

PRODRUGS OF GANAXOLONE

BACKGROUND

[0001] Ganaxolone is a positive allosteric modulator of gamma-aminobutyric acid (GABA) receptors (GABA_A), and can increase GABA activity and inhibit neuronal excitability. Ganaxolone has a very low aqueous solubility which greatly reduces its oral bioavailability and limits its potential clinical use.

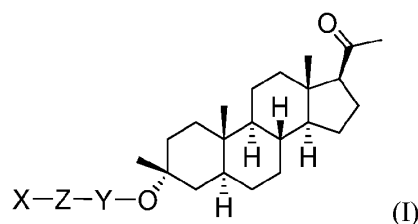
[0002] Prodrugs are molecules with typically little or no pharmacological activity of their own, that can be metabolized to release a pharmacologically active drug (i.e., parent drug) following administration (e.g., in the blood). Some prodrugs can be absorbed more readily, and have superior oral bioavailability, relative to the parent drug. However, success in creating a stable prodrug with superior bioavailability relative to a parent drug and suitable conversion to the parent drug and safety (e.g., toxicity profile) is unpredictable.

[0003] As such, there is an unmet need for a ganaxolone prodrug.

SUMMARY

[0004] The present disclosure relates to ganaxolone derivatives. The compounds disclosed herein may be metabolized to ganaxolone (e.g., *in vivo*, e.g., by a metabolic process). Compounds disclosed herein are also more soluble in aqueous solutions such as plasma, gastric fluid, or intestinal fluid, than ganaxolone. Also disclosed herein are methods of using the compounds, methods of making the compounds, and pharmaceutical compositions and kits comprising the same.

[0005] A compound of the present disclosure may be a compound of Formula (I):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Y is $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^{\text{A}})(\text{R}^{\text{B}})-$ (e.g., $-\text{CH}_2-$);

Z is absent, alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, $-\text{NR}^1-$, $-\text{O}-$, or $-\text{S}-$, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

X is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, heterocyclylene-heteroalkyl, $-\text{OC}(\text{O})\text{-alkyl}$, $-\text{C}(\text{O})\text{O-alkyl}$, $-\text{OC}(\text{O})\text{-heteroalkyl}$, $-\text{C}(\text{O})\text{O-heteroalkyl}$, $-\text{N}_3$, $-\text{NR}^1\text{R}^2$, $-\text{OR}^3$, or $-\text{SR}^4$, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-

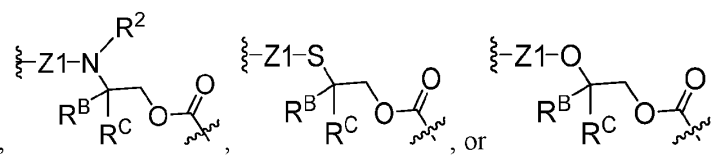
heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0006] For example, the compound may be a compound of Formula (I), wherein Y is $-C(O)-$.

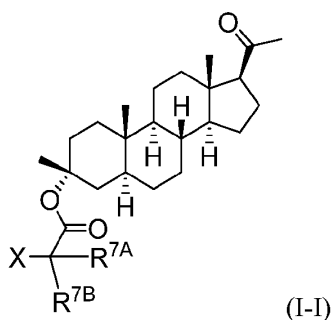
[0007] The compound may be a compound of Formula (I), wherein Z is methylene (e.g.,

unsubstituted methylene),



wherein Z1 is absent, alkylene (e.g., methylene, e.g., unsubstituted methylene), alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, or heteroarylene, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted; R^2 is hydrogen or alkyl; R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and each $\sim$ denotes the point of attachment of Z to X or Y.

[0008] A compound of the present disclosure may be a compound of Formula (I-I):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

X is as defined herein, e.g., alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl,

heterocyclylene-heteroalkyl, $-\text{OC}(\text{O})\text{-alkyl}$, $-\text{C}(\text{O})\text{O-alkyl}$, $-\text{OC}(\text{O})\text{-heteroalkyl}$, $-\text{C}(\text{O})\text{O-heteroalkyl}$, $-\text{N}_3$, $-\text{NR}^1\text{R}^2$, $-\text{OR}^3$, or $-\text{SR}^4$, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

$\text{R}^{7\text{A}}$ and $\text{R}^{7\text{B}}$ are each independently hydrogen or optionally substituted alkyl.

[0009] The compound may be a compound of Formula (I) or (I-I), wherein X is a moiety selected from the group consisting of



M is $\text{C(H)(R}^{\text{D}}\text{)}$ (e.g., $\text{—CH}_2\text{—}$), —O— , or $\text{—N(R}^{\text{D}}\text{)—}$ (e.g., —N(Me)—);

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or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

Q is heteroalkyl or heterocyclyl, wherein the heteroalkyl or heterocyclyl is optionally substituted;

V is $-O-$, $-N(H)-$, or $-N(Me)-$;

X₂ and X₃ are each independently $-CH_2-$, $-O-$, $-S-$, or $-N(R^{G3})-$ (e.g., $-NH-$);

R^A, R^B, R^C, R^D, R^E, and R^K are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R¹⁰ is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$, $-NO_2$, $-CN$, or $-NC$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-N(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

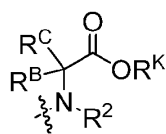
or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{15} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted;

m is an integer of 1-5;

p is an integer between 0 and 4; and

$\sim$ in Formula (I) denotes the point of attachment of X to Z, or X to Y when Z is absent, and $\sim$ in Formula (I-I) denotes the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group.



[0010] For example, X may be $\sim N(R^2)C(R^B)(R^C)C(=O)OR^K$, wherein R^2 is H, R^B and R^C are each independently alkyl (e.g., methyl), and R^K is hydrogen.

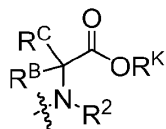
[0011] The compound may be a compound of Formula (I), wherein Y is $-C(O)-$ and Z is alkylene (e.g., methylene). The compound may be a compound of Formula (I) or (I-I), wherein R^1 and R^2 are not both hydrogen.

[0012] The compound may be a compound of Formula (I), wherein Y is $C(O)-$ and Z is alkylene

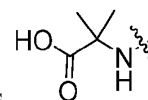
(e.g., methylene), and X is $\sim N(R^2)H$. For example, the compound may be a compound of

Formula (I), wherein Y is $C(O)-$ and Z is methylene, X is $\sim N(R^2)H$, and R^2 is hydrogen.

[0013] The compound may be a compound of Formula (I), wherein Y is $-\text{C}(\text{O})-$ and Z is

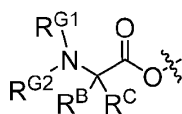


alkylene (e.g., methylene), and X is . For example, the compound may be a

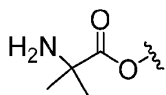


compound of Formula (I), wherein Y is $\text{C}(\text{O})-$ and Z is methylene, and X is .

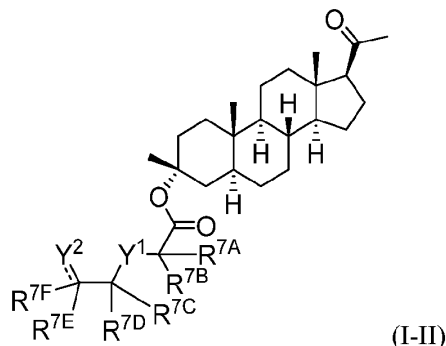
[0014] Alternatively, the compound may be a compound of Formula (I), wherein Y is $-\text{C}(\text{O})-$



and Z is alkylene (e.g., methylene), and X is . For example, the compound may be a compound of Formula (I), wherein Y is $-\text{C}(\text{O})-$ and Z is alkylene (e.g., methylene), and X is



[0015] A compound of the present disclosure may be a compound of Formula (I-II):



(I-II)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

$\text{--}\text{--}$ denotes a single bond or a double bond;

Y^1 is alkylene (e.g., methylene), alkenylene, alkynylene, heteroalkylene, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{NR}^1-$, $-\text{O}-$, or $-\text{S}-$, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

Y^2 is heteroalkyl, heterocyclyl, heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, $-NR^1R^2$, $-OR^3$, $-SR^4$, $=NR^1$, or $=O$, wherein the heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

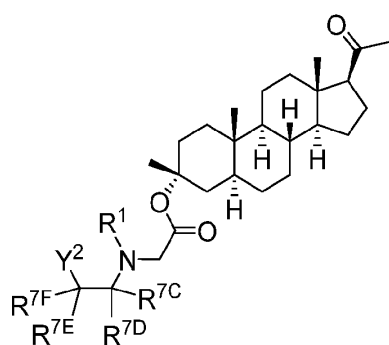
R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl, or one of R^{7A} and R^{7B} is bonded to Y^1 through one or more carbon atoms or heteroatoms to form a cyclic moiety (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl, e.g., pyrrole), and the other of the R^{7A} and R^{7B} groups is hydrogen or optionally substituted alkyl;

R^{7C} and R^{7D} are each independently hydrogen or optionally substituted alkyl, or R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group; and

R^{7E} and R^{7F} are each independently absent, hydrogen, alkyl, heteroalkyl, $-NR^1R^2$, $-OR^3$, or $-SR^4$, wherein the alkyl or heteroalkyl is optionally substituted, or R^{7E} and R^{7F} are each bonded to the same oxygen to form an oxo group, with the proviso that when  is a double bond, one of R^{7E} and R^{7F} is absent.

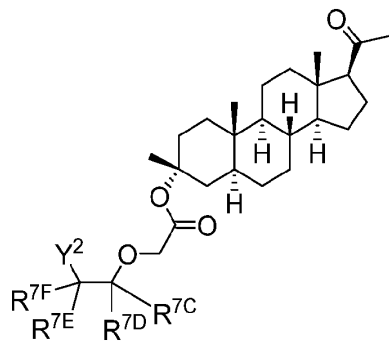
[0016] Y^1 of Formula (I-II) may be $-O-$ or $-N(R^1)-$ (e.g., $-N(H)-$, $-N(alkyl)-$, or $-N(heteroalkyl)-$). For example, Y^1 of Formula (I-II) may be $-O-$ or $-N(H)-$. Alternatively, Y^1 of Formula (I-II) may be $-N(Me)-$, $-N(Et)-$, $-N(EtOH)-$, or $-N(^nPrOH)-$.

[0017] The compound of Formula (I-II) may be a compound of Formula (I-IIa):



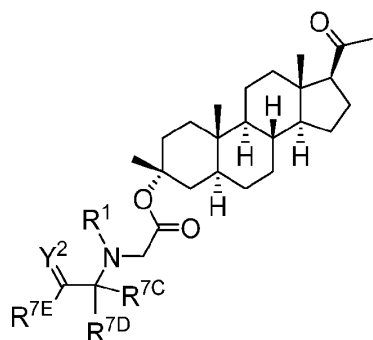
(I-IIa), wherein Y^2 , R^1 , R^{7C} , R^{7D} , R^{7E} , and R^{7F} are as defined

above; or the compound of Formula (I-II) may be a compound of Formula (I-IIb):



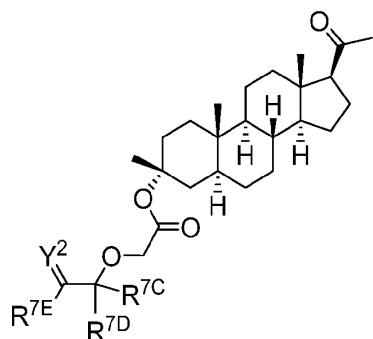
(I-IIb), wherein Y^2 , R^{7C} , R^{7D} , R^{7E} , and R^{7F} are as defined

above; or the compound of Formula (I-II) may be a compound of Formula (I-IIc):



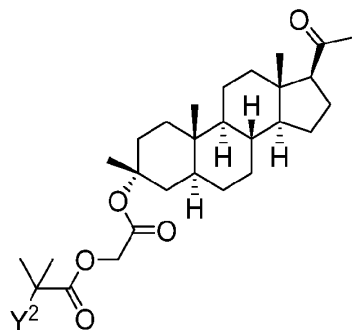
(I-IIc), wherein Y^2 , R^1 , R^{7C} , R^{7D} , and R^{7E} are as defined above;

or the compound of Formula (I-II) may be a compound of Formula (I-IId):



(I-IId), wherein Y^2 , R^{7C} , R^{7D} , and R^{7E} are as defined above;

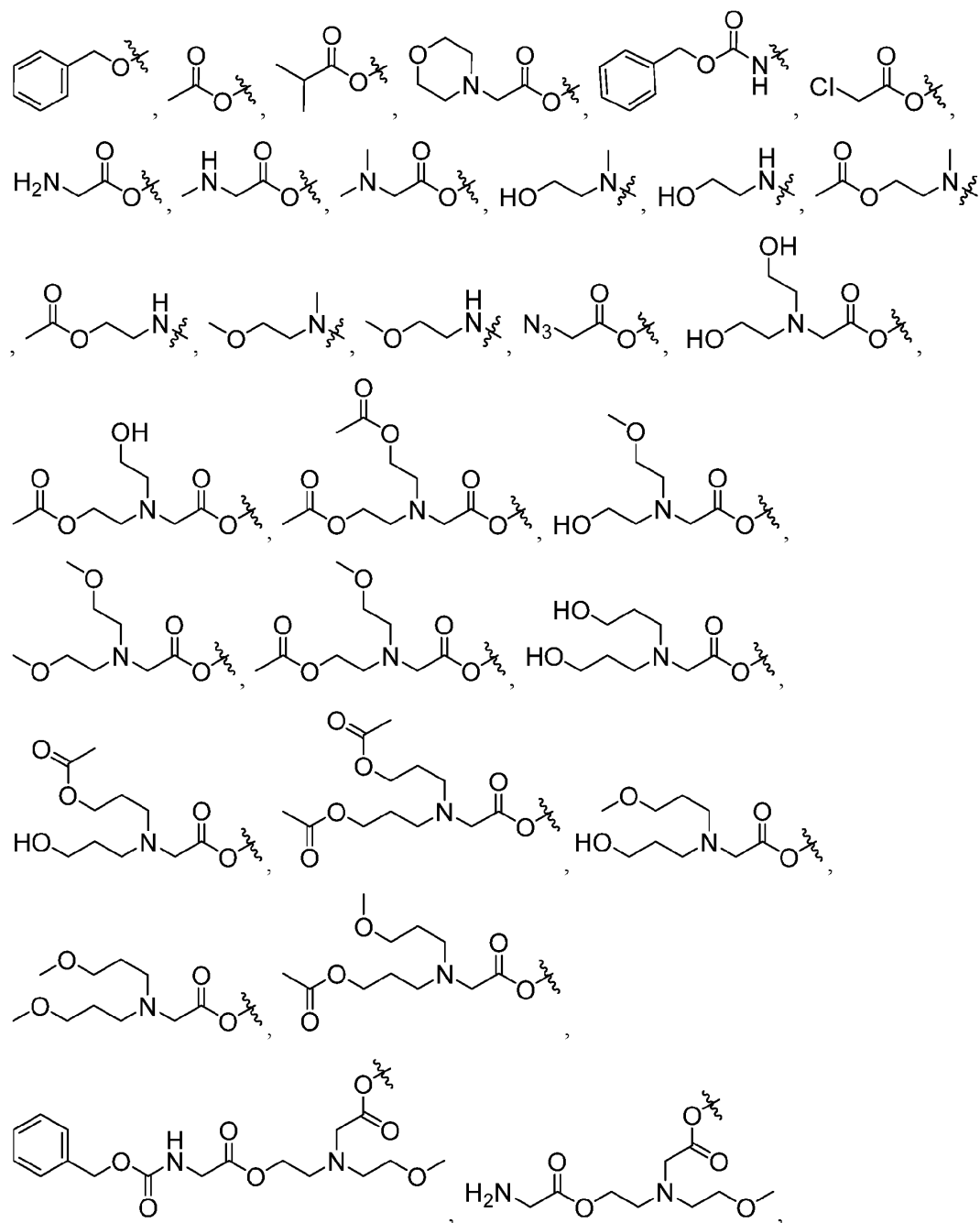
the compound of Formula (I-II) may be a compound of Formula (I-IIe):



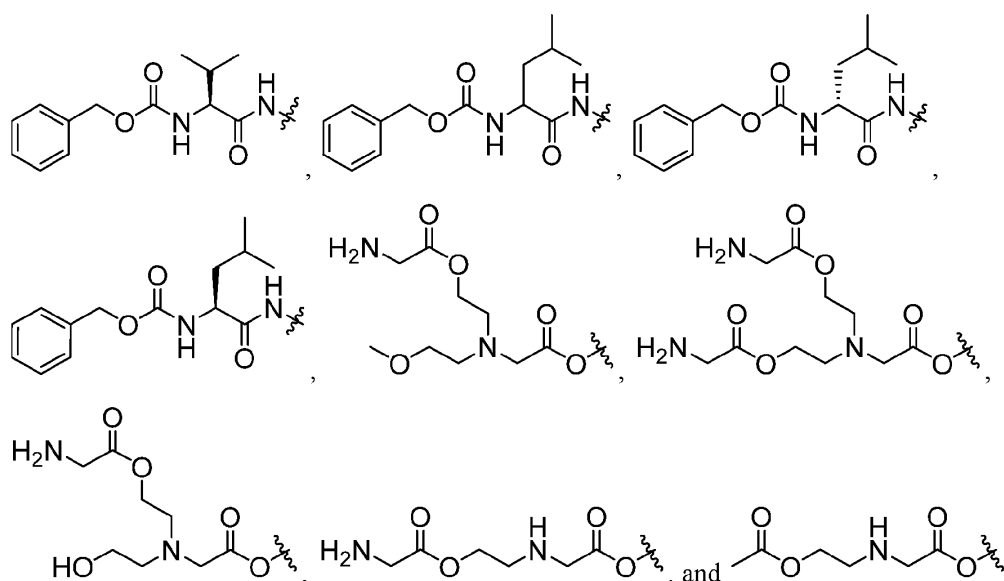
(I-IIe), wherein Y^2 is as defined above.

