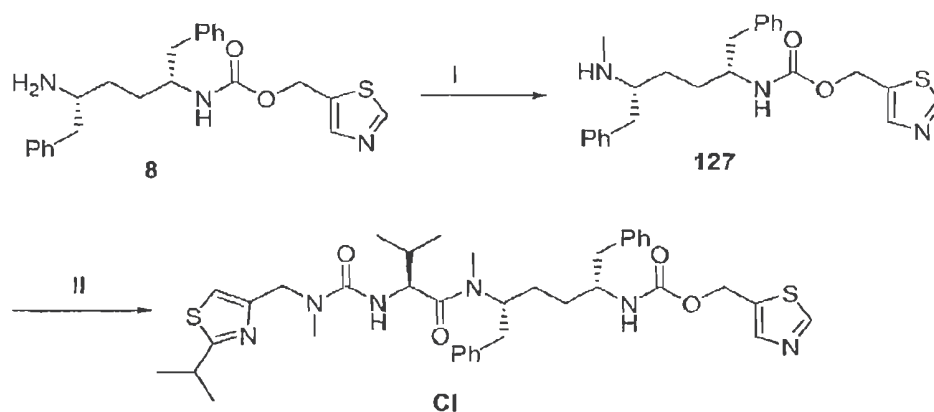
To a solution of Compound **125** (120 mg, 0.21 mmol) in CH_3CN (1 mL) was added 37% formaldehyde solution (17 μ L, 0.23 mmol), followed by HOAc (24 μ L, 0.42 mmol). The mixture was stirred for 2 hours, and $\text{NaBH}(\text{OAc})_3$ (140 mg, 0.63 mmol) was added. The mixture was stirred for 2 additional hours and diluted
15 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 ($\text{M}+\text{H}$) $^+$

Example CH

Example **CH** (26 mg) was prepared following the procedure used to
20 prepare Example **L**, except that Compound **126** was used instead of Compound **22**. $^1\text{H-NMR}$ (CDCl_3) 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 ($\text{M}+\text{H}$) $^+$

25 Preparation of Example CI

Scheme 72



I. HCHO/NaBH(OAc)₃/HOAc/CH₃CN; II. Compd. 29/EDCI/HOBt/iPr₂NEt/THF

Compound 127

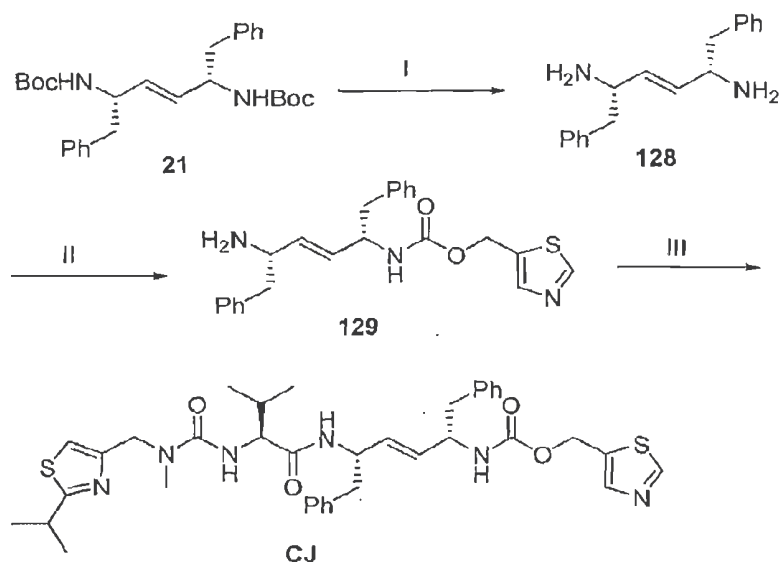
Compound **127** (110 mg) was prepared following the procedure used to
5 prepare Compound **126**, except that Compound **8** was used instead of
Compound **125**. m/z 424.4 (M+H)⁺

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**. ¹H-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 CI

Scheme 73



I. a. TFA/CH₂Cl₂; b. Na₂CO₃; II. Cmpd. 16/iPr₂NEt/CH₃CN;
 III. Cmpd. 29/EDCI/HOBt/iPr₂NEt/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 Na₂CO₃ solution (2x), water (2x), and brine, and dried over Na₂SO₄. 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)⁺

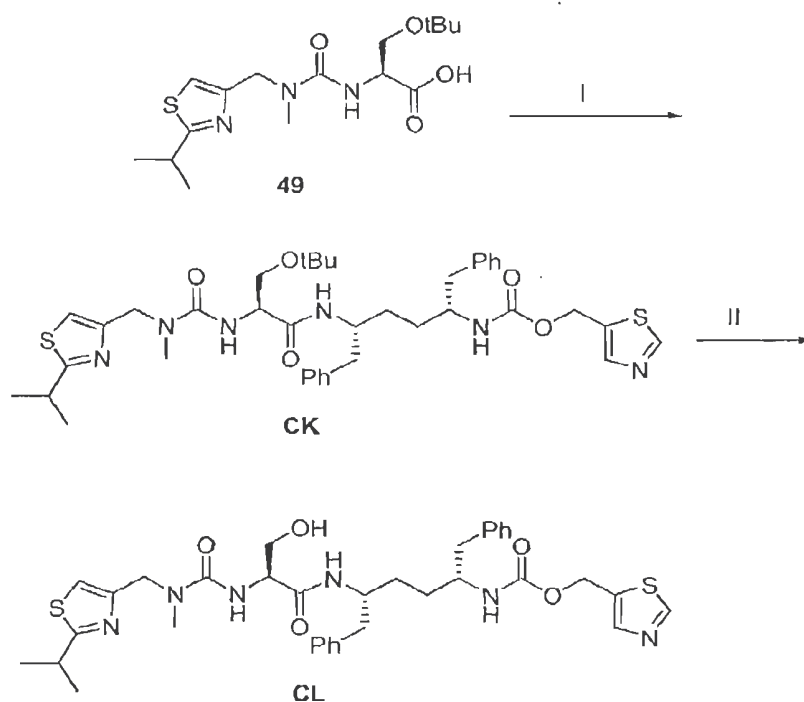
Example CJ

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

5 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**.