[0018] Y^2 of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or R^{7E} when R^{7E} is a double bond, may be optionally substituted heteroalkyl, $-\text{NR}^1\text{R}^2$ (e.g., $-\text{NH}_2$, $-\text{NHMe}$, or $-\text{NMe}_2$), $-\text{OR}^3$ (e.g., $-\text{OH}$, $-\text{OMe}$, $-\text{OEt}$, or $-\text{OBu}$), or $=\text{O}$. For example, Y^2 of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or R^{7E} when R^{7E} is a double bond, may be $-\text{NH}_2$, $-\text{NHMe}$, or $-\text{OH}$. Alternatively, Y^2 of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or

R^{7E} when  is a double bond, may be optionally substituted heteroalkyl, for example a substituted or unsubstituted heteroalkyl selected from the group consisting of:



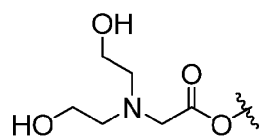




[0019] The compound may be a compound of Formula (I-II) wherein R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, and R^{7E} and R^{7F} are each alkyl (e.g., methyl).

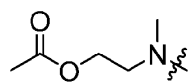
[0020] The compound may be a compound of Formula (I-II) wherein Y^1 is $-NR^1-$, $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is heteroalkyl or $-OR^3$. For example, the compound may be a compound of Formula (I-II) wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is $-OH$. Alternatively, the compound may be a compound of Formula (I-II) wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g.,

methyl), and Y^2 is $-N(CH_3)CH_2CO_2R^3$. Alternatively, the compound may be a compound of Formula (I-II) wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is

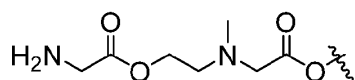


Alternatively, the compound may be a compound of Formula (I-II)

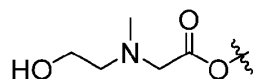
wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is



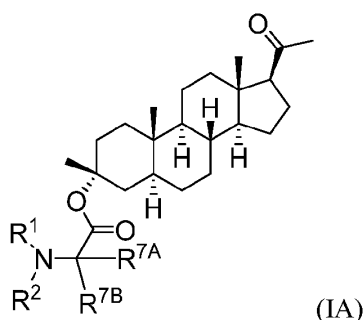
Alternatively, the compound may be a compound of Formula (I-II) wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is



Alternatively, the compound may be a compound of Formula (I-II) wherein Y^1 is $-O-$, R^{7A} and R^{7B} are each hydrogen, R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group, R^{7E} and R^{7F} are each alkyl (e.g., methyl), and Y^2 is



[0021] A compound of the present disclosure may be a compound of Formula (IA)



(IA)

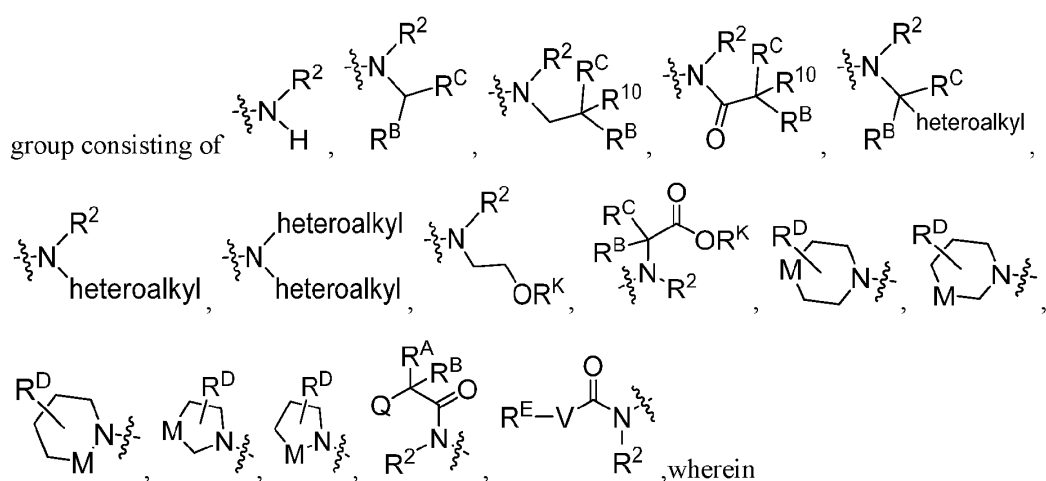
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R¹ and R², together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0022] The compound may be a compound of Formula (I), (I-I), or (IA), wherein the X group of Formula (I) or (I-I), or the $-N(R^1)(R^2)$ group of Formula (IA), is a moiety selected from the



R² is hydrogen or alkyl;

M is $\text{C(H)(R}^{\text{D}}\text{)}$ (e.g., $\text{--CH}_2\text{--}$), --O-- , or $\text{--N(R}^{\text{D}}\text{)}$ (e.g., --N(Me)--);

Q is heteroalkyl or heterocyclyl, wherein the heteroalkyl or heterocyclyl is optionally substituted;

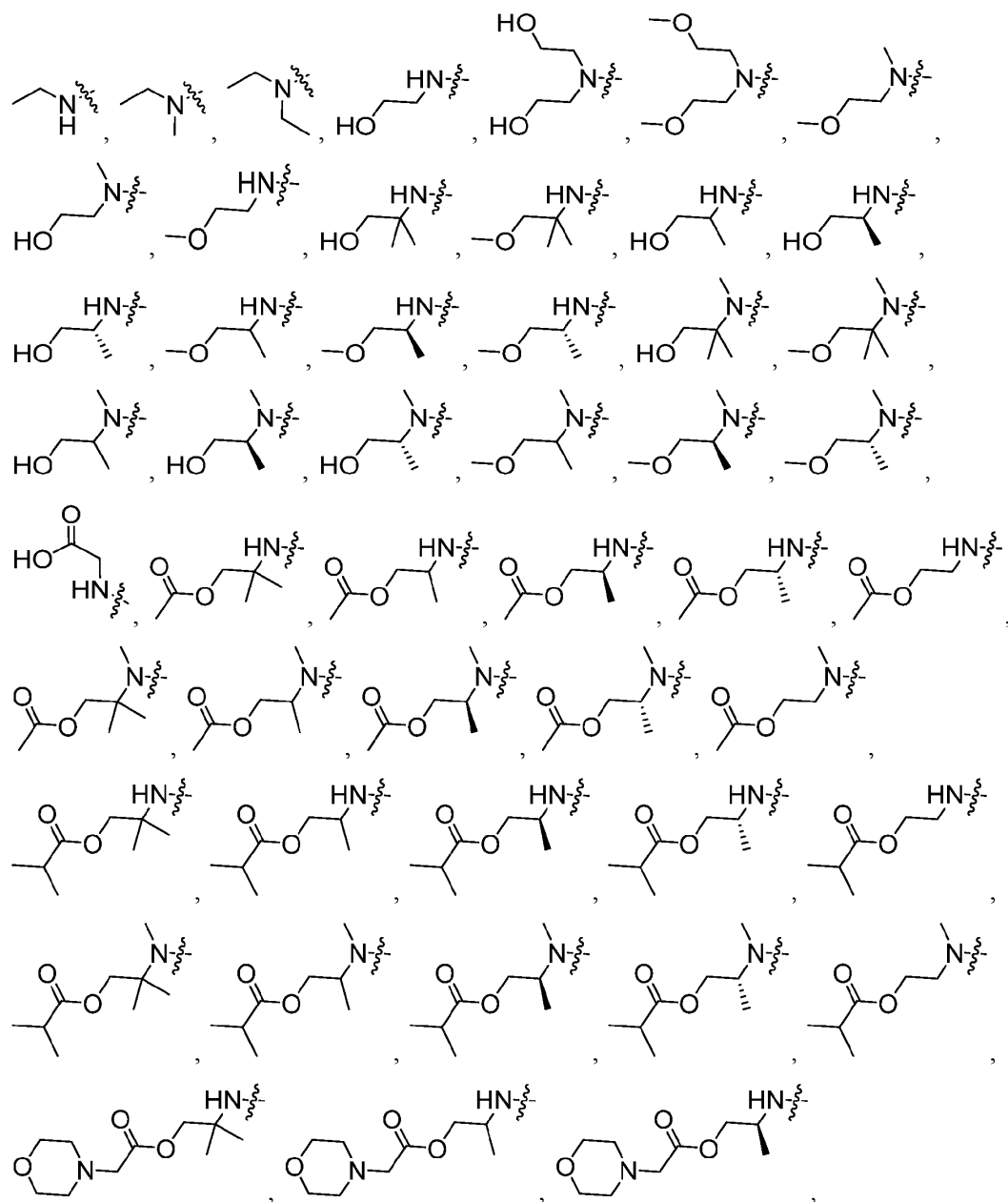
V is -O-, -N(H)-, or -N(Me)-;

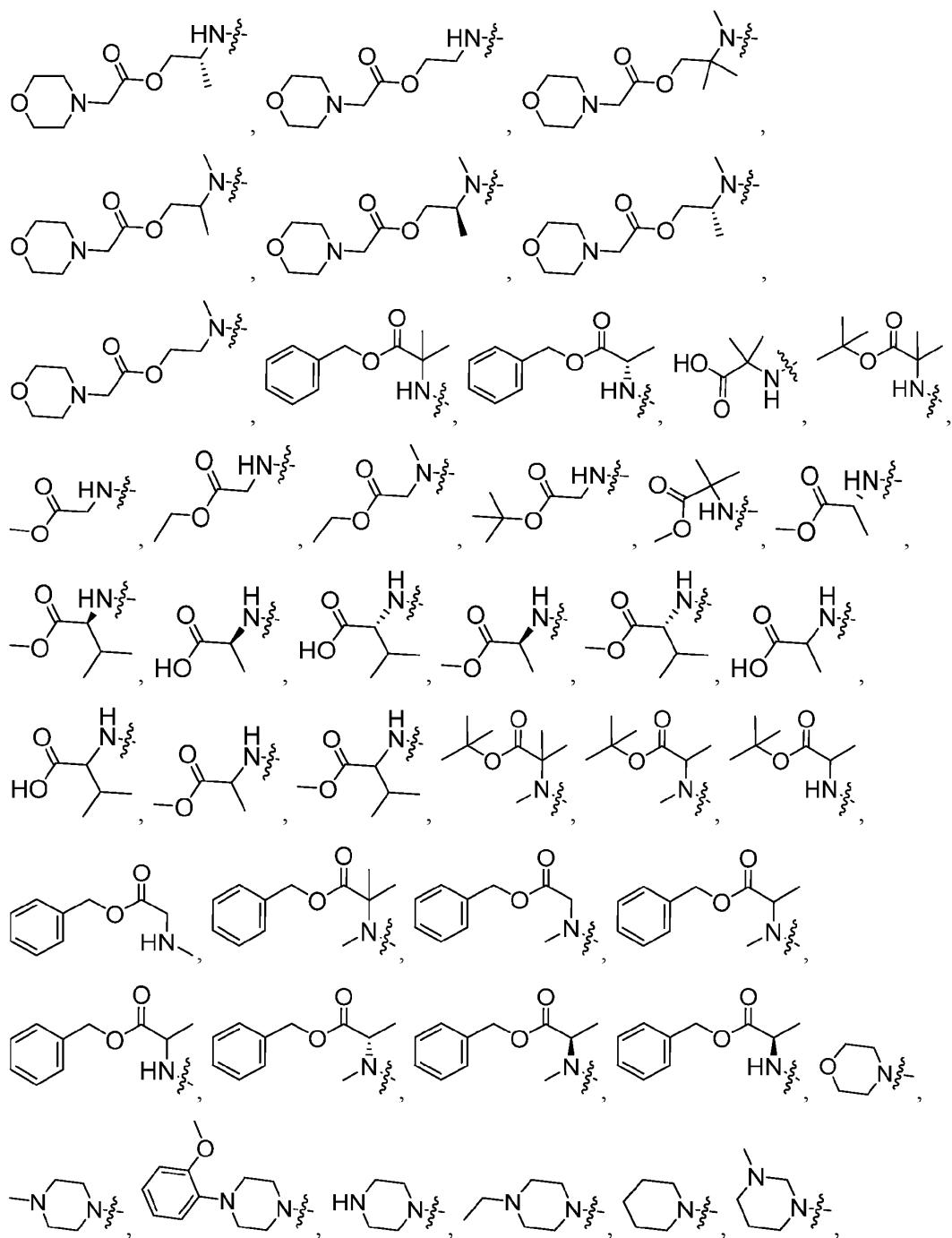
R^A, R^B, R^C, R^D, R^E and R^K are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

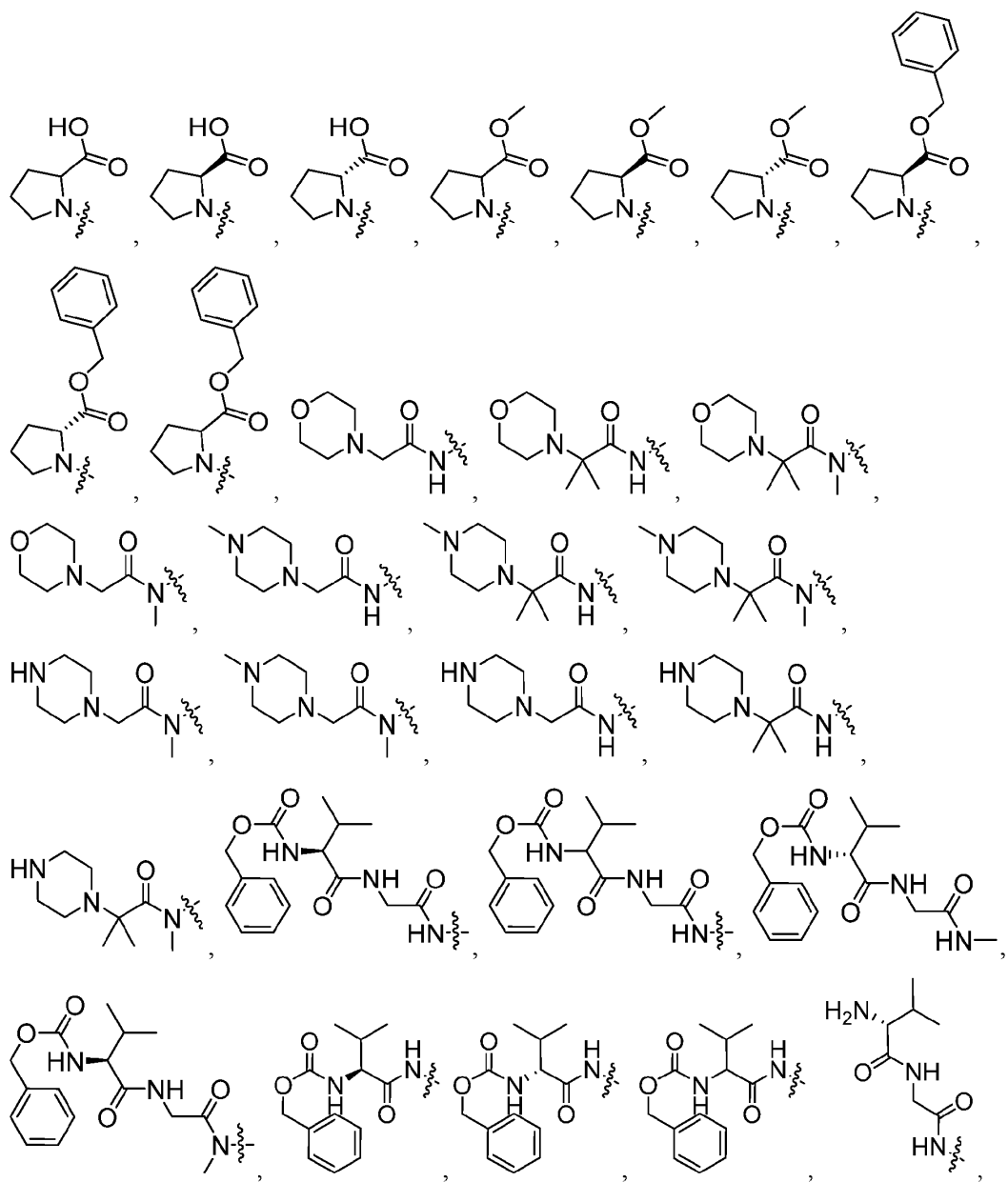
^z denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I);
 the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I); or
 the point of attachment of the nitrogen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in
 Formula (IA).

[0023] In some embodiments, the X group of Formula (I) or Formula (I-I), or the $-N(R^1)(R^2)$

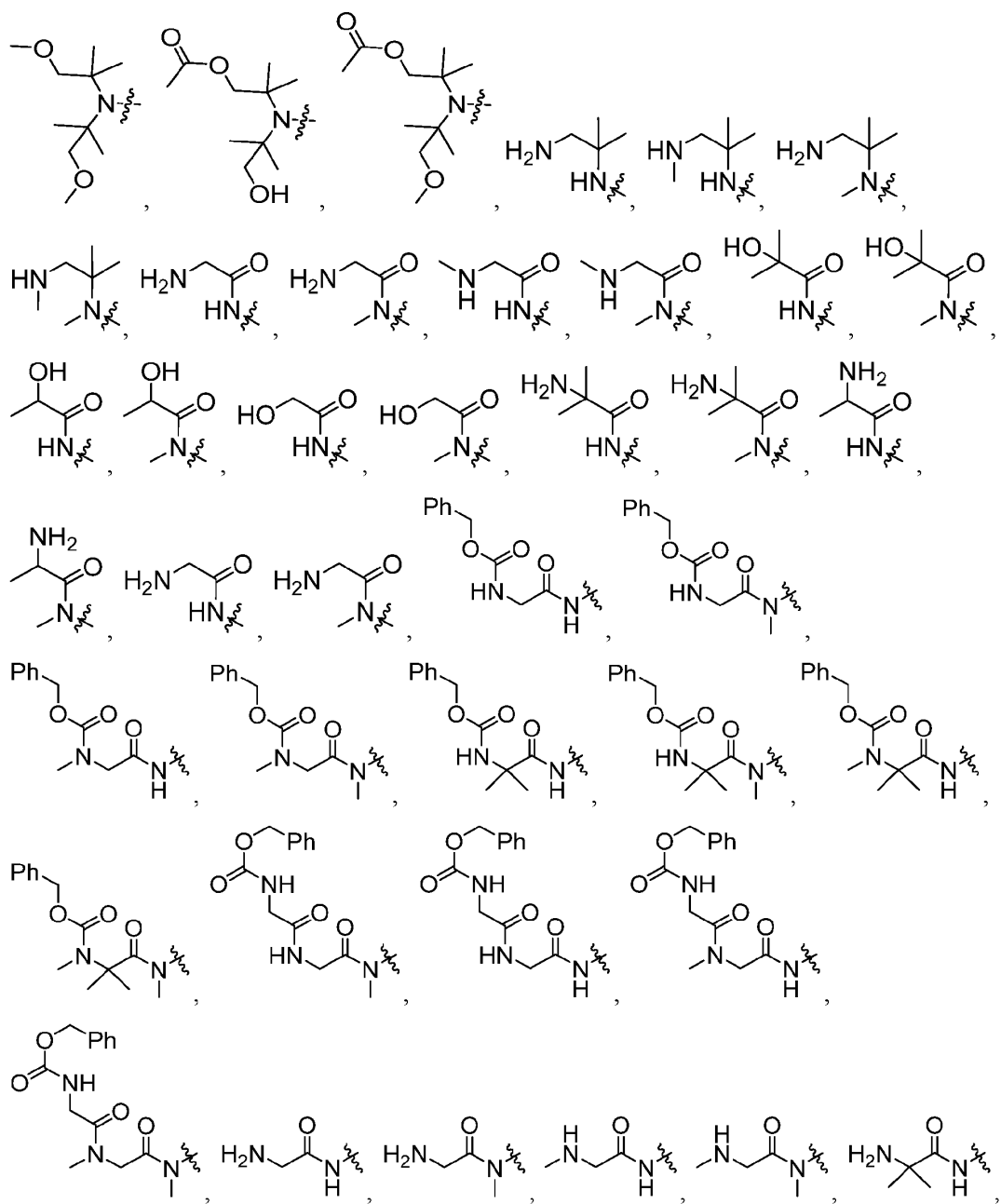
group of Formula (IA), is a moiety selected from the group consisting of H_2N , NH , N ,

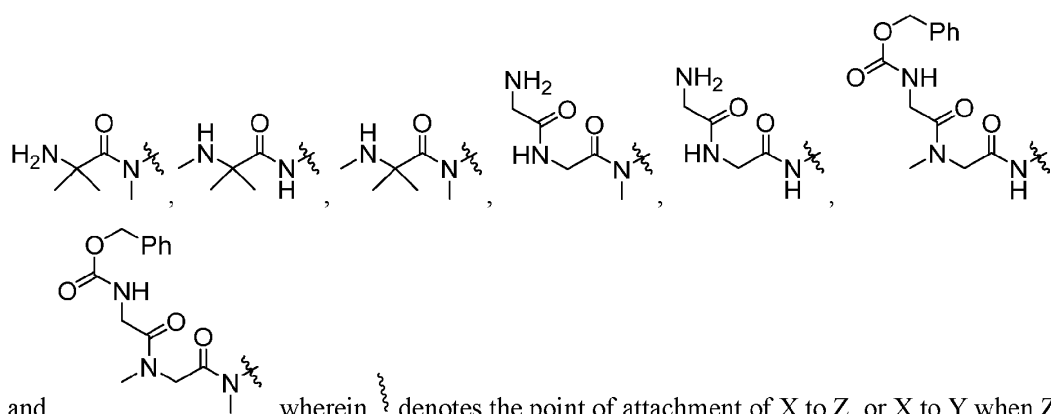






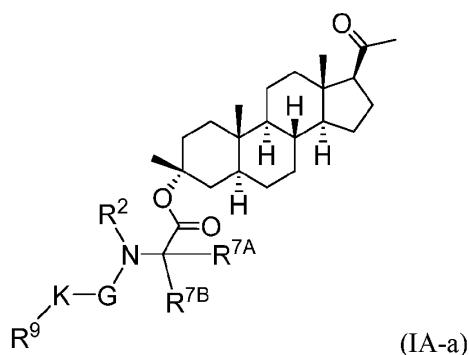






and , wherein  denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $-\text{C}(\text{R}^{7\text{A}})(\text{R}^{7\text{B}})$ group in Formula (I-I); or the point of attachment of the nitrogen atom to the carbon atom of the $-\text{C}(\text{R}^{7\text{A}})(\text{R}^{7\text{B}})$ group in Formula (IA).

[0024] A compound of the present disclosure may be a compound of Formula (IA-a)



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

G is absent, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$ (e.g., $-\text{CH}_2-$),

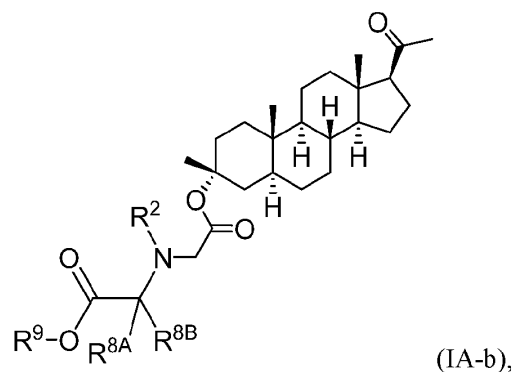
K is alkylene, heteroalkylene, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{O}-(\text{CH}_2)-$, or $-(\text{CH}_2)-\text{O}-$, wherein the alkylene or heteroalkylene is optionally substituted;

R^2 , $\text{R}^{7\text{A}}$, $\text{R}^{7\text{B}}$, $\text{R}^{8\text{A}}$, and $\text{R}^{8\text{B}}$ are each independently hydrogen or optionally substituted alkyl; and

R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0025] In some embodiments, the compound of Formula (I), (I-I), or (IA) is a compound of Formula (IA-a), wherein G is $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$; K is $-\text{OC}(\text{O})-$; R^2 , $\text{R}^{7\text{A}}$, $\text{R}^{7\text{B}}$, and R^9 are each hydrogen; and $\text{R}^{8\text{A}}$ and $\text{R}^{8\text{B}}$ are each independently hydrogen or alkyl (e.g., methyl), wherein the carbon atom of the carbonyl group in $-\text{OC}(\text{O})-$ is bonded to G.

[0026] A compound of the present disclosure may be a compound of Formula (IA-b)



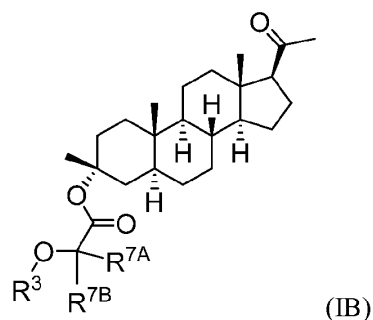
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^2 , $\text{R}^{8\text{A}}$, and $\text{R}^{8\text{B}}$ are each independently hydrogen or optionally substituted alkyl; and

R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0027] For example, the compound of Formula (I), (I-I), (IA), or (IA-a) may be a compound of Formula (IA-b), wherein R^2 is hydrogen; and $\text{R}^{8\text{A}}$ and $\text{R}^{8\text{B}}$ are each independently methyl.

[0028] A compound of the present disclosure may be a compound of Formula (IB):

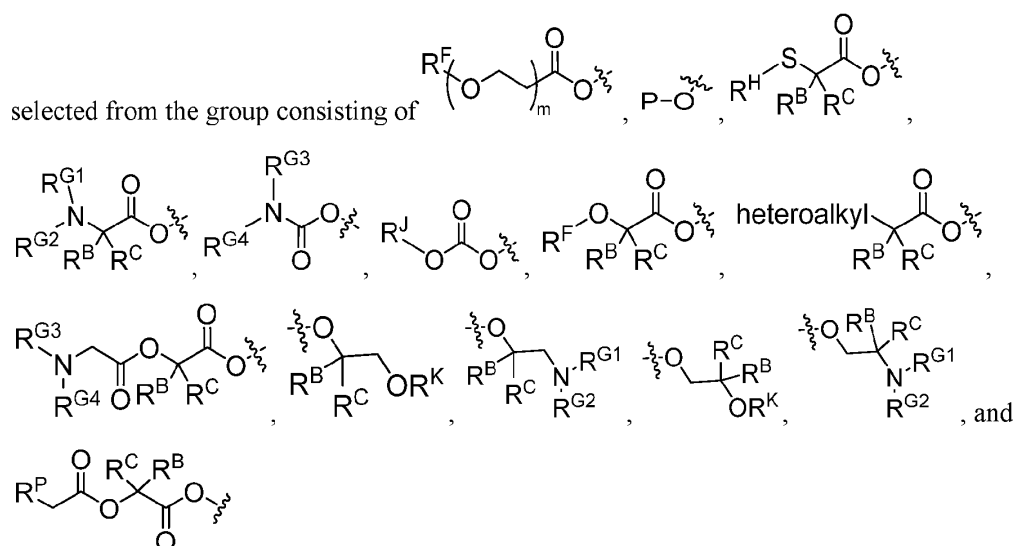


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0029] The X of Formula (I) or (II), or the $-O-(R^3)$ group of Formula (IB), may be a moiety



wherein

P is an amino acid residue (e.g., glycine, alanine, valine, leucine, or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^I is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^P is halo, -NH-alkyl, -NH-heteroalkyl, -N-(alkyl)₂ (e.g., -N(Me)₂), -N-(heteroalkyl)₂ (e.g., -N(CH₂CH₂OH)₂), or heterocyclyl (e.g., morpholinyl);

m is an integer of 1-5; and

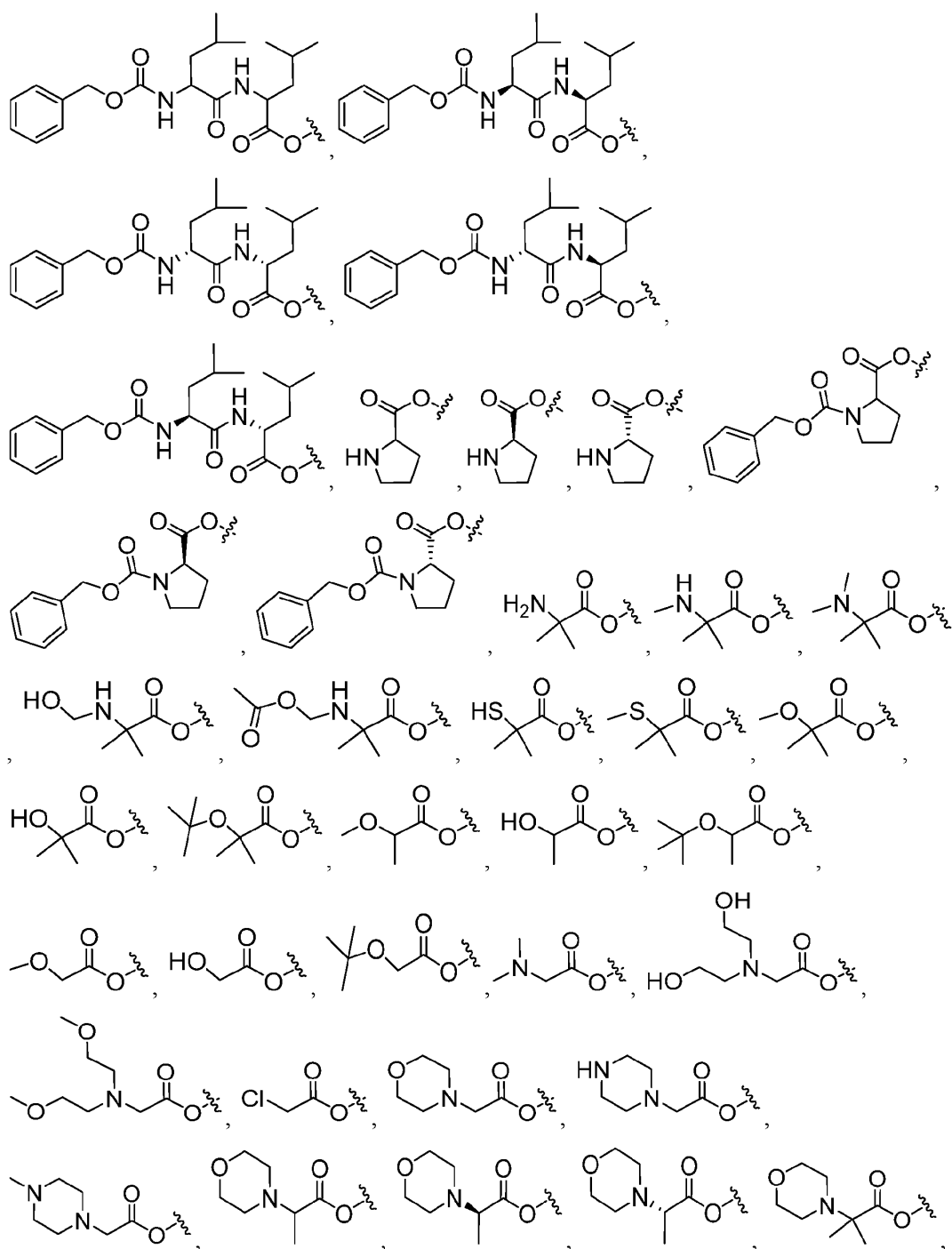
$\text{~}\text{~}\text{~}$ denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); $\text{~}\text{~}\text{~}$ denotes the point of attachment of X to the carbon atom of the -C(R^{7A})(R^{7B}) group in Formula (I-I); and $\text{~}\text{~}\text{~}$ denotes the point of attachment of the oxygen atom to the carbon atom of the -C(R^{7A})(R^{7B}) group in Formula (IB).