10 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

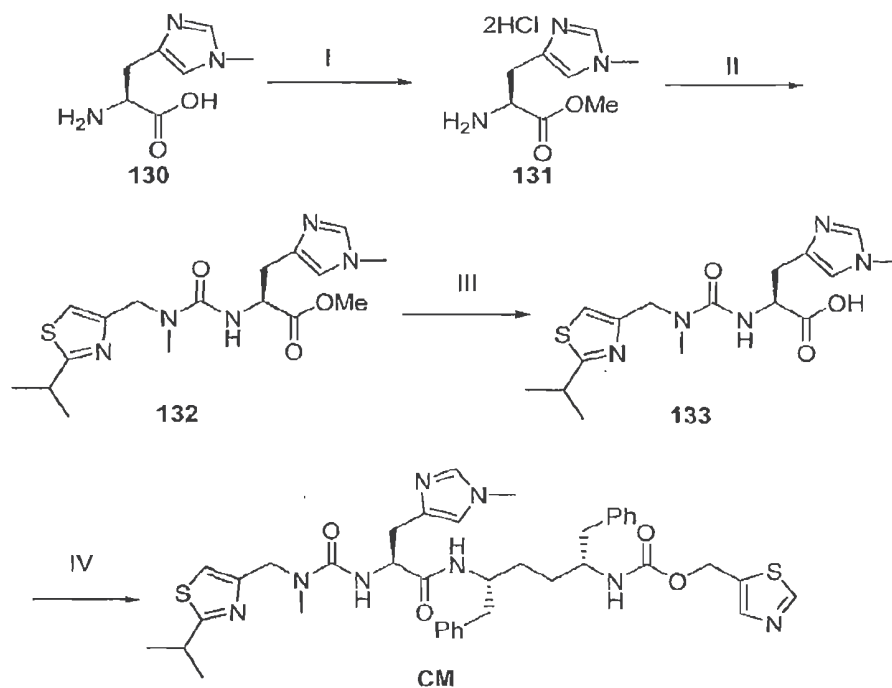
15

extracted with EtOAc. The organic phase was washed with water, brine, and dried over Na₂SO₄.

Concentration and purification by flash column chromatography (EtOAc) gave Example CL (66 mg). ¹H-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. SOCl₂/MeOH; II. a. CDI/iPr₂NEt; b. Cmpd. 9; III. a. NaOH/THF/H₂O; b. HCl; IV. Cmpd. 8/EDC/HOBt;

10

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 °C was added thionyl chloride (0.5 mL, 6.6 mmol), dropwise. The mixture was stirred at 0 °C for 30 minutes and brought to reflux for 3 hours. Concentration

5 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

10 added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (CH₂Cl₂/iPrOH = 10/1) gave Compound **132** (414 mg). m/z 380.0 (M+H)⁺

Compound 133

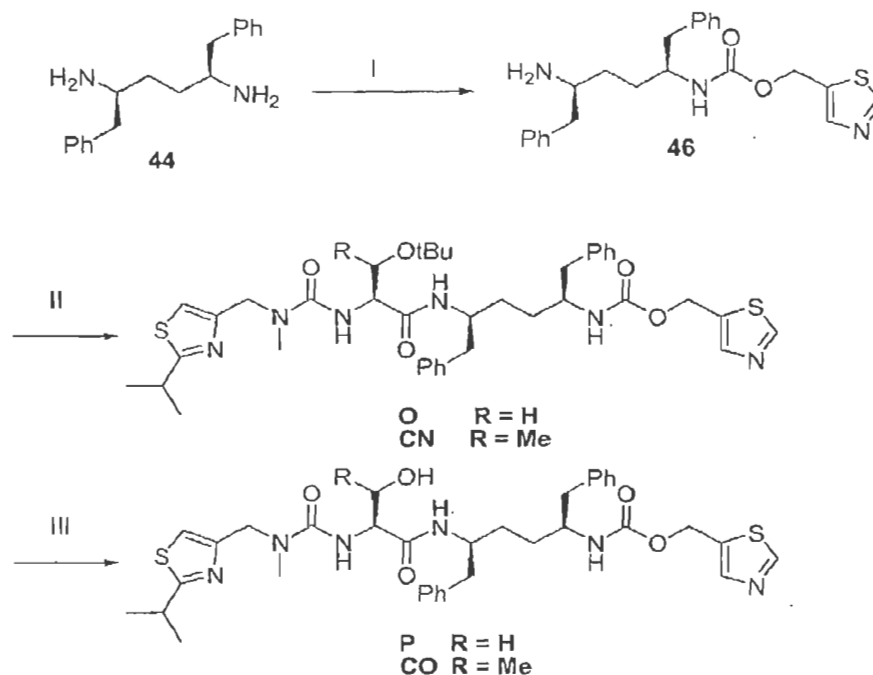
Compound **133** was prepared following the procedure for Compound **67**,

15 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**. ¹H-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)⁺

20

Preparation of Examples O, P, CN, and CO**Scheme 76**

I. Cmpd. 16/*i*Pr₂NEt; II. Cmpd. 13d or Cmpd. 49/EDC/HOBt; III. a. TFA; b. NaOH/THF

Example O

- 5 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

- 10 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

- 15 Example **P** (12 mg) was prepared following the procedure used to prepare Example **CM**, except Example **O** was used instead of Example **CL**. ¹H-NMR (CDCl₃) 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,

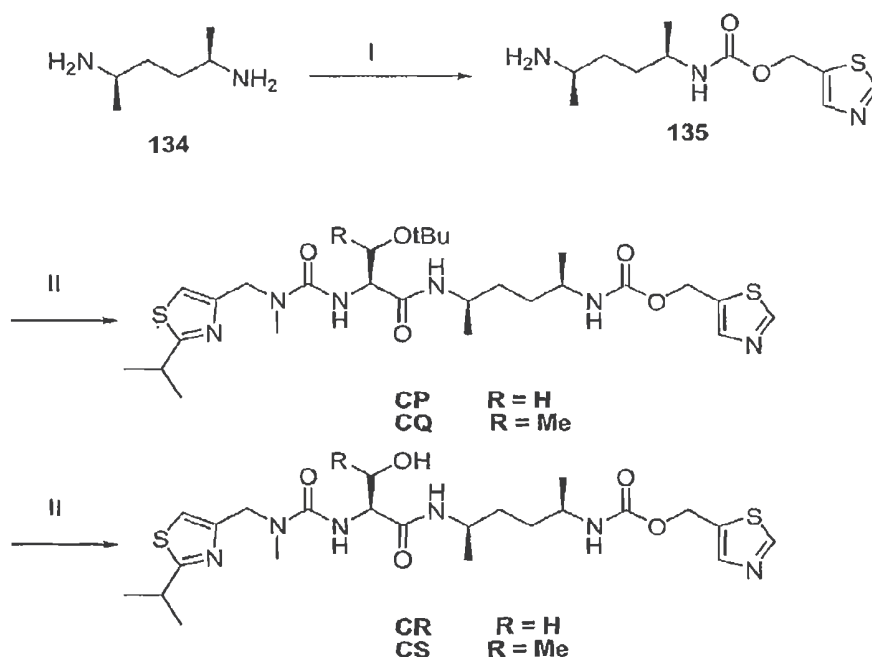
m), 5.18 (2 H, m), 4.42 (2 H, m), 4.22 (1 H, m), 4.10 (1 H, m), 3.95 (1 H, m), 3.79 (1 H, m), 3.58 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.9-2.5 (4 H, m), 1.6-1.2 (10 H, m); m/z: 693.2 (M+H)⁺.

Compound CO

- 5 Example CO (13 mg) was prepared following the procedure used to prepare Example CL, except Example CN was used instead of Compound CK.
- ¹H-NMR (CDCl₃) 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)⁺.
- 10

Preparation of Examples CP-CS

Scheme 77



I. Cmpd. 16/iPr₂NEt; 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
5 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)⁺.

10 Example CQ

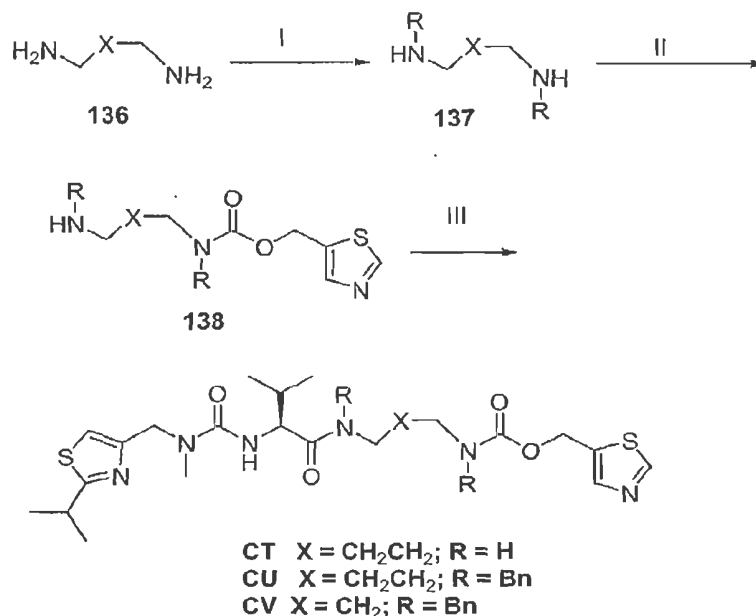
Example **CQ** (11 mg) was prepared following the procedure used to prepare Example **C**, except Compounds **135** and **13d** were used instead of Compounds **8** and **7**. m/z 611.2 (M+H)⁺.

Example CR

15 Example **CR** (7 mg) was prepared following the procedure used to prepare Example **P**, except that Example **CP** was used instead of Example **O**. ¹H-NMR (CDCl₃) 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)⁺.

20 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**. ¹H-NMR (CDCl₃) 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
25 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/NaBH₄; II. Cmpd 16/iPr₂NEt; III. Cmpd 13d/EDC/HOBt;

Compound 136

- 5 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 °C. Sodium borohydride (44 mmol) was added in portions. The mixture was warmed to 25 °C 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 Na₂SO₄.
- 10
- 15 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
5 prepare Example C, except that Compounds 29 and 138a was used instead of
Compounds 13a and 8. ¹H-NMR (CDCl₃) 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)⁺.

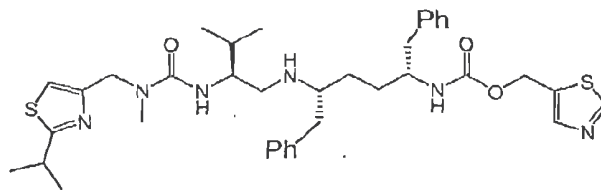
10 Example CU

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 13a and 8. ¹H-NMR (CDCl₃) 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),
15 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)⁺.

Example 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
20 Compounds 13a and 8. ¹H-NMR (CDCl₃) 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)⁺.

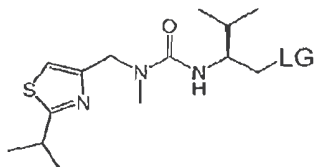
Preparation of Example CW



CW

295

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.

IC₅₀ Determinations for Human Liver Cytochrome P450

10 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 K_m 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
5 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
10 in electrospray ionization mode. The column was a Waters Acquity UPLC BEH C₁₈ 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.
15 Concentrations of metabolites were determined by reference to standard curves generated with authentic analytes under the same conditions as the incubations.

IC₅₀ 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.

20 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
25 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 μ M 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
5 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
10 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

15 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 μ M, respectively. Metabolic reactions were terminated by treatment with
20 three volumes of quench solution containing 1 μ M 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
25 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.