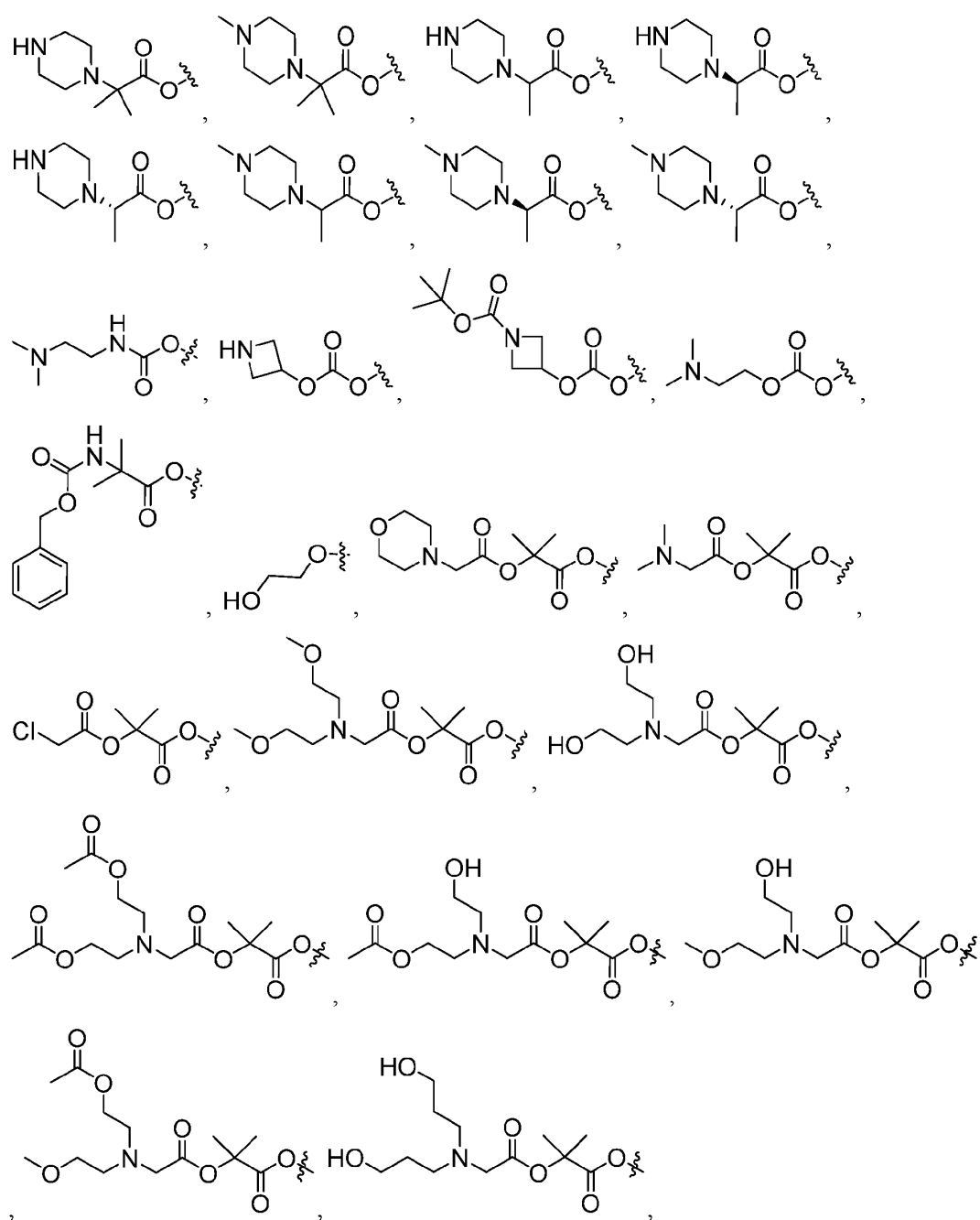
[0030] In some aspects, the compound is a compound of Formula (I), (I-I), or (IB), wherein the X group of Formula (I) or (I-I), or the -O- R^3 group of Formula (IB), is a moiety selected from

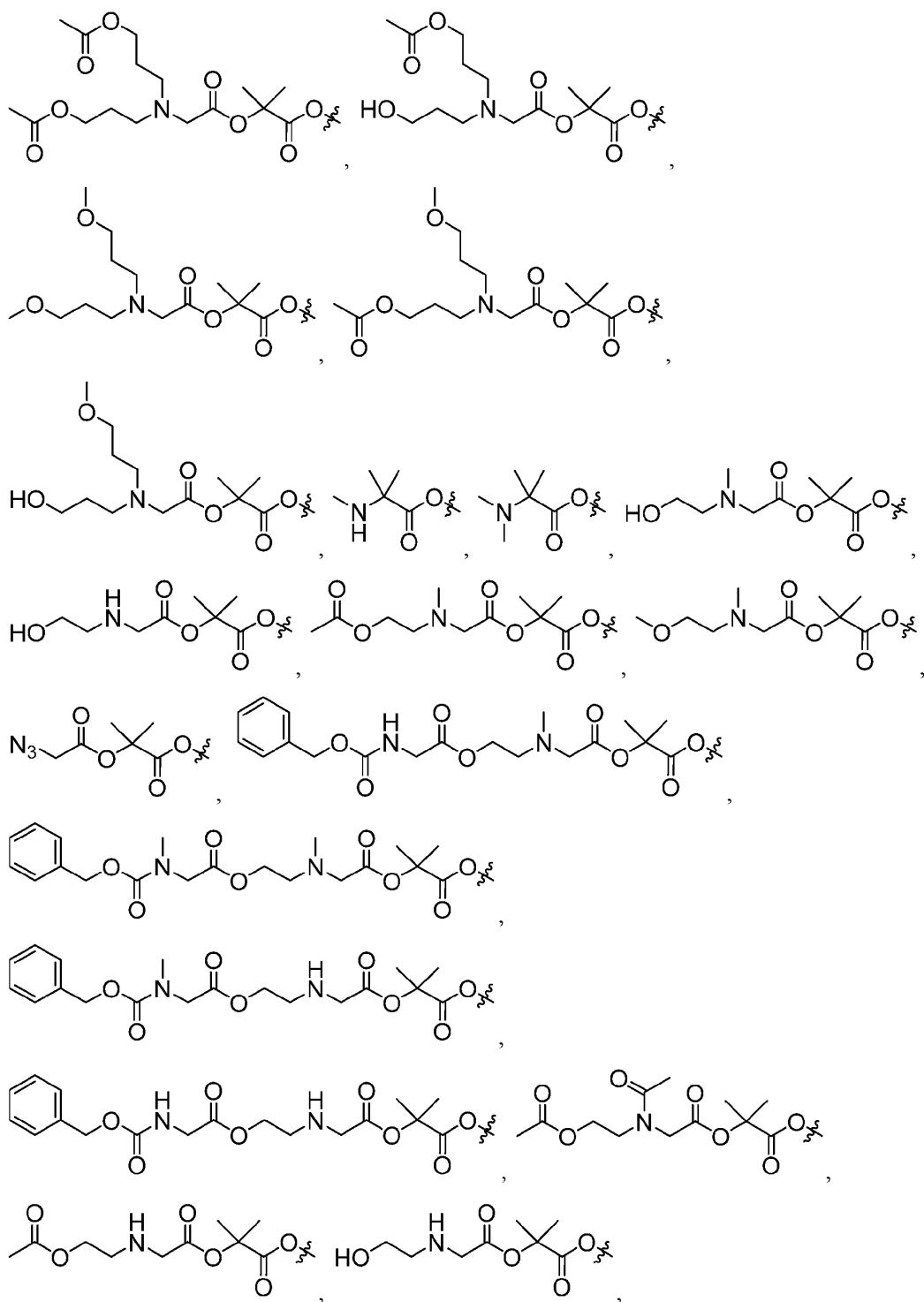
the group consisting of

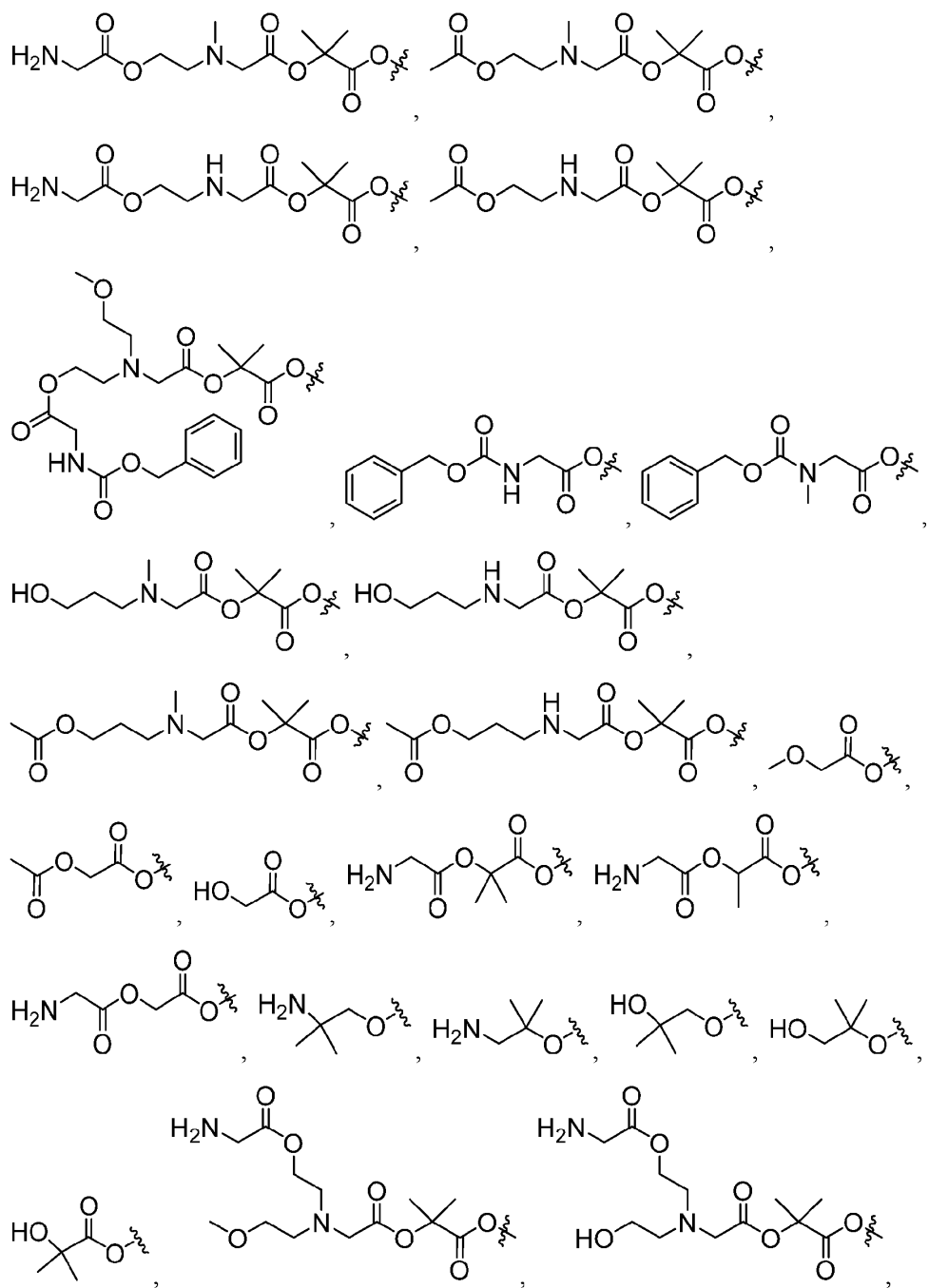
The image displays a series of chemical structures representing various prodrugs of valacyclovir. The structures are arranged in rows, separated by commas. They include:

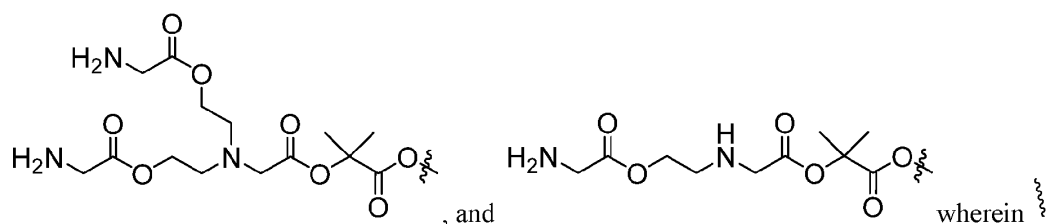
- Linear polymeric forms with repeating units of valacyclovir linked by ester bonds.
- Valacyclovir ester prodrugs with various side chains, including hydroxyethyl, hydroxypropyl, and hydroxybutyl groups.
- Valacyclovir amide prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir ester prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir amide prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir ester prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir amide prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir ester prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.
- Valacyclovir amide prodrugs with various side chains, including isopropyl, phenyl, and benzyl groups.





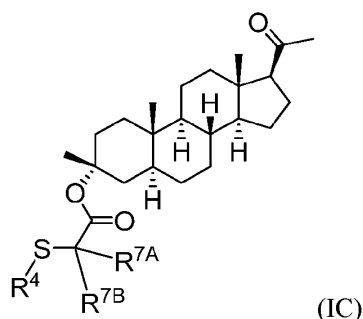






denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I); or the point of attachment of the oxygen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (IB).

[0031] A compound of the present disclosure may be a compound of Formula (IC)

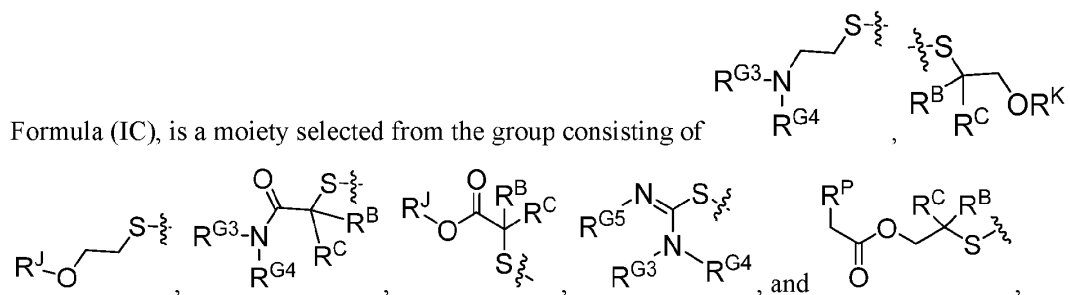


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, or heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0032] In some embodiments, the X group of Formula (I) or (I-I), or the $-S-(R^4)$ group of



wherein

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

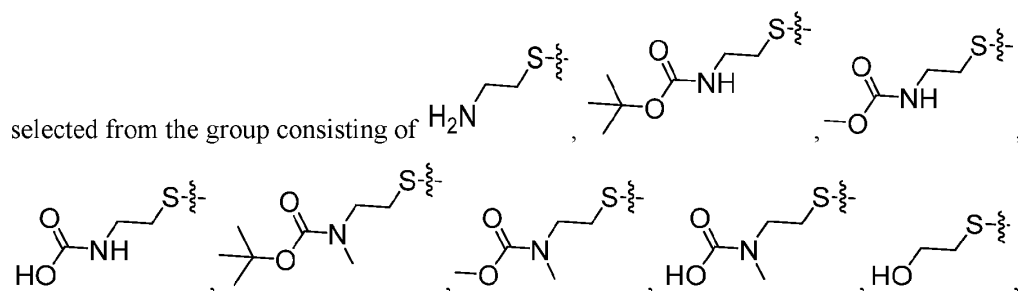
R^I is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

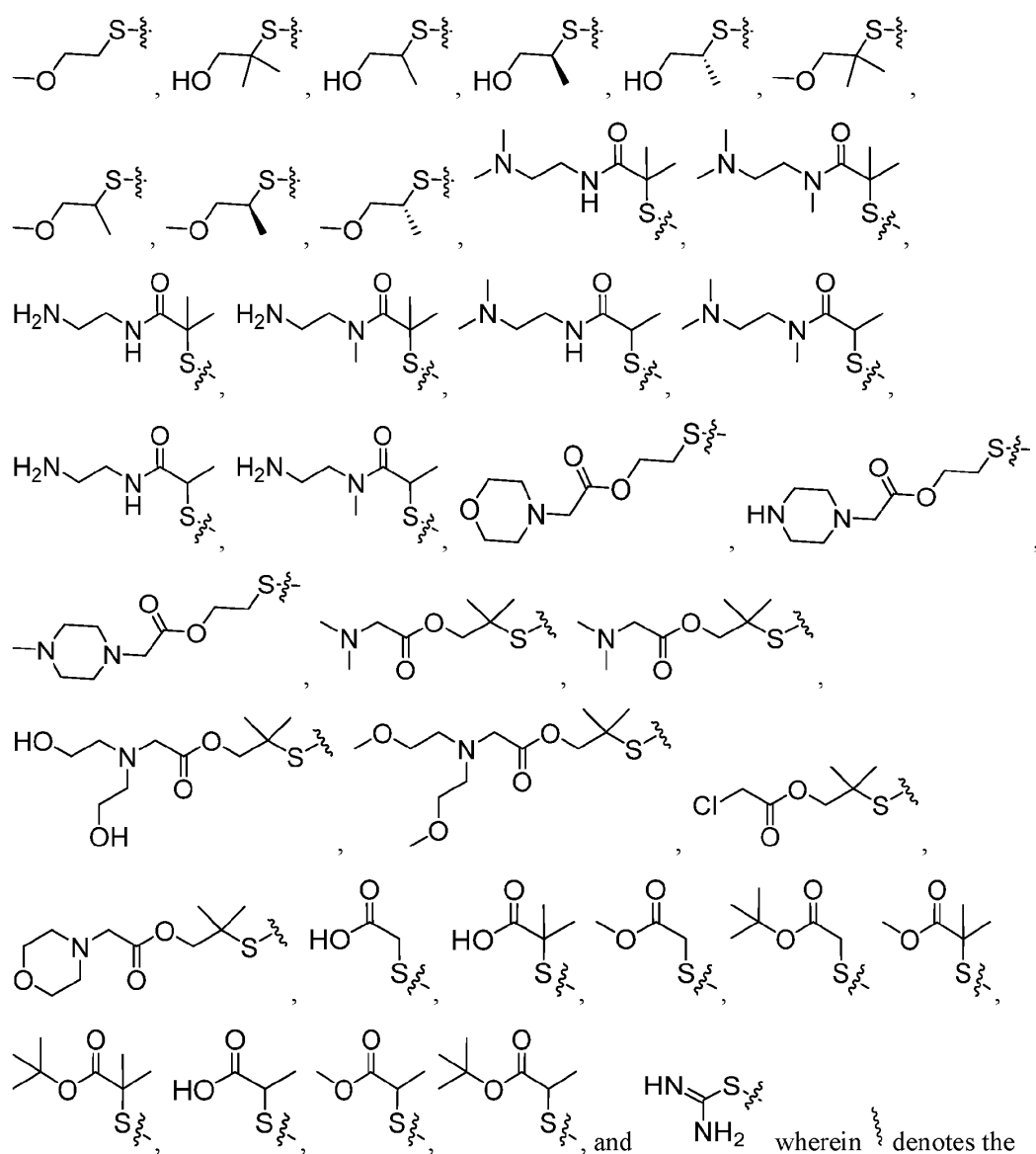
R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^P is halo, $-NH$ -alkyl, $-NH$ -heteroalkyl, $-N$ -(alkyl)₂ (e.g., $-N(Me)_2$), $-N$ -(heteroalkyl)₂ (e.g., $-N(CH_2CH_2OH)_2$), or heterocyclyl (e.g., morpholinyl); and

--- denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I); or the point of attachment of the sulfur atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (IC).

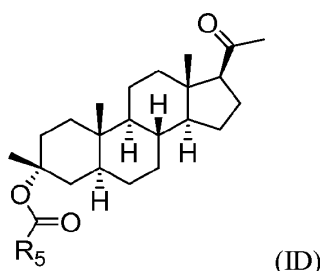
[0033] In some embodiments, the compound is a compound of Formula (I), (I-I), or (IC), wherein the X group of Formula (I) or (I-I), or the $-S-R^4$ group of Formula (IC), is a moiety





point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I); or the point of attachment of the sulfur atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (IC).

[0034] A compound of the present disclosure may be a compound of Formula (ID)

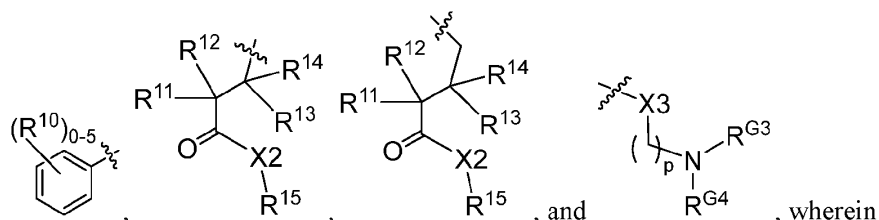


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,
wherein

R^5 is alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted.

[0035] In some embodiments, the X group of Formula (I) or Formula (I-I), or the R^5 group in

Formula (ID), is a moiety selected from group consisting of alkyl, haloalkyl,



X_2 and X_3 are each independently $-CH_2-$, $-O-$, $-S-$, or $-N(R^{G3})-$ (e.g., $-NH-$);

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$, $-NO_2$, $-CN$, or $-NC$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-N(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R¹⁵ is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

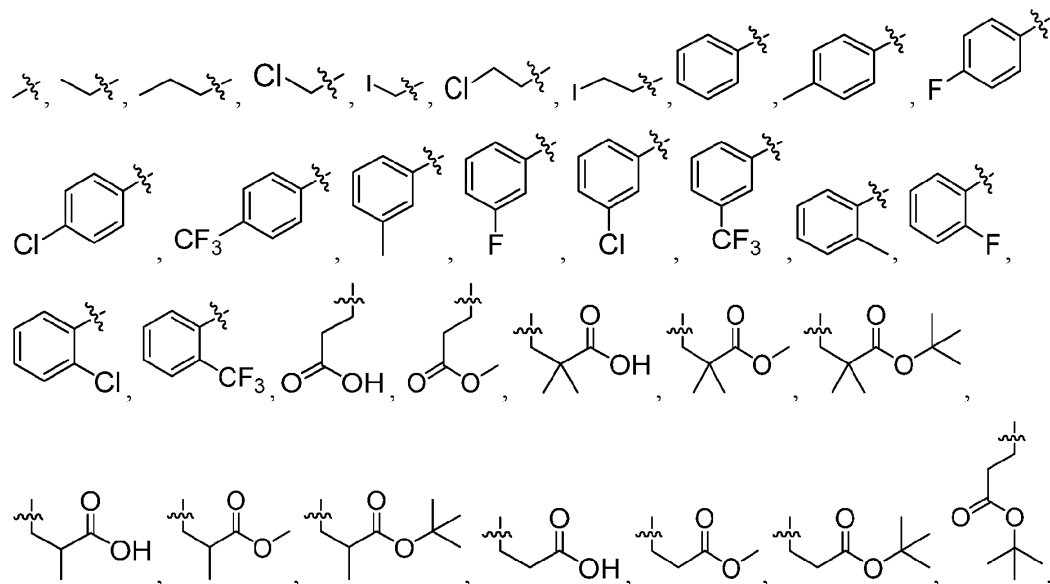
R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

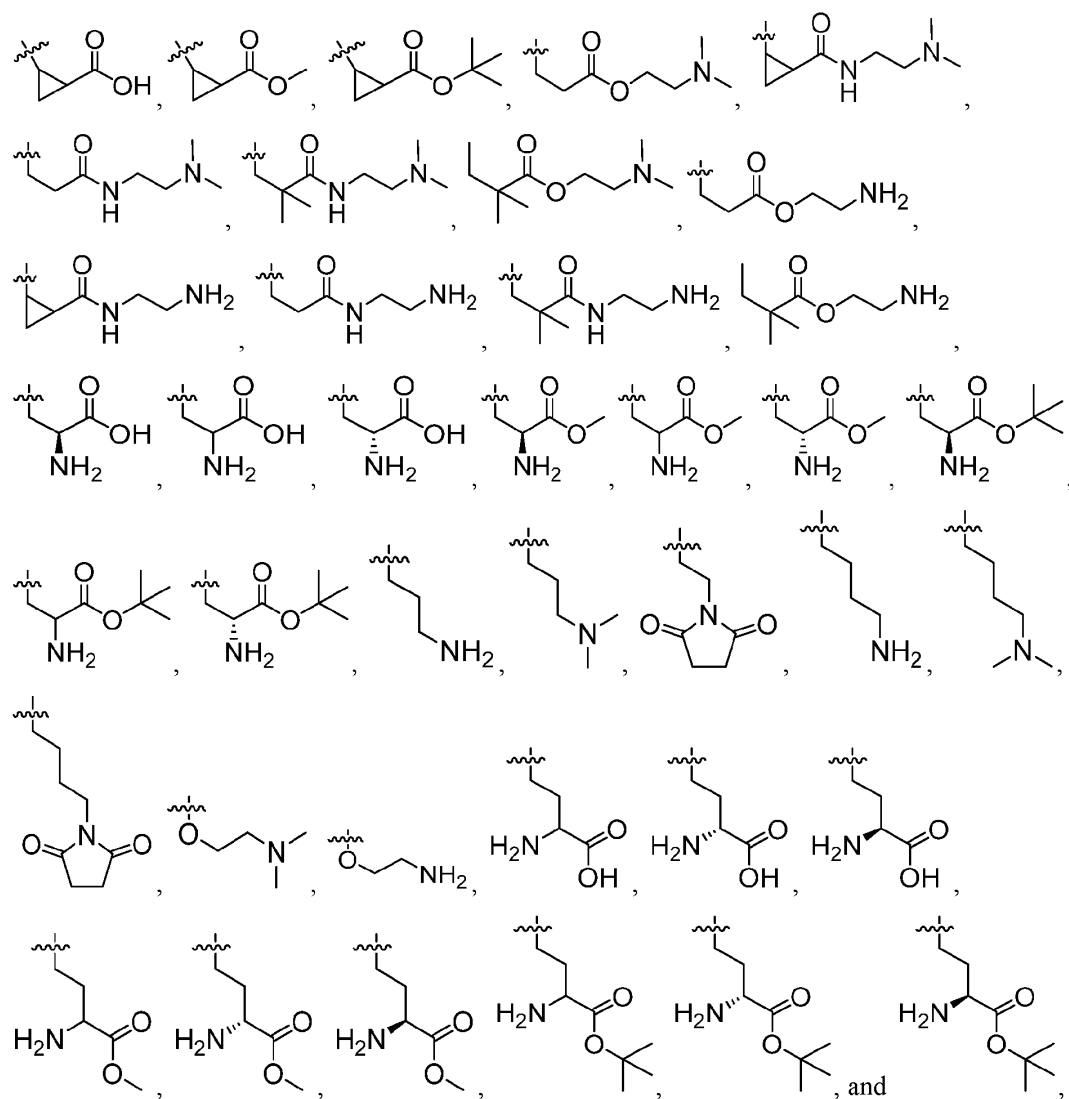
and

p is an integer between 0 and 4; and

^z denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I);
 the point of attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I); or
 the point of attachment of the R^5 group to the carbon atom of the $-C(O)-$ group in Formula (ID).

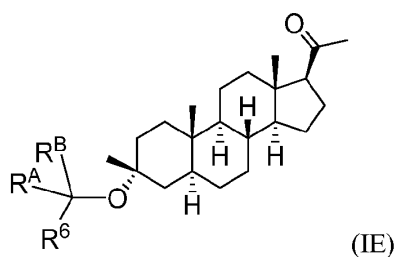
[0036] The compound may be a compound of Formula (I), (I-I), or (ID), wherein the X group of Formula (I) or (I-I), or the R⁵ group of Formula (ID), is a moiety selected from the group consisting of





wherein $\overset{z}{\curvearrowright}$ denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $-\text{C}(\text{R}^{7\text{A}})(\text{R}^{7\text{B}})$ group in Formula (I-I); or the point of attachment of the R^5 group to the carbon atom of the $-\text{C}(\text{O})-$ group in Formula (I-D).

[0037] A compound of the present disclosure may be a compound of Formula (IE)



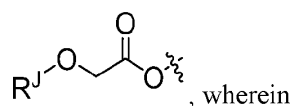
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^6 is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, $-OC(O)$ -alkyl, $-C(O)O$ -alkyl, $-OC(O)$ -heteroalkyl, $-C(O)O$ -heteroalkyl, $-N_3$, $-SH$, or $-S$ -alkyl (e.g., $-S$ -Me), wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0038] In some embodiments, the X group of Formula (I) or Formula (I-I), or the R^6 group of

Formula (IE), is a moiety selected from the group consisting of $R^{G4}-N(R^{G3})CH_2C(=O)O^{\frac{z}{2}}$, and



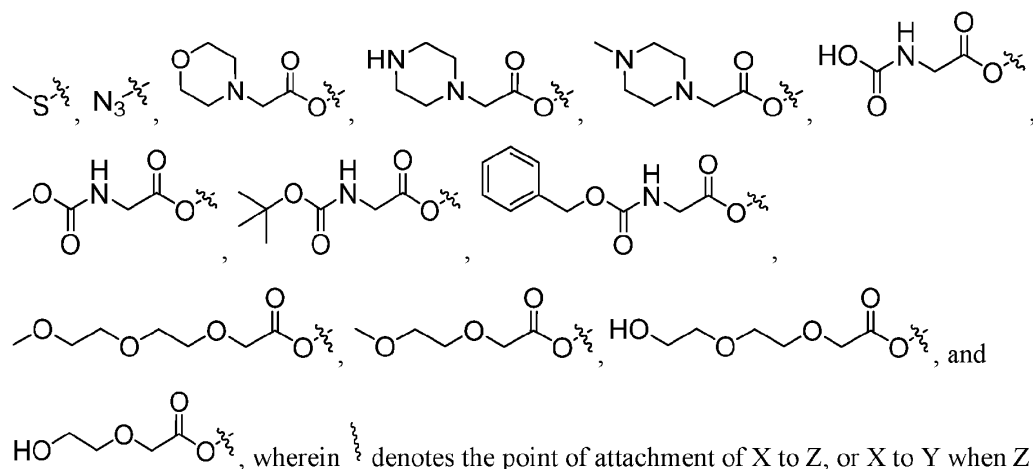
R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

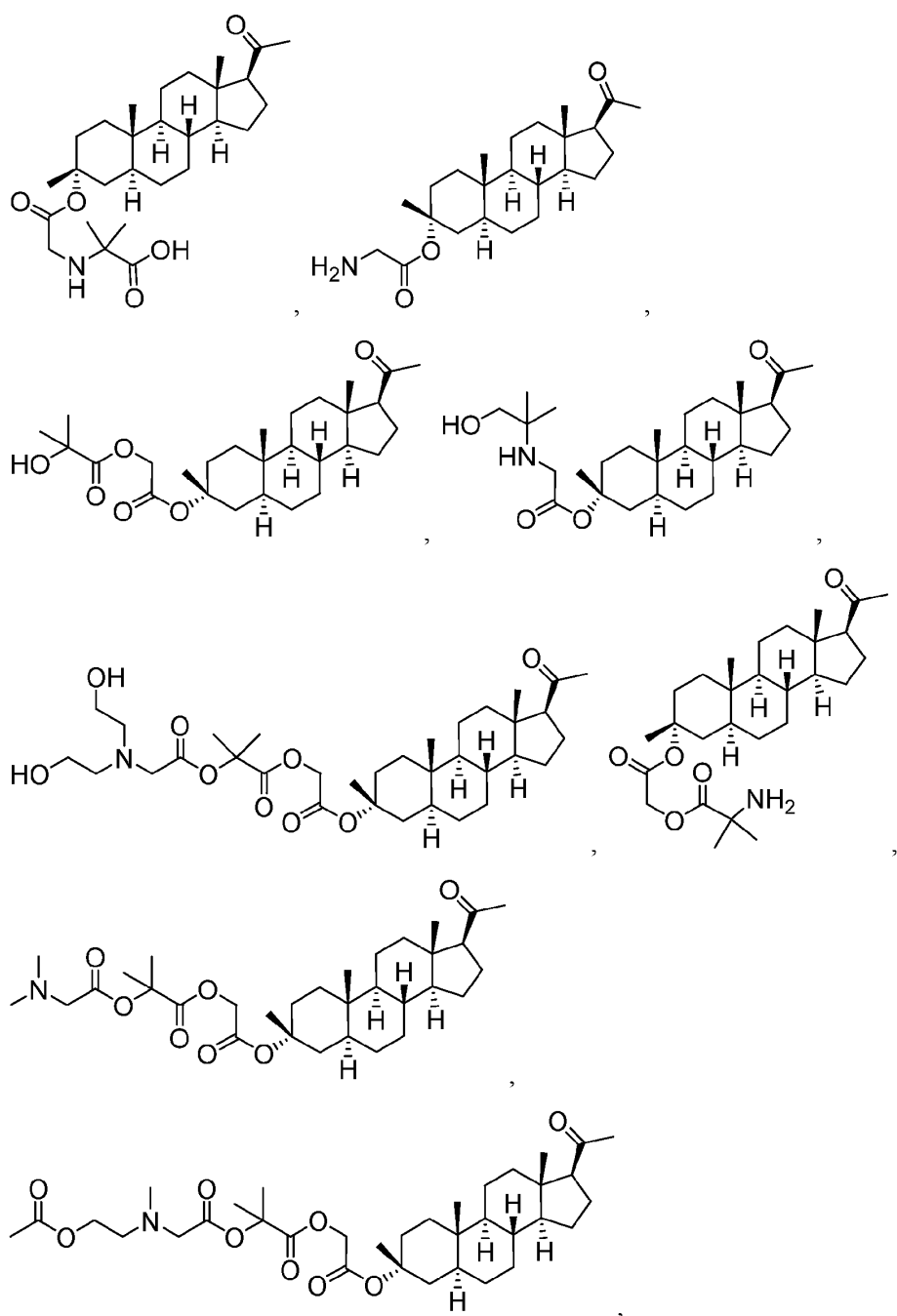
R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

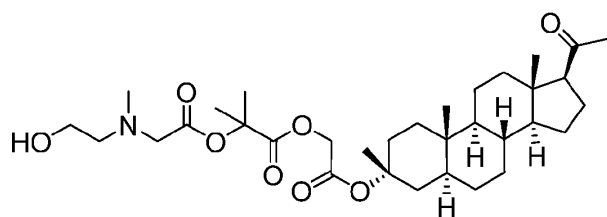
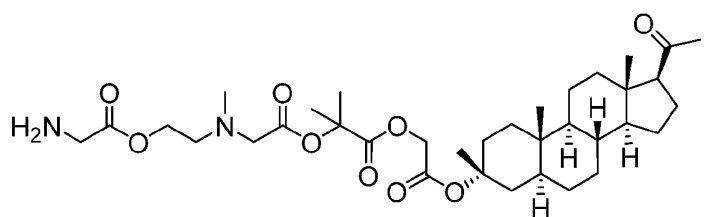
and $\text{---}\overset{\text{~}}{\text{~}}\text{---}$ denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); the point of attachment of X to the carbon atom of the $\text{---C(R}^{7A}\text{)(R}^{7B}\text{)}$ group in Formula (I-I); or the point of attachment of the R^6 group to the carbon atom of the $\text{---C(R}^A\text{)(R}^B\text{)}\text{---}$ group in Formula (IE).