5 **Biological Assays Used for the Characterization of HIV Protease Inhibitors**

HIV-1 Protease Enzyme Assay (K_i)

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
10 (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,
15 pH 5.3, 1 M sodium chloride, 1 mM ethylenediaminetetraacetic 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
20 solutions were subsequently transferred into a white 96-well plate (190 μ l each) and preincubated for 15 min at 37 °C. The substrate was solubilized in 100% dimethylsulfoxide at a concentration of 800 μ M and 10 μ l of 800 μ M substrate was added into each well to reach a final substrate concentration of 40 μ M. The real-time reaction kinetics was measured at 37 °C using a Gemini 96-well plate
25 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 IC₅₀ assay is based on the fluorimetric
5 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.
10 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 ethylenediaminetetraacetic acid, and 1 mM dithiothreitol, and 10% dimethylsulfoxide.

15 To determine the IC₅₀ value, 170 μ L 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 μ L of the resulting dilutions was transferred into the wells of the microtiter plate. 10 μ L of a 20-50 nM enzyme stock solution in reaction buffer was added to each well of the 96-
20 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 solubilized in 100% dimethylsulfoxide at a concentration of 400 μ M and 10 μ L of the 400 μ M substrate was added into each well to reach a final substrate concentration of 20 μ M. The real-time reaction kinetics were measured using a Gemini 96-well plate
25 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 IC₅₀ 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 CO₂ incubator. To

inactivate the virus, 20 μ l 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 (EC₅₀) 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.

10 Anti-HIV-1 Cell Culture Assay (EC₅₀) 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.

20 Cytotoxicity Cell Culture Assay (CC₅₀)

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 μ L/well) and incubated in the presence or absence of 5-fold serial dilutions of the tested inhibitor (100 μ L/well) for 5 days at 37 °C. Controls included untreated
5 infected cells and infected cells protected by 1 μ M 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 μ L of N-methylphenazonium
10 methasulfate (5 μ g/mL) was added per 6 mL of XTT solution. After removing 100 μ L media from each well on the assay plate, 100 μ L 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 CO₂ incubator. To inactivate the virus, 20 μ L of 2% Triton X-
100 was added to each well. Viability, as determined by the amount of XTT
15 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 (EC₅₀) was calculated as the concentration of compound that effected an increase in the percentage of cell
20 growth in compound treated cells to 50% of the cell growth provided by uninfected, compound-free cells.

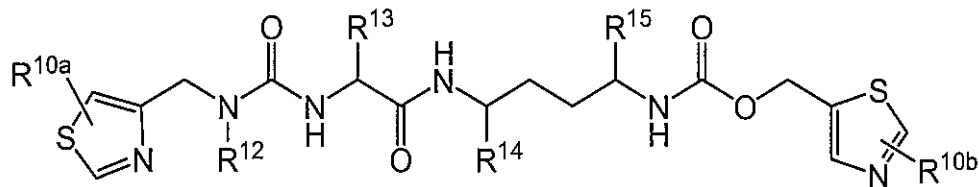
Experimental data based on representative Examples A-CV demonstrate that the compounds of Formula (I) of the present invention can have a CYP450
25 3A4 inhibition activity in a range represented by an IC₅₀ from about 100 nM to about 4700 nM, and a CYP450 2C9 inhibition activity in a range represented by an IC₅₀ from about 100 nM to about 4200 nM.

Experimental data based on representative Examples A-CV demonstrate that the compounds of Formula (I) of the present invention can have a protease inhibition activity in a range represented by HIV EC₅₀ from about 140 nM to greater than about 1000 nM.

- 5 Experimental data based on representative Examples P, S, and T have a CYP450 3A4 inhibition activity in a range represented by an IC₅₀ from about 80-150 nM, a CYP450 2C9 inhibition activity in a range represented by an IC₅₀ from about 1000-10,000 nM, and a protease inhibition activity in a range represented by HIV EC₅₀ greater than about 20,000 nM.

What is claimed:

1. A compound of formula IIB:



Formula IIB

or a pharmaceutically acceptable salt, solvate, stereoisomer or ester thereof, wherein:

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;

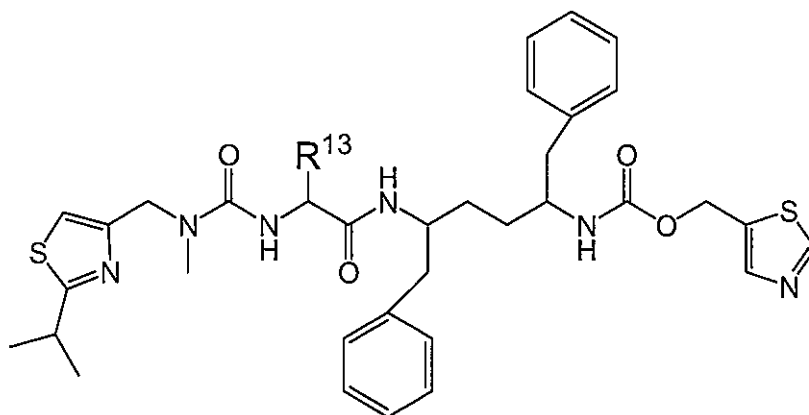
wherein said unsubstituted or substituted 5-6 membered heterocyclyl ring formed by R^{20} and R^{21} and said unsubstituted or substituted 5-6 membered heterocyclyl ring of R^{23} are each independently unsubstituted or substituted with a C_{1-2} alkyl.

2. A compound of claim 1 or a pharmaceutically acceptable salt, solvate, stereoisomer or ester thereof wherein 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 $-(CH_2)_{1-3}-R^{23}$.

3. A compound of claim 2 or a pharmaceutically acceptable salt, solvate,

stereoisomer or ester thereof, wherein R^{13} is $-(CH_2)_{0-3}CR^{17}R^{18}NR^{20}R^{21}$ or $-(CH_2)_{0-3}CR^{17}R^{18}NR^{17}C(O)-NR^{20}R^{21}$.