[0039] The compound may be a compound of Formula (I), (I-I), or (IE), wherein the X group of Formula (I) or (I-I), or the R^6 group of Formula (IE), is a moiety selected from the group consisting of

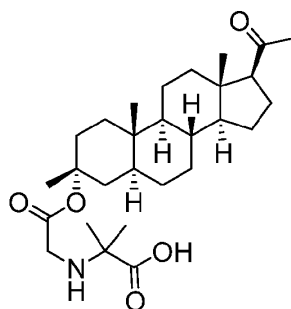


[0040] A compound of the present disclosure may be a compound provided in Table 1. For example, the compound may be

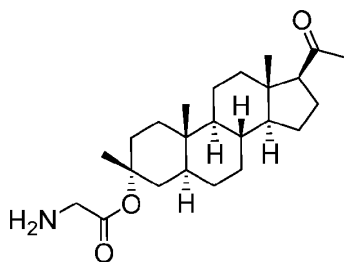




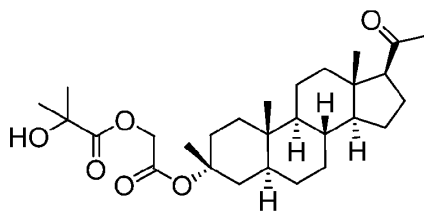
, or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some



embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some

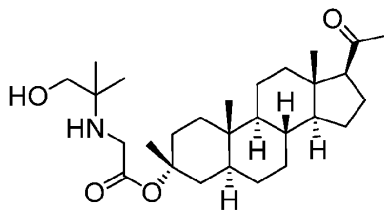


embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain

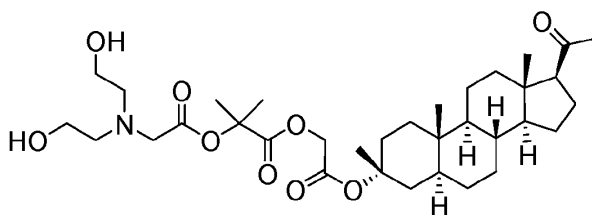


embodiments, the compound is or a pharmaceutically

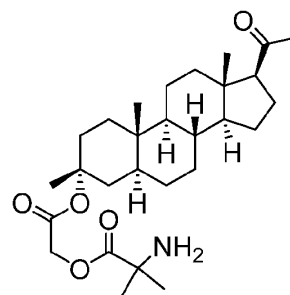
acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In



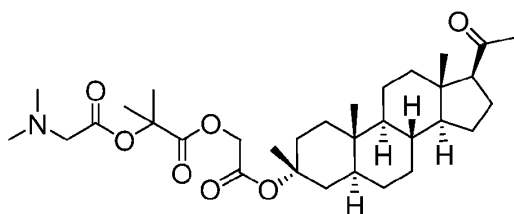
certain embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In



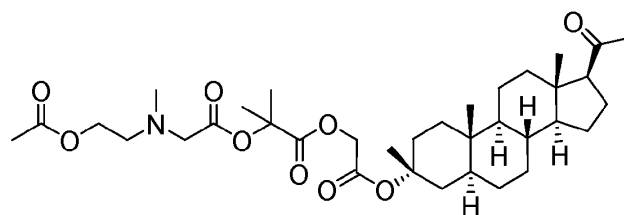
certain embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or



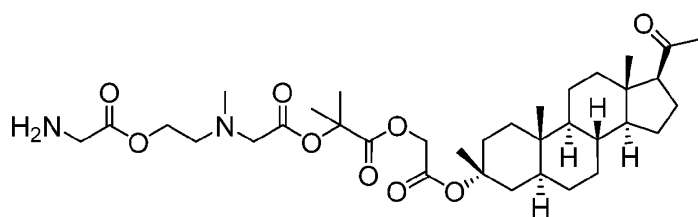
stereoisomer thereof. In certain embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain embodiments, the compound is



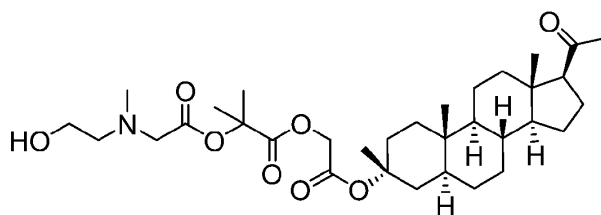
or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain embodiments,



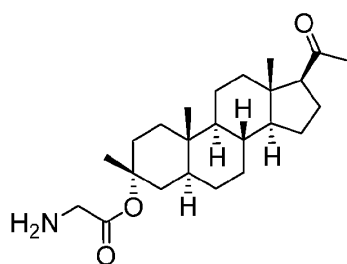
the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain embodiments, the compound is



or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain

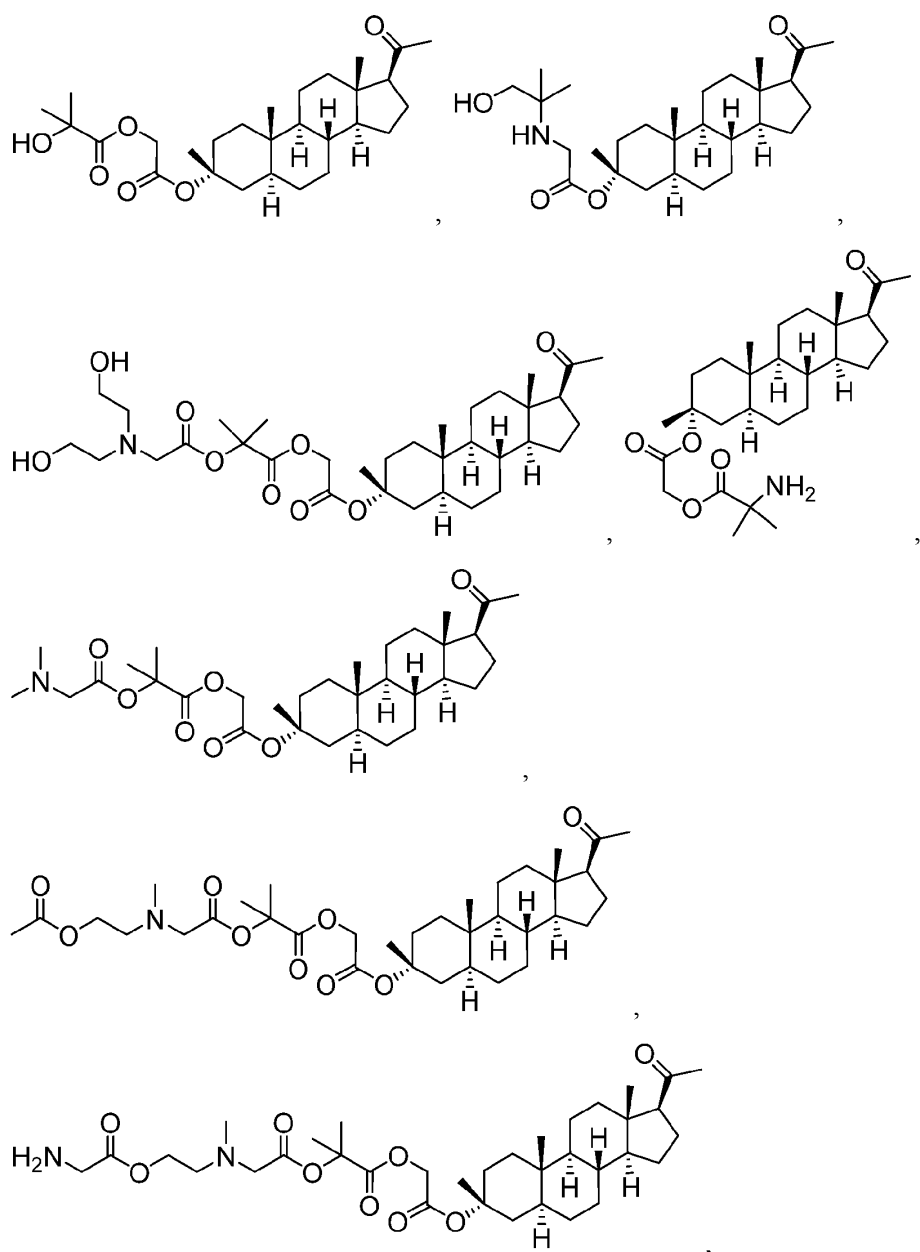


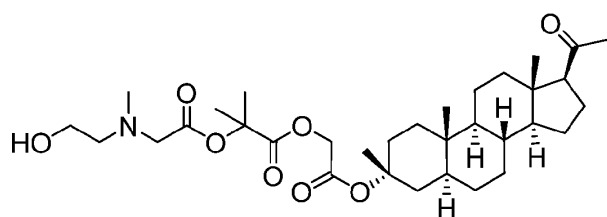
embodiments, the compound is or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof. In certain aspects, this disclosure does not include the compound



, or a pharmaceutically acceptable salt (e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0041] In some embodiments, a compound of the present disclosure is





, or a pharmaceutically acceptable salt

(e.g., hydrochloride salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0042] A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may have a higher aqueous solubility and/or hydrophilicity relative to ganaxolone, *e.g.*, as determined by a suitable measurement of solubility and/or hydrophilicity, such as logS, logP, logD, topological polar surface area (TPSA), acid pKa, base pKa, or a combination thereof.

[0043] In some aspects, a compound disclosed herein may be administered to a subject without a solubility-enhancing agent such as a cyclodextrin (e.g., CAPTISOL[®]). For example, a compound disclosed herein may be administered to a subject without cyclodextrin (e.g., CAPTISOL[®]), or may be administered with relatively low amounts of cyclodextrin (e.g., CAPTISOL[®]) such as in a ratio of compound:cyclodextrin of less than 1:1, *e.g.*, less than 2:1, less than 3:1, less than 4:1, less than 5:1, less than 6:1, less than 7:1, less than 8:1, less than 9:1, less than 10:1, less than 15:1, less than 20:1, less than 25:1, less than 50:1, less than 99:1, or lower. Similarly, a pharmaceutical composition disclosed herein may comprise relatively low amounts of a solubility-enhancing agent (e.g., a cyclodextrin, such as CAPTISOL[®]), or no solubility-enhancing agent. For example, a pharmaceutical composition disclosed herein may comprise no cyclodextrin (e.g., CAPTISOL[®]), or relatively low amounts of cyclodextrin (e.g., CAPTISOL[®]) such as less than 25 wt%, less than 20 wt%, less than 15 wt%, less than 10 wt%, less than 5 wt%, less than 4 wt%, less than 3 wt%, less than 2 wt%, less than 1 wt%, less than 0.5 wt%, of cyclodextrin in the composition.

[0044] A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may have a higher aqueous solubility and/or hydrophilicity relative to a lipid-based derivative of ganaxolone, *e.g.*, as determined by a suitable measurement of solubility and/or hydrophilicity, such as logS, logP, logD, topological polar surface area (TPSA), acid pKa, base pKa, or a combination thereof. The compounds of the present disclosure may also have a higher melting

point relative to a lipid-based derivative of ganaxolone. For example, the compounds of the present disclosure may be solid (e.g., in powder or crystal form) at ambient temperature (e.g., about 25 °C), or at temperature between about 25 to about 100 °C, or at temperature between about 25 to about 80 °C, or at temperature between about 25 to about 60 °C, or at temperature between about 25 to about 40 °C. As such, the compounds of the present disclosure have certain advantages over lipid-based derivatives of ganaxolone, e.g., more suitable for oral or intravenous administration, greater bioavailability, and/or more easily handled or formulated into pharmaceutical compositions for oral or intravenous administration.

[0045] A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may be converted (e.g., substantially converted) to ganaxolone by a metabolic process, e.g., following administration of the compound to a subject. For example, following administration of the compound to a subject (e.g., orally or intravenously), about 1% or more (e.g., about 2%, about 4%, about 6%, about 8%, about 10%, about 15%, about 20%, about 25%, about 30%, about 40%, about 50%, about 60%, about 70%, about 80%, about 90%, about 95%, about 99%, about 99.9%, or more) of the compound may be converted to ganaxolone, e.g., within a period of about 1 minute or longer (e.g., about 2 minutes, about 4 minutes, about 6 minutes, about 8 minutes, about 10 minutes, about 15 minutes, about 20 minutes, about 30 minutes, about 45 minutes, about 1 hour, about 1.5 hours, about 2 hours, about 3 hours, about 4 hours, about 5 hours, about 6 hours, about 7 hours, about 8 hours, about 9 hours, about 10 hours, about 11 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, about 24 hours, about 36 hours, about 48 hours, or longer).

[0046] A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may provide a higher bioavailability of ganaxolone, relative to the bioavailability of ganaxolone following administration of ganaxolone itself, e.g., by the same route of administration and at an equivalent dosage. The bioavailability of ganaxolone may be determined by measuring the serum concentration of ganaxolone (e.g., to obtain $C_{\max}$ or AUC).

[0047] A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may provide a higher serum concentration of ganaxolone (e.g., $C_{\max}$ or AUC), relative to the

serum concentration achieved following administration of ganaxolone itself, e.g., by the same route of administration and at an equivalent dosage. A compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) may provide longer serum half-life of ganaxolone, e.g., following administration to a subject, relative to the serum half-life obtained following administration of ganaxolone itself, e.g., by the same route of administration and at an equivalent dosage.

[0048] For example, administering a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) orally may achieve a higher ganaxolone C_{max} , relative to administering an equivalent amount of ganaxolone orally. Administering a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) orally may achieve a higher ganaxolone AUC, relative to administering an equivalent amount of ganaxolone orally. Alternatively, administering a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) intravenously may achieve a higher ganaxolone C_{max} , relative to administering an equivalent amount of ganaxolone intravenously. Administering a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) intravenously may achieve a higher ganaxolone AUC, relative to administering an equivalent amount of ganaxolone intravenously.

[0049] Also disclosed herein are pharmaceutical compositions comprising a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1) and a pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable excipient disclosed herein).

[0050] Also disclosed herein are methods of using a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1). For example, disclosed herein are methods of treating a disease or disorder in a subject, comprising administering a compound disclosed herein, or a pharmaceutical composition disclosed herein, to a subject in need thereof.

[0051] For example, the method of treating a disease or disorder in a subject may comprise administering a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1, to a subject in need thereof. The method of treating a disease or disorder in a subject may comprise administering a composition comprising a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1, and a pharmaceutically acceptable excipient, to a subject in need thereof. The compound or composition may be administered by any suitable route of administration, e.g., a route of administration disclosed herein, such as by oral administration, or by intravenous administration..

[0052] Also disclosed herein are compositions for use in treating a disease or disorder in a subject, comprising a therapeutically effective amount of a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1.

[0053] In other aspects, the present disclosure relates to a use of a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound of Table 1), or use of a pharmaceutical composition disclosed herein, for the production of a medicament effective for treating a disease or disorder in a subject.

[0054] The disease or disorder treated by a method, compound, composition, or medicament disclosed herein may be any suitable disease or disorder, such as a disease or disorder described herein. For example, the disease or disorder may be a neurological disorder. The disease or disorder may be a seizure disorder, epilepsy disorder, genetic epilepsy disorder, epilepsy-related disorder, central nervous system disorder, neurological disorder, or a neurodegenerative disorder. The disease or disorder may be status epilepticus (SE). The disease or disorder may be CDKL5 Deficiency Disorder. The disease or disorder may be Tuberous Sclerosis Complex. The disease or disorder may be PCDH19-related epilepsy. The disease or disorder may be Lennox-Gastaut syndrome (LGS).

BRIEF DESCRIPTION OF THE DRAWINGS

[0055] **FIGS. 1A-1B** depict the pharmacokinetics of an exemplary ganaxolone prodrug disclosed herein in a dog model. **FIG. 1A** is a graph depicting the mean plasma concentration of

Compound 111 (ng/mL) over time (h) following either intravenous (5 mg/kg) or oral (25 mg/kg) administration of Compound 111 (with vehicle) in a dog model. **FIG. 1B** is a graph depicting the mean plasma concentration of ganaxolone (ng/mL) over time (h) following either intravenous (5 mg/kg) or oral (25 mg/kg) administration of Compound 111 (with vehicle) in a dog model.

[0056] FIGS. 2A-2B depict the pharmacokinetics of an intravenous (IV) dose of an exemplary ganaxolone prodrug disclosed herein in a dog model. **FIG. 2A** is a graph depicting the mean plasma concentration (ng/mL) of ganaxolone (GNX) and Compound 224 over 8 hours following intravenous (2 mg/kg; bolus) administration of Compound 224 (with vehicle) in a dog model. **FIG. 2B** is a graph depicting the same pharmacokinetic study following IV administration of Compound 224, with a compressed x axis (0-1 hours).