4. A compound of claim 1 of formula IIC:



Formula IIC

or a pharmaceutically acceptable salt, solvate, stereoisomer or ester thereof, 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

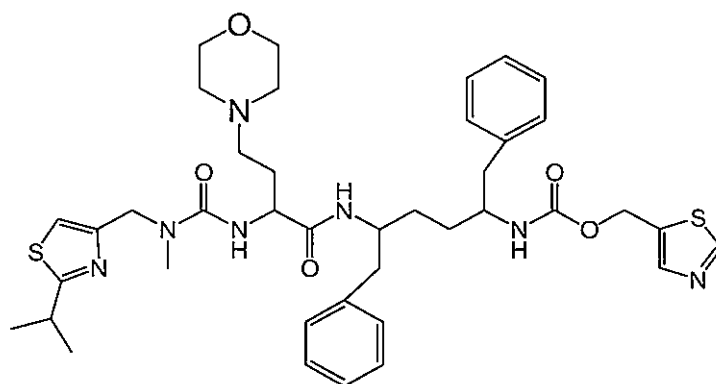
R^{20} and R^{21} , taken together with the nitrogen atom to which they are attached, form an unsubstituted or substituted 5-6 membered heterocyclyl ring containing 1-2 heteroatoms selected from the group consisting of N and O;

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;

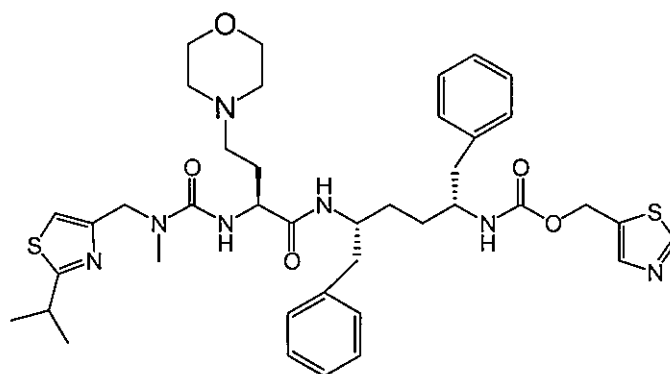
wherein said unsubstituted or substituted 5-6 membered heterocyclyl ring formed by R^{20} and R^{21} and said unsubstituted or substituted 5-6 membered heterocyclyl ring of R^{23} are each independently unsubstituted or substituted with a C_{1-2} alkyl.

5. A compound of claim 1 of the formula



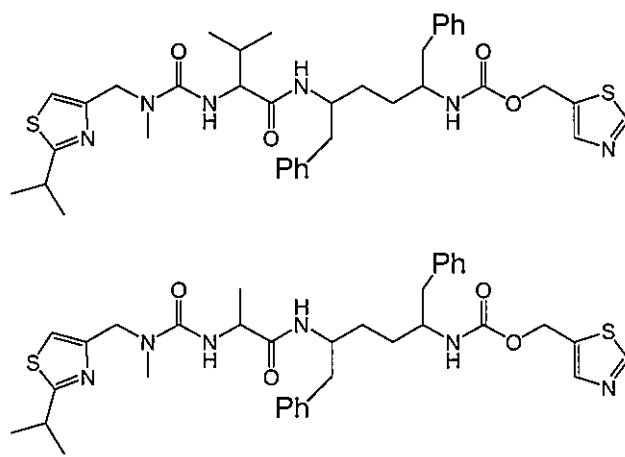
or a pharmaceutically acceptable salt , stereoisomer or solvate thereof.

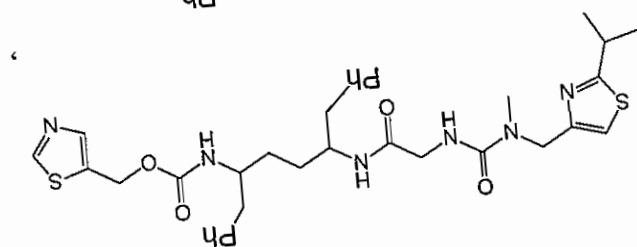
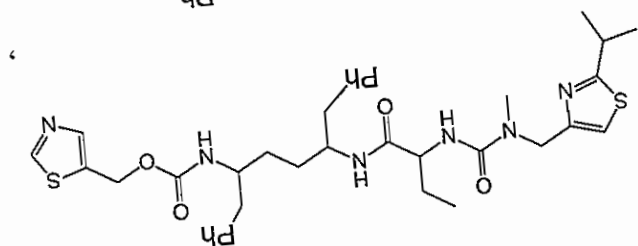
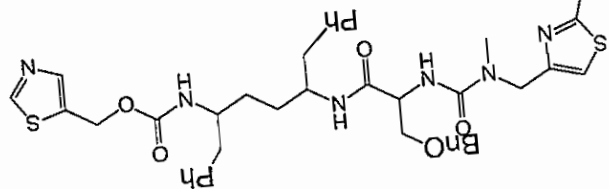
6. The compound of claim 5 which is:



or a pharmaceutically acceptable salt thereof.

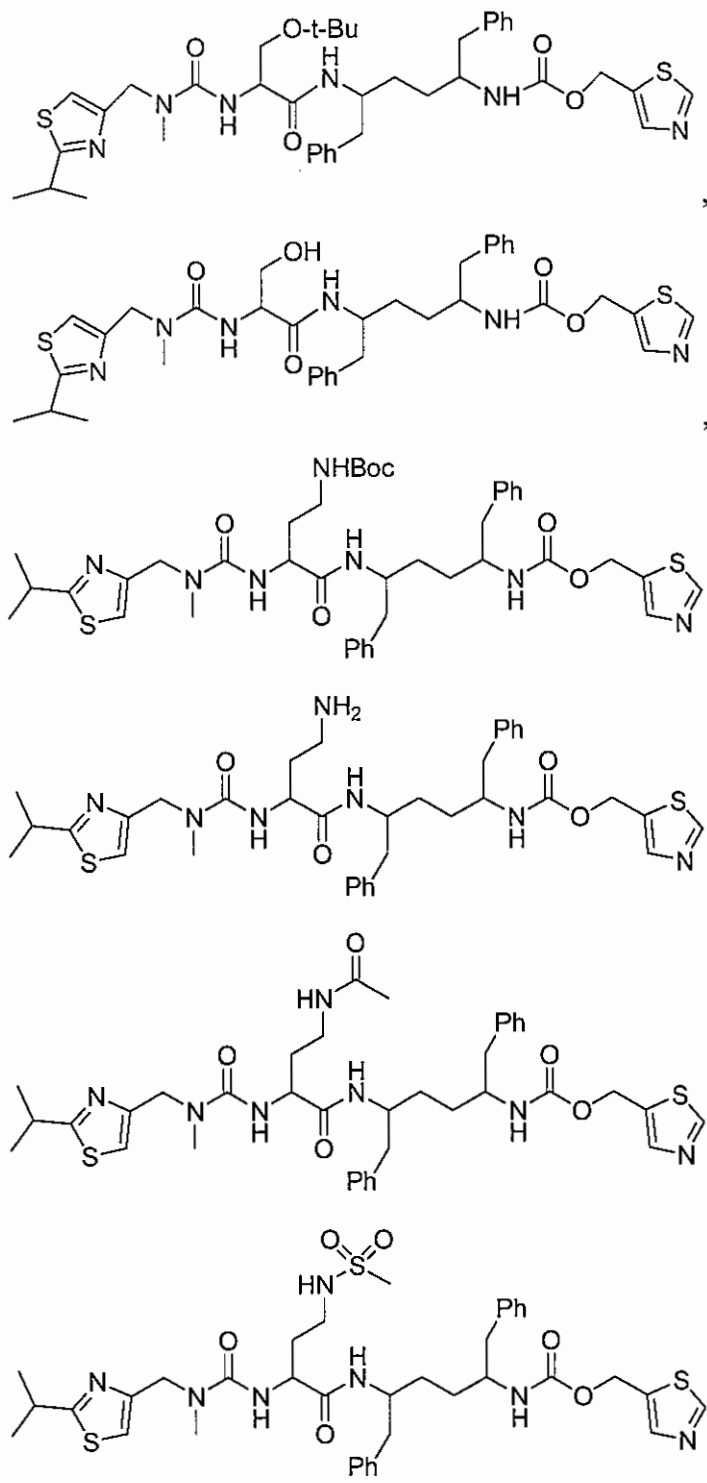
7. A compound of claim 1 selected from the group consisting of:

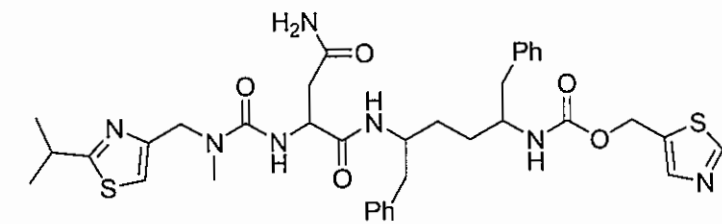
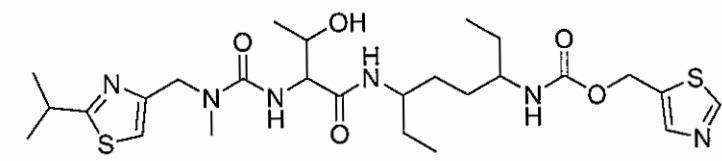
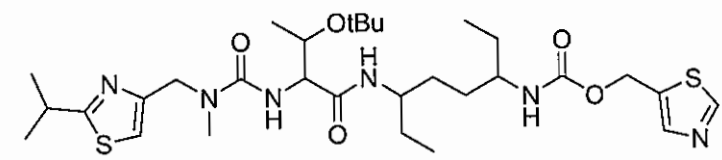
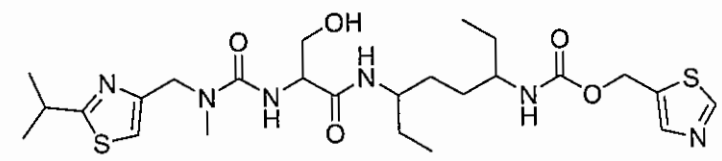
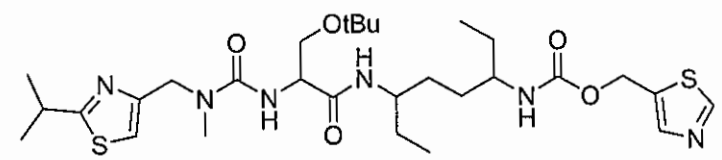
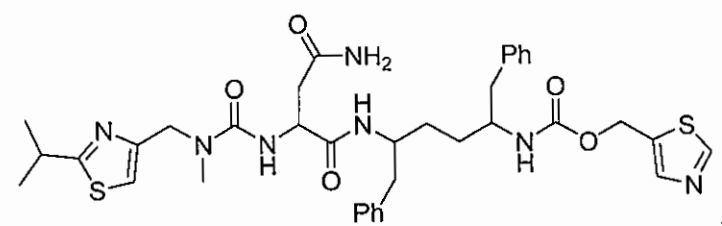
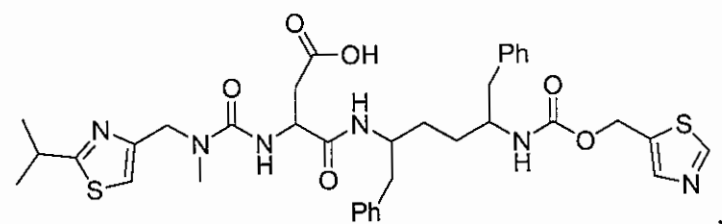
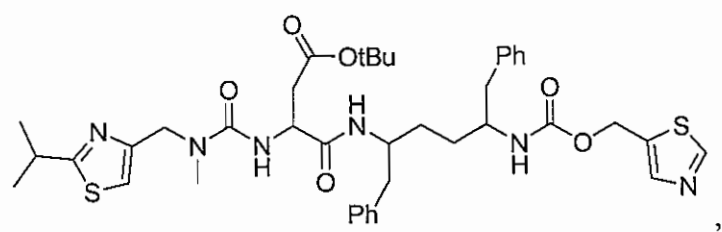