[0057] FIGS. 3A-3B depict the pharmacokinetics of an oral (PO) dose of an exemplary ganaxolone prodrug disclosed herein in a dog model. **FIG. 3A** is a graph depicting the mean plasma concentration (ng/mL) of ganaxolone (GNX) and Compound 224 over 36 hours following oral (10 mg/kg; bolus) administration of Compound 224 (with vehicle) in a dog model. **FIG. 3B** is a graph depicting the same pharmacokinetic study following PO administration of Compound 224, with a compressed x axis (over 0-4 hours).

[0058] FIGS. 4A-4B depict the pharmacokinetics of an exemplary ganaxolone prodrug disclosed herein in a dog model. **FIG. 4A** is a graph depicting the mean plasma concentration of Compound 218 (ng/mL) over time (h) following either intravenous (5 mg/kg) or oral (25 mg/kg) administration of Compound 218 (with vehicle) in a dog model. **FIG. 4B** is a graph depicting the mean plasma concentration of ganaxolone (ng/mL) over time (h) following either intravenous (5 mg/kg) or oral (25 mg/kg) administration of Compound 218 (with vehicle) in a dog model.

DETAILED DESCRIPTION

[0059] This disclosure relates to ganaxolone derivatives. The compounds disclosed herein can be metabolized to ganaxolone (*e.g., in vivo*), and may be referred to as ganaxolone prodrugs. Also disclosed herein are methods of using the compounds, methods of making the compounds, and pharmaceutical compositions and kits comprising the same.

[0060] Ganaxolone may be used for modulation of GABA_A, which provides the ability to treat neurological disorders including seizures and epilepsy, among other disorders disclosed herein. However, due to the poor aqueous solubility and low oral bioavailability of ganaxolone,

administering therapeutically effective amounts of ganaxolone is best achieved through intravenous infusion or through oral formulations of ganaxolone, such as aqueous suspensions, that require frequent administration and/or that a large amount of the formulation be administered. The compounds disclosed herein can address this shortcoming of ganaxolone, as they have greater aqueous solubility and bioavailability compared to ganaxolone, and can be metabolized to ganaxolone after administration (e.g., oral administration). Without wishing to be bound by theory, it is believed that the greater oral bioavailability of the compounds, relative to ganaxolone, allows for the compound to be readily absorbed from the gut into the bloodstream, and the compounds are subsequently converted to ganaxolone (e.g., by metabolic processes) to achieve therapeutic concentrations of ganaxolone in the bloodstream and/or in the central nervous system (CNS).

[0061] Accordingly, this disclosure relates to compounds that comprise a ganaxolone moiety that is modified at the hydroxyl group by a cleavable moiety, e.g., an enzymatically cleavable moiety. For example, the cleavable moiety may be cleavable by an enzyme (e.g., an esterase) or through other mechanisms (e.g., direct chemical mechanisms). For example, following administration of a compound disclosed herein, the cleavable moiety may be cleaved (e.g., enzymatically) to provide ganaxolone. Compounds or compositions of the present disclosure may be administered, without limitation, orally, subcutaneously, intramuscularly, intravenously, intradermally, by inhalation, topically, rectally, nasally, buccally, vaginally, or by an implanted reservoir. In preferred embodiments, the compounds or compositions of the present disclosure are suitable for oral administration. In other preferred embodiments, the compounds or compositions of the present disclosure are suitable for intravenous administration. The disclosure also relates to methods for treating a neurological disorder, such as epilepsy or seizures. The methods disclosed herein can comprise orally administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein. Alternatively, the methods disclosed herein can comprise intravenously administering to a subject in need thereof a therapeutically effective amount of a compound disclosed herein.

Definitions

[0062] All publications (e.g., scientific journal articles, patent publications, and the like) cited in this disclosure are incorporated by reference in their entirety. To the extent the material

incorporated by reference contradicts or is inconsistent with this specification, the specification will supersede any such material. The citation of any references herein is not an admission that such references are prior art to the present disclosure. Various terms relating to aspects of the description are used throughout the specification and claims. Such terms are to be given their ordinary meaning in the art unless otherwise indicated. Other specifically defined terms are to be construed in a manner consistent with the definitions provided herein.

[0063] As used herein, the term “alkyl” refers to a radical of a saturated hydrocarbon group having 1 to 18 carbon atoms (C₁₋₁₈-alkyl), such as 1 to about 12 carbon atoms (C₁₋₁₂-alkyl), or 1 to about 6 carbon atoms (C₁₋₆-alkyl). An alkyl group can be straight chain or branched chain hydrocarbon group. Examples of alkyl groups include methyl, ethyl, propyl, isopropyl, butyl, *iso*-butyl, *sec*-butyl, *tert*-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, norbornyl, and the like. Throughout this disclosure, abbreviations that are well known in the art to describe various alkyl groups or their derivatives may be used, such as Me (methyl), Et (ethyl), Pr (propyl) including iPr (isopropyl), Bu (butyl) including tBu (tert-butyl), Bn (benzyl). Each instance of an alkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkyl”) or substituted (a “substituted alkyl”) with one or more substituents e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0064] As used herein, the term “alkenyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 18 carbon atoms, one or more carbon-carbon double bonds, and no triple bonds. For example, an alkenyl group may have 2 to 8 carbon atoms (C₂₋₈-alkenyl), 2 to 6 carbon atoms (C₂₋₆-alkenyl), 2 to 5 carbon atoms (C₂₋₅-alkenyl), 2 to 4 carbon atoms (C₂₋₄-alkenyl), or 2 to 3 carbon atoms (C₂₋₃-alkenyl). The one or more carbon-carbon double bonds can be internal (such as in 2-butenyl) or terminal (such as in 1-butenyl). Examples of alkenyl groups include ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, butadienyl, pentenyl, pentadienyl, hexenyl, heptenyl, octenyl, octatrienyl, and the like. Each instance of an alkenyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkenyl”) or substituted (a “substituted alkenyl”) with one or more substituents, e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0065] As used herein, the term “alkynyl” refers to a radical of a straight-chain or branched hydrocarbon group having from 2 to 18 carbon atoms, and one or more carbon-carbon triple bonds. The alkynyl group may have 2 to 8 carbon atoms (C₂₋₈-alkynyl), 2 to 6 carbon atoms (C₂₋₆-alkynyl), or 2 to 4 carbon atoms (C₂₋₄-alkynyl).

6-alkynyl), 2 to 5 carbon atoms (C₂₋₅-alkynyl), 2 to 4 carbon atoms (C₂₋₄-alkynyl), or 2 to 3 carbon atoms (C₂₋₃-alkynyl). The one or more carbon-carbon triple bonds can be internal (such as in 2-butyne) or terminal (such as in 1-butyne). Examples of alkynyl groups include ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, and the like. Each instance of an alkynyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted alkynyl”) or substituted (a “substituted alkynyl”) with one or more substituents, e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent

[0066] As used herein, the term “heteroalkyl” refers to a non-cyclic stable straight or branched chain, or combinations thereof, including at least one carbon atom and at least one heteroatom selected from the group consisting of O, N, P, Si, and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized, and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N, P, S, and Si may be placed at any position of the heteroalkyl group. Where “heteroalkyl” is recited, followed by recitations of specific heteroalkyl groups, such as –(CH₂)–C(O)–OH, –N(R^{G1})(R^{G2}), or the like, it will be understood that the terms heteroalkyl and –(CH₂)–C(O)–OH, –N(R^{G1})(R^{G2}) are not redundant or mutually exclusive. Rather, the specific heteroalkyl groups are recited to add clarity. Thus, the term “heteroalkyl” should not be interpreted herein as excluding specific heteroalkyl groups, such as –(CH₂)–C(O)–OH, –N(R^{G1})(R^{G2}), or the like. Each instance of a heteroalkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted heteroalkyl”) or substituted (a “substituted heteroalkyl”) with one or more substituents, e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0067] As used herein, the term “haloalkyl” refers to a non-cyclic straight or branched chain, or combinations thereof, including at least one carbon atom and at least one halogen (e.g., F, Cl, Br, and I). The halogen atom(s) may be placed at any position of the haloalkyl group. Exemplary haloalkyl groups include, but are not limited to: –CF₃, –CCl₃, –CH₂–CF₃, –CH₂–CCl₃, –CH₂–Cl, and –CH₂–I. Each instance of a haloalkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted haloalkyl”) or substituted (a “substituted haloalkyl”) with one or more substituents, e.g., for instance from 1 to 5 substituents, 1 to 3 substituents, or 1 substituent.

[0068] As used herein, the term “alkoxy” refers to a group of formula –O–alkyl. The term “alkoxy” or “alkoxy” includes substituted and unsubstituted alkyl, alkenyl and alkynyl groups

covalently linked to an oxygen atom. Examples of alkoxy groups or alkoxy radicals include, but are not limited to, methoxy, ethoxy, isopropoxy, propoxy, butoxy, and pentoxy groups. Examples of substituted alkoxy groups include halogenated alkoxy groups. The alkoxy groups can be substituted with groups such as alkenyl, alkynyl, halogen, hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino, and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfates, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, nitro, trifluoromethyl, cyano, azido, heterocyclyl, alkylaryl, or an aromatic or heteroaromatic moieties. Examples of halogen substituted alkoxy groups include, but are not limited to, fluoromethoxy, difluoromethoxy, trifluoromethoxy, chloromethoxy, dichloromethoxy and trichloromethoxy.

[0069] As used herein, the term “aryl,” refers to stable aromatic ring system, that may be monocyclic or polycyclic, of which all the ring atoms are carbon, and which may be substituted or unsubstituted. The aromatic ring system may have, for example, 3-7 ring atoms. Examples include phenyl (Ph), naphthyl, anthracyl, and the like. Each instance of an aryl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted aryl”) or substituted (a “substituted aryl”) with one or more substituents.

[0070] As used herein, the term “heteroaryl” refers to an aryl group that includes one or more ring heteroatoms. For example, a heteroaryl can include a stable 5-, 6-, or 7-membered monocyclic or 7-, 8-, or 9-membered bicyclic aromatic heterocyclic ring which consists of carbon atoms, and one or more heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur. The nitrogen atom may be substituted or unsubstituted (e.g., N or NR” wherein R” is H or another substituent, as defined). Examples of heteroaryl groups include pyrrole, furan, indole, thiophene, thiazole, isothiazole, imidazole, triazole, tetrazole, pyrazole, oxazole, isoxazole, pyridine, pyrazine, pyridazine, pyrimidine, and the like.

[0071] As used herein, the term “cycloalkyl” refers to a radical of a non-aromatic cyclic hydrocarbon group having from three to ten carbon atoms in the cyclic structure, and zero heteroatoms in the non-aromatic cyclic structure. Cycloalkyl can include cyclobutyl,

cyclopropyl, cyclopentyl, cyclohexyl and the like. The cycloalkyl group can be either monocyclic (“monocyclic cycloalkyl”) or contain a fused, bridged or spiro ring system such as a bicyclic system (“bicyclic cycloalkyl”) and can be saturated or can be partially unsaturated. “Cycloalkyl” also includes ring systems wherein the cycloalkyl ring, as defined above, is fused with one or more aryl groups wherein the point of attachment is on the cycloalkyl ring, and in such instances, the number of carbons continue to designate the number of carbons in the cycloalkyl ring system. Each instance of a cycloalkyl group may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted cycloalkyl”) or substituted (a “substituted cycloalkyl”) with one or more substituents.

[0072] As used herein, the term “heterocyclyl” refers to a radical of a 3- to 10-membered non-aromatic cyclic structure comprising atoms of at least two different elements in the ring or rings (i.e., a radical of a heterocyclic ring). The heteroatom may be selected from nitrogen, oxygen, sulfur, boron, phosphorous, and silicon. In heterocyclyl groups that contain one or more nitrogen atoms, the point of attachment can be a carbon or nitrogen atom, as valency permits. A heterocyclyl group can be either monocyclic (“monocyclic heterocyclyl”) or a fused, bridged, or spiro ring system such as a bicyclic system (“bicyclic heterocyclyl”), and can be saturated or can be partially unsaturated. Heterocyclyl bicyclic ring systems can include one or more heteroatoms in one or both rings. “Heterocyclyl” also includes ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more cycloalkyl groups wherein the point of attachment is either on the cycloalkyl or heterocyclyl ring, or ring systems wherein the heterocyclyl ring, as defined above, is fused with one or more aryl or heteroaryl groups, wherein the point of attachment is on the heterocyclyl ring, and in such instances, the number of ring members continue to designate the number of ring members in the heterocyclyl ring system. Each instance of heterocyclyl may be independently optionally substituted, i.e., unsubstituted (an “unsubstituted heterocyclyl”) or substituted (a “substituted heterocyclyl”) with one or more substituents. Additional reference is made to: Oxford Dictionary of Biochemistry and Molecular Biology, Oxford University Press, Oxford, 1997 as evidence that heterocyclic ring is a term well-established in field of organic chemistry.

[0073] The terms “alkylene,” “alkenylene,” “alkynylene,” or “heteroalkylene,” alone or as part of another substituent, mean, unless otherwise stated, a divalent radical derived from an alkyl, alkenyl, alkynyl, or heteroalkyl, respectively. For instance, the term “alkenylene,” by itself or as

part of another substituent, means, unless otherwise stated, a divalent radical derived from an alkene. In the case of heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (e.g., alkyleneoxy, alkyleneedioxy, alkyleneamino, alkylene-diamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied by the direction in which the formula of the linking group is written. For example, the formula $-C(O)_2R'$ may represent both $-C(O)_2R'$ and $-R'C(O)_2-$. Each instance of an alkylene, alkenylene, alkynylene, or heteroalkylene group may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted alkylene”) or substituted (a “substituted heteroalkylene”) with one or more substituents.

[0074] As used herein, the terms “cycloalkylene,” “heterocyclylene,” “arylene,” and “heteroarylene,” alone or as part of another substituent, mean a divalent radical derived from a cycloalkyl, heterocyclyl, aryl, and heteroaryl, respectively. Each instance of a cycloalkylene, heterocyclylene, arylene, or heteroarylene may be independently optionally substituted, *i.e.*, unsubstituted (an “unsubstituted arylene”) or substituted (a “substituted heteroarylene”) with one or more substituents.

[0075] As used herein, the term “dipeptide” refers to a moiety that is composed of two amino acid residues. For example, a dipeptide disclosed herein may be leucine-leucine (Leu-Leu), glycine-alanine (Gly-Ala), glycine-valine (Gly-Val). The dipeptide may be substituted or modified at either amino acid residue, or both, for example to attach the dipeptide at a C-terminus or N-terminus, or both, to another group or atom. For example, a compound disclosed herein may comprise a dipeptide that has a free N-terminus (*i.e.*, $-NH_2$), and a C-terminus that is modified to form an ester group, or a compound disclosed herein may comprise a dipeptide that has an N-terminus modified to form a carbamate group, and a C-terminus that is modified to form an ester group.

[0076] As used herein, the term “cyano” or “ $-CN$ ” refer to a substituent having a carbon atom joined to a nitrogen atom by a triple bond, *e.g.*, $C\equiv N$.

[0077] As used herein, the term “halo” or “halogen” refers to F, Cl, Br, or I.

[0078] As used herein, the term “hydroxy” refers to a group of formula $-OH$.

[0079] As used herein, the term “nitro” refers to a substituent having two oxygen atoms bound to a nitrogen atom, *e.g.*, $-NO_2$.

[0080] As used herein, the term “oxo” refers to an oxygen group which is double bonded to another atom, e.g., carbon. For example, “oxo” refers to the =O in a carbonyl group (C=O). Oxo may be used in reference to a compound that is substituted with a double bonded oxygen, for example “oxo” may be used to refer to the oxygen substituent in $-\text{CH}_2\text{-C(O)-CH}_3$.