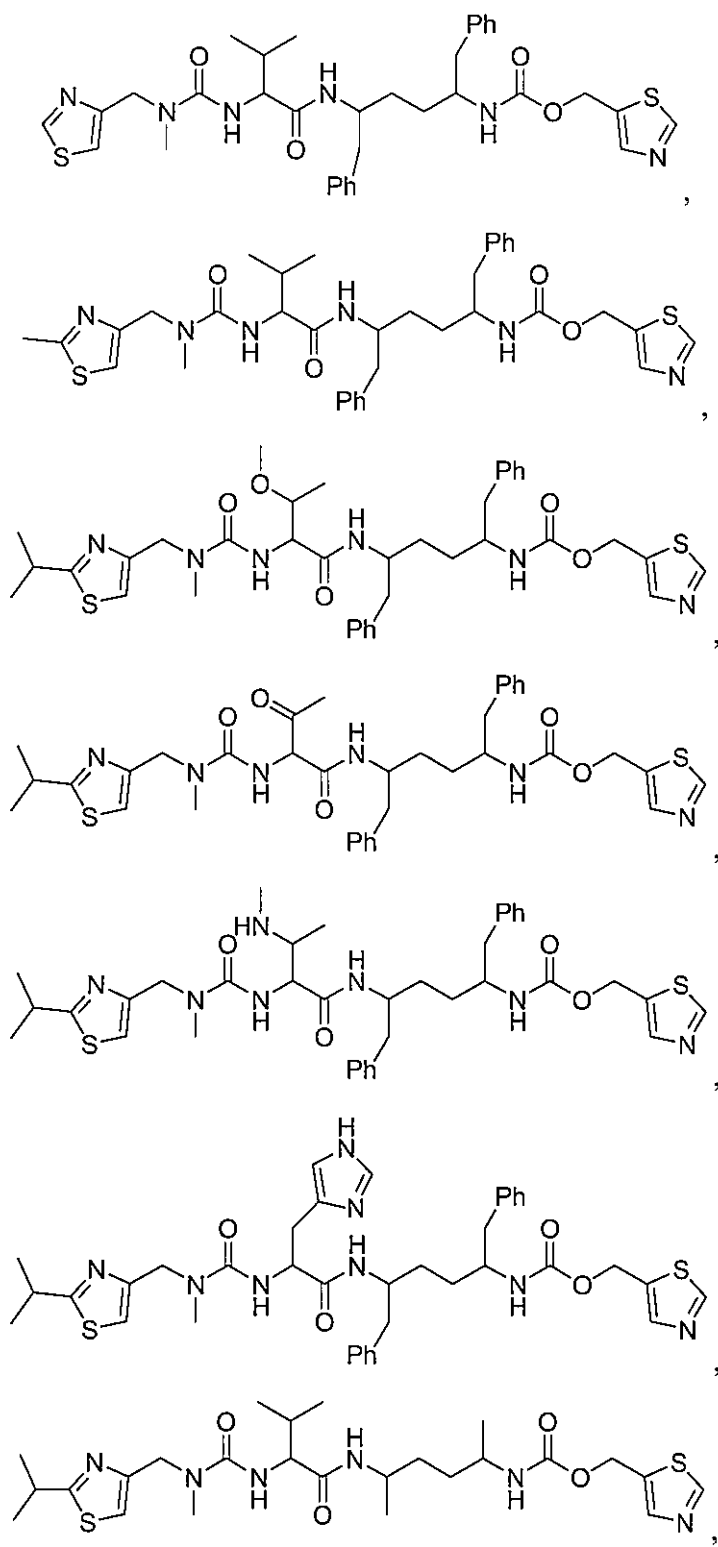


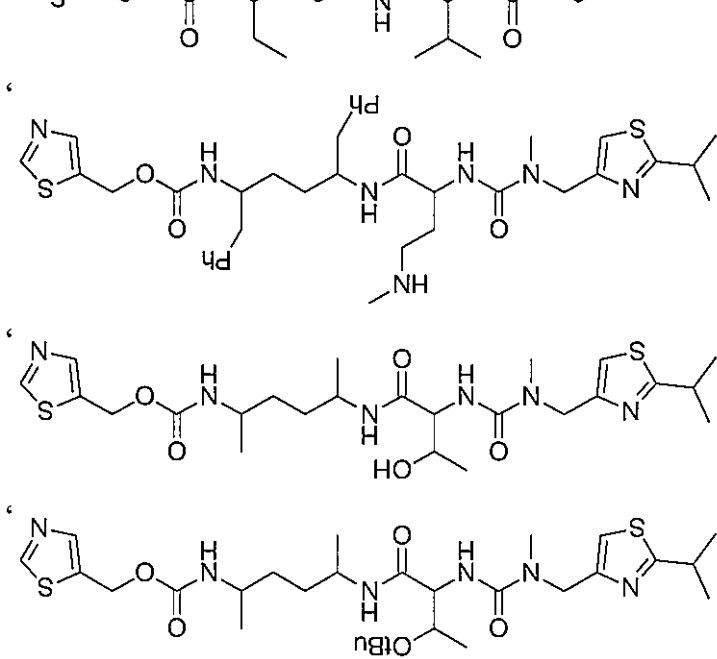
pharmaceutically acceptable salts, solvates, stereoisomers or esters thereof.

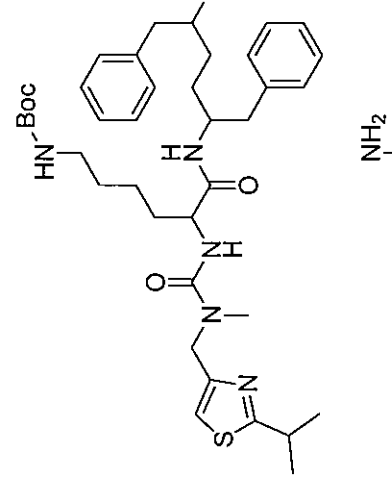
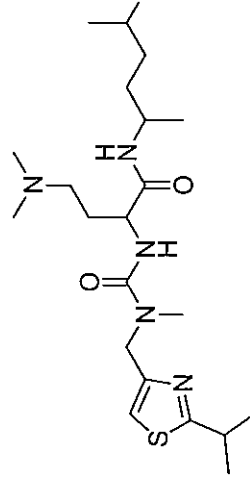
8. A compound of claim 1 selected from the group consisting of

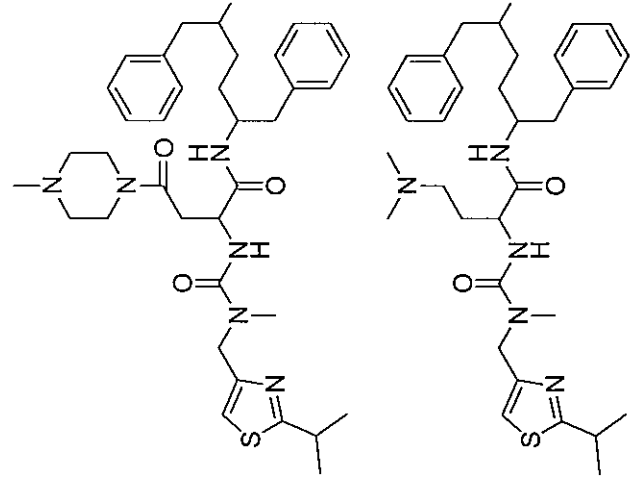


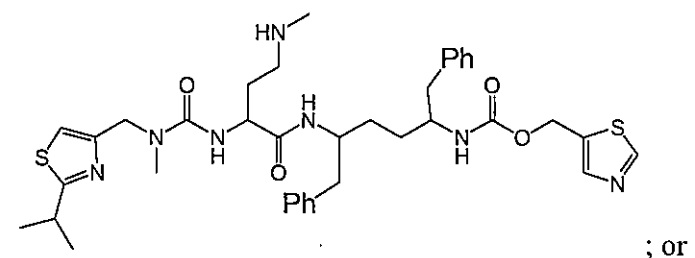
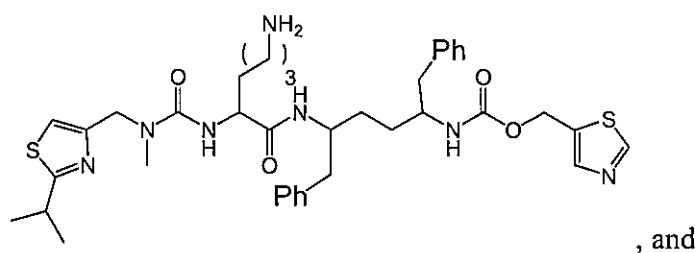
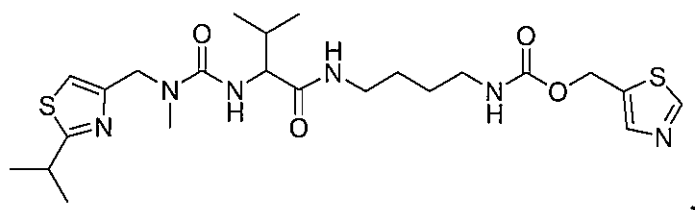
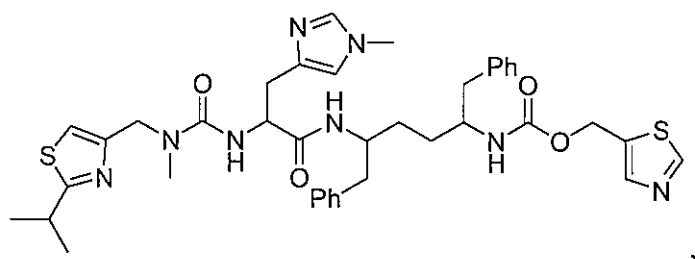












pharmaceutically acceptable salts, solvates, stereoisomers or esters thereof.

9. A compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, stereoisomer or ester thereof for use in therapy.

10. A compound of any one of claims 1 to 8 or a pharmaceutically acceptable salt, solvate, stereoisomer or ester thereof for use in 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.

11. A compound for use according to claim 10 or a pharmaceutically acceptable salt,

solvate, stereoisomer or ester thereof, wherein the cytochrome P450 monooxygenase is cytochrome P450 monooxygenase 3A.

12. A pharmaceutical composition comprising a compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or ester thereof, and a pharmaceutically acceptable carrier or excipient for use in treating an HIV infection, or treating an HCV infection in a patient.

13. The pharmaceutical composition of claim 12, further comprising at least one additional therapeutic agent.

14. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is metabolized by cytochrome P450 monooxygenase.

15. The pharmaceutical composition of claim 13, wherein the 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, entry inhibitor, gp120 inhibitors, G6PD and NADH-oxidase inhibitors, CCR5 inhibitors, other drugs for treating HIV, interferons, rebetol, copegus, viramidine (taribavirin), NS5b polymerase inhibitors, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

16. The pharmaceutical composition of claim 15, 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 ($\pm$ -FTC), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine (AVX754), 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 and adefovir;

(5) said HIV integrase inhibitors are selected from the group consisting of curcumin, chicoric acid, 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, caffeic acid phenethyl ester, tyrphostin, quercetin, S-1360, zintevir (AR-177), elvitegravir, L-870812, and L-870810, MK-0518 (raltegravir), 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, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta;

(14) 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;

(15) 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;

(16) said alpha-galactosidase 1 inhibitors are selected from the group consisting of MX-

3253 (celgosivir) and UT-231B;

(17) said hepatoprotectants are selected from the group consisting of IDN-6556, ME 3738, LB-84451, and MitoQ;

(18) said non-nucleoside inhibitors of HCV are selected from the group consisting of benzimidazole, benzo-1,2,4-thiadiazine, phenylalanine, A-831, and A-689; and

(19) 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).

17. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is darunavir.

18. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is atazanavir.

19. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is elvitegravir.

20. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is GS-7340.

21. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is tenofovir.

22. The pharmaceutical composition of claim 13, wherein the at least one additional therapeutic agent is tenofovir disoproxil fumarate.