[0081] As used herein, the term “substituted” in reference to a substituted alkyl, substituted alkylene, substituted alkenyl, substituted alkenylene, substituted alkynyl, substituted alkynylene, substituted heteroalkyl, substituted heteroalkylene, substituted heteroalkenyl, substituted heteroalkenylene, substituted heteroalkynyl, substituted heteroalkynylene, substituted cycloalkyl, substituted cycloalkylene, substituted heterocyclyl, substituted heterocyclylene, substituted aryl, substituted arylene, substituted heteroaryl, substituted heteroarylene, and the like, refers to alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, heteroalkenyl, heteroalkenylene, heteroalkynyl, heteroalkynylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, arylene, heteroaryl, heteroarylene moieties, and the like, respectively, having substituents replacing one or more hydrogen atoms on one or more carbons or heteroatoms of the moiety. In general, the term “substituted” means that at least one hydrogen present on a group (e.g., a hydrogen bonded to carbon or nitrogen atom of said group) is replaced with a suitable substituent, such as a substituent described herein. Such substituents can be any suitable substituent including, for example, alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{I}$, $-(\text{CH}_2)_2\text{Cl}$, $-(\text{CH}_2)_2\text{I}$, or $-\text{CF}_3$), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., $-\text{F}$, $-\text{Cl}$, $-\text{Br}$, or $-\text{I}$), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., $-\text{OMe}$, $-\text{OEt}$, or $-\text{OBn}$), alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., $-\text{NH}_2$, $-\text{NHMe}$, or $-\text{NMe}_2$), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl,

cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, $-C(O)OH$, $-C(O)O$ -alkyl (e.g., $-C(O)O$ -tBu or $-C(O)OMe$), $-C(O)O$ -heteroalkyl, $-C(O)O$ -alkylaryl, $-OC(O)O$ -alkyl, $-OC(O)O$ -heteroalkyl, $-OC(O)O$ -alkylaryl, $-C(O)NH_2$, $-C(O)NH$ -alkyl, $-C(O)NH$ -heteroalkyl, $-C(O)NH$ -alkylaryl, $-NHC(O)O$ -alkyl (e.g., $-NHC(O)OtBu$), $-NHC(O)O$ -heteroalkyl, $-NHC(O)O$ -alkylaryl (e.g., $-NH$ -Cbz), $-C(O)N(alkyl)_2$, $-C(O)N(alkyl)(heteroalkyl)$, $-C(O)N(heteroalkyl)_2$, $-N(alkyl)C(O)O$ -alkyl (e.g., $N(Me)C(O)OtBu$), $-N(alkyl)C(O)O$ -heteroalkyl, $-N(alkyl)C(O)O$ -alkylaryl, $-N(alkyl)C(O)N(alkyl)_2$, $-N(alkyl)C(O)N(alkyl)(heteroalkyl)$, $-N(alkyl)C(O)N(heteroalkyl)_2$, $-N(alkyl)C(O)NH$ -alkylaryl, $=NH$, or $=N$ -alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0082] As used herein, the term “protecting group” refers to a group that acts to temporarily block a particular functional moiety, e.g., O, S, or N, so that a reaction can be carried out selectively at another reactive site in a multifunctional compound. It will be appreciated by one of ordinary skill in the art that the synthetic methods and compounds described herein may utilize a variety of protecting groups. Protecting groups may be introduced and removed at appropriate stages during the synthesis of a compound using methods that are known to one of ordinary skill in the art. The protecting groups are applied according to standard methods of organic synthesis as described in the literature (Theodora W. Greene and Peter G. M. Wuts (2007) *Protecting Groups in Organic Synthesis*, 4th edition, John Wiley and Sons, incorporated by reference in its entirety).

[0083] Exemplary protecting groups include, but are not limited to, oxygen, sulfur, nitrogen and carbon protecting groups. For example, oxygen protecting groups include, but are not limited to, methyl ethers, substituted methyl ethers (e.g., MOM (methoxymethyl ether), MTM (methylthiomethyl ether), BOM (benzyloxymethyl ether), PMB (p-methoxybenzyl ether), optionally substituted ethyl ethers, optionally substituted benzyl ethers, silyl ethers (e.g., TMS (trimethylsilyl ether), TES (triethylsilyl ether), TIPS (triisopropylsilyl ether), TBDMS (t-butyl dimethylsilyl ether), tribenzyl silyl ether, TBDPS (t-butyl diphenyl silyl ether), esters (e.g., formate, acetate, benzoate (Bz), trifluoroacetate, dichloroacetate) carbonates, cyclic acetals and ketals. In addition, nitrogen or amino protecting groups include, but are not limited to, carbamates (including methyl, ethyl and substituted ethyl carbamates (e.g., Boc or Troc), amides,

cyclic imide derivatives, N-Alkyl and N-Aryl amines, imine derivatives, and enamine derivatives, etc. Amino protecting groups include, but are not limited to fluorenylmethyloxycarbonyl (Fmoc), tert-butyloxycarbonyl (Boc), carboxybenzyl (Cbz), acetamide, trifluoroacetamide, etc. Certain other exemplary protecting groups are detailed herein, however, it will be appreciated that the present disclosure is not intended to be limited to these protecting groups; rather, a variety of additional equivalent protecting groups may be utilized according to methods known to one skilled in the art.

[0084] The compounds provided herein may exist in one or more particular geometric, optical, enantiomeric, diastereomeric, epimeric, stereoisomeric, tautomeric, conformational, or anomeric forms, including but not limited to: cis- and trans- forms; E- and Z-forms; endo- and exo- forms; R-, S-, and meso-forms; D- and L-forms; d- and l- forms; (+) and (-) forms; keto-, enol-, and enolate-forms; syn- and anti-forms; synclinal- and anticlinal-forms; α - and β -forms; axial and equatorial forms; boat-, chair-, twist-, envelope- and half chair-forms; and combinations thereof, hereinafter collectively referred to as “isomers” (or “isomeric forms”).

[0085] Compounds described herein may comprise one or more asymmetric centers, and thus can exist in various isomeric forms, e.g., enantiomers and/or diastereomers. For example, the compounds described herein can be in the form of an individual enantiomer, diastereomer, or geometric isomer, or can be in the form of a mixture of stereoisomers, including racemic mixtures and mixtures enriched in one or more stereoisomer. In an embodiment, the stereochemistry depicted in a compound is relative rather than absolute. Isomers can be isolated from mixtures by methods known to those skilled in the art, including chiral high-pressure liquid chromatography (HPLC) and the formation and crystallization of chiral salts; or preferred isomers can be prepared by asymmetric syntheses. This disclosure additionally encompasses compounds described herein as individual isomers substantially free of other isomers, and alternatively, as mixtures of various isomers.

[0086] As used herein, a pure enantiomeric compound is substantially free from other enantiomers or stereoisomers of the compound (i.e., in enantiomeric excess). In other words, an “S” form of the compound is substantially free of the “R” form of the compound, and is thus, in enantiomeric excess of the “R” form. Or, using another notation, the (+) form of a compound is substantially free of the (-) form of the compound, and is thus, in enantiomeric excess of the (-) form. The term “enantiomerically pure,” or “enantiopure,” or “pure enantiomer” denotes that the

compound comprises more than 75 wt%, more than 80 wt%, more than 85 wt%, more than 90 wt%, more than 91 wt%, more than 92 wt%, more than 93 wt%, more than 94 wt%, more than 95 wt%, more than 96 wt%, more than 97 wt%, more than 98 wt%, more than 99 wt%, more than 99.5 wt%, more than 99.9 wt%, or more, of the enantiomer. The weights may be based upon total weight of all enantiomers or stereoisomers of the compound.

[0087] Enantiomerically pure compounds disclosed herein may be present with other active or inactive components. For example, a pharmaceutical composition comprising an enantiomerically pure R-compound can comprise, for example, about 90% excipient and about 10% enantiomerically pure R-compound. A diastereomerically pure compound disclosed herein can also be present with other active or inactive components. For example, a pharmaceutical composition comprising a diastereomerically pure exo compound can comprise, for example, about 90% excipient and about 10% diastereomerically pure exo compound.

[0088] The active ingredient of a composition disclosed herein can be formulated with little or no excipient or carrier.

[0089] Compounds disclosed herein may also comprise one or more isotopic substitutions. For example, H may be in any isotopic form, including ^1H , ^2H (D or deuterium), ^3H (T or tritium); C may be in any isotopic form, including ^{12}C , ^{13}C , and ^{14}C ; O may be in any isotopic form, including ^{16}O and ^{18}O ; N may be in any isotopic form, including ^{14}N and ^{15}N ; F may be in any isotopic form, including ^{18}F , ^{19}F , and the like.

[0090] The term “pharmaceutically acceptable salt” as used herein refers to a salts of the compound prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the respective compound. When compounds of the present disclosure contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired base, either neat or in a suitable solvent (e.g., an inert solvent). Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable solvent (e.g., an inert solvent). Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic,

phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from organic acids like acetic, propionic, isobutyric, maleic, malonic, benzoic, succinic, suberic, fumaric, lactic, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galacturonic acids and the like. Certain compounds of the present disclosure can contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts. These salts may be prepared by methods known to those skilled in the art. Other pharmaceutically acceptable carriers known to those of skill in the art are suitable for the present invention.

[0091] The term “solvate” as used herein refers to forms of a compound that are associated with a solvent, usually by a solvolysis reaction. This physical association may include hydrogen bonding. Conventional solvents include water, methanol, ethanol, acetic acid, dimethylsulfoxide (DMSO), tetrahydrofuran (THF), diethyl ether, and the like. Compounds of the present disclosure may be prepared, *e.g.*, in crystalline form, and may be solvated. Suitable solvates include pharmaceutically acceptable solvates and further include both stoichiometric solvates and non-stoichiometric solvates. In certain instances, the solvate will be capable of isolation, for example, when one or more solvent molecules are incorporated in the crystal lattice of a crystalline solid. “Solvate” encompasses both solution-phase and isolable solvates.

Representative solvates include hydrates, ethanolates, and methanolates.

[0092] The term “hydrate” as used herein refers to a compound which is associated with water. Typically, the number of the water molecules contained in a hydrate of a compound is in a definite ratio to the number of the compound molecules in the hydrate. Therefore, a hydrate of a compound may be represented, for example, by the general formula $R \cdot xH_2O$, wherein R is the compound and wherein x is a number greater than 0. A given compound may form more than one type of hydrates, including, *e.g.*, monohydrates (x is 1), lower hydrates (x is a number greater than 0 and smaller than 1, *e.g.*, hemihydrates ($R \cdot 0.5H_2O$)), and polyhydrates (x is a number greater than 1, *e.g.*, dihydrates ($R \cdot 2H_2O$) and hexahydrates ($R \cdot 6H_2O$)).

[0093] The term “tautomer” as used herein refers to compounds that are interchangeable forms of a particular compound structure, and that vary in the displacement of hydrogen atoms and electrons. Thus, two structures may be in equilibrium through the movement of π electrons and

an atom (usually H). For example, enols and ketones are tautomers because they are rapidly interconverted by treatment with either acid or base. Another example of tautomerism is the aci- and nitro- forms of phenylnitromethane that are likewise formed by treatment with acid or base. Tautomeric forms may be relevant to the attainment of the optimal chemical reactivity and biological activity of a compound of interest.

Other Definitions

[0094] The articles “a” and “an” are used herein to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, “an element” means one element or more than one element.

[0095] The term “about” when referring to a measurable value such as an amount, a temporal duration, and the like, is meant to encompass variations of $\pm 20\%$ or less, or in some instances $\pm 15\%$ or less, or in some instances $\pm 10\%$ or less, or in some instances $\pm 5\%$ or less, or in some instances $\pm 1\%$ or less, or in some instances $\pm 0.1\%$ or less, from the specified value, as such variations are appropriate, e.g., to perform the disclosed methods.

[0096] The phrase “and/or” as used herein should be understood to mean “either or both” of the elements so conjoined, i.e., elements that are conjunctively present in some cases and disjunctively present in other cases. Multiple elements listed with “and/or” should be construed in the same fashion, i.e., “one or more” of the elements so conjoined. Other elements may optionally be present other than the elements specifically identified by the “and/or” clause, whether related or unrelated to those elements specifically identified. Thus, as a non-limiting example, a reference to “A and/or B,” when used in conjunction with open-ended language such as “comprising” can refer, in one embodiment, to A only (optionally including elements other than B); in another embodiment, to B only (optionally including elements other than A); in yet another embodiment, to both A and B (optionally including other elements); etc.

[0097] The term “effective amount” as used herein refers to an amount of a compound, or a composition or formulation of the compound, described herein (e.g., a ganaxolone derivative or prodrug, or pharmaceutical composition thereof), which is sufficient to achieve a desired result under the conditions of administration. For example, an effective amount of a compound disclosed herein, or a composition or formulation of the compound, for the treatment of an epilepsy disorder is an amount that can manage seizure activity, suppress seizure, allow the patient to recover from a hyperexcitable state, prevent seizure-relapse, or can provide continued

suppression of seizure. A skilled clinician can determine appropriate dosing based on a variety of considerations including the severity of the disorder, the subject's age, weight, general health and other considerations. Typically compounds are administered in an amount of about 0.01 mg to about 1800 mg.

[0098] As used herein, the term “pharmaceutical compositions” are compositions comprising at least one active agent (which may be any compound disclosed herein or a pharmaceutically acceptable salt, solvate, or hydrate thereof, such as any ganaxolone derivative or prodrug disclosed herein) and at least one other substance, such as an excipient (e.g., a pharmaceutically acceptable excipient). Pharmaceutical compositions optionally contain one or more additional active agents. When specified, pharmaceutical compositions meet the U.S. FDA's GMP (good manufacturing practice) standards for human or non-human drugs. “Pharmaceutical combinations” are combinations of at least two active agents which may be combined in a single dosage form or provided together in separate dosage forms with instructions that the active agents are to be used together to treat a disorder, such as a neurological disorder, e.g., a seizure disorder, an epilepsy disorder, a genetic epilepsy disorder, an epilepsy-related disorder, a central nervous system disorder, a neurological disorder, or a neurodegenerative disorder, such as status epilepticus, CDKL5 Deficiency Disorder, Tuberous Sclerosis Complex, PCDH19-related epilepsy, or Lennox-Gastaut syndrome (LGS).

[0099] The term “pharmaceutically acceptable excipient” as used herein refers to a non-toxic material that may be formulated with a compound disclosed herein to provide a pharmaceutical composition. Preferably, the pharmaceutically acceptable excipient is inert and does not interfere with the pharmacological activity of a compound which it is formulated with. Pharmaceutically acceptable excipients useful in the manufacture of the pharmaceutical compositions disclosed herein are any of those well known in the art, and include without limitation, diluents, dispersing agents, granulating agents, surface active agents, emulsifiers, disintegrating agents, binding agents, preservatives, buffering agents, lubricating agents, ion exchangers, salts, electrolytes, waxes, and/or oils. For example, a pharmaceutically acceptable excipient may be alumina, aluminum stearate, lecithin, a serum protein (e.g., human serum albumin), a phosphate, glycine, sorbic acid, potassium sorbate, a glyceride mixture (e.g., saturated vegetable fatty acids), water, protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, a zinc salt, colloidal silica, magnesium

trisilicate, polyvinyl pyrrolidone, cellulose or a derivative thereof, polyethylene glycol or a derivative thereof (e.g., PEG-300), sodium carboxymethylcellulose, a polyacrylate, a polyethylene-polyoxypropylene-block polymer, wool fat, a cyclodextrin (e.g., CAPTISOL[®]), dimethylacetamide (DMA), a polysorbate (e.g., a TWEEN[®], e.g., TWEEN-20[®]), or a combination thereof.

[0100] The term “subject” as used herein refers to any animal, such as any mammal, including but not limited to, humans, non-human primates, rodents, and the like. Non-human primates include chimpanzees, cynomolgus monkeys, spider monkeys, and macaques (e.g., Rhesus). Rodents include mice, rats, woodchucks, ferrets, rabbits, and hamsters. Domestic and game animals include cows, horses, pigs, deer, bison, buffalo, feline species (e.g., domestic cat), canine species (e.g., dog, fox, wolf), avian species, and fish. In some embodiments, the subject is a mammal (e.g., a human, a rat, or a mouse). The subject can be male or female. The subject may be of any age, including an elderly human subject (e.g., 65 years or older), a human subject that is not elderly (e.g., less than 65 years old), or a human pediatric subject (e.g., 18 years old or less). In some embodiments, the subject is a human.

[0101] As used herein, the terms “treat,” “treatment,” “treating,” or grammatically related terms, refer to a method of reducing the effects of a disease or disorder. As is readily appreciated in the art, full eradication of the disease, disorder, or symptoms thereof is preferred but not a requirement for treatment. Desirable effects of treatment include, but are not limited to, preventing occurrence or recurrence of the disease or disorder, alleviation of symptoms, diminishment of any direct or indirect pathological consequences of the disease or disorder, or other improvement of any sign, symptom, or consequence of the disease or disorder, such as prolonged survival, less morbidity, and/or a lessening of side effects.

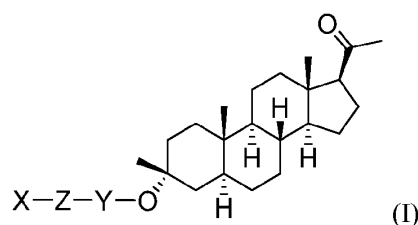
[0102] Throughout this disclosure, various embodiments can be presented in a range format. It should be understood that the description in range format is merely for convenience and brevity and should not be construed as an inflexible limitation on the scope of the invention. Accordingly, the description of a range should be considered to have specifically disclosed all the possible subranges as well as individual numerical values within that range. For example, description of a range such as from 1 to 6 should be considered to have specifically disclosed subranges such as from 1 to 5, from 1 to 4, from 1 to 3, from 2 to 6, from 2 to 4, from 3 to 6, etc., as well as individual numbers within that range, e.g., 1, 2, 2.8, 3, 3.6, 4, 5, 5.4, and 6. As another

example, a range such as 95-99% includes 95%, 96%, 97%, 98%, or 99% and all subranges such as 96-99%, 96-98%, 96-97%, 97-99%, 97-98%, etc. This applies regardless of the breadth of the range.

[0103] Various embodiments of the compounds, compositions, kits, and methods herein are described in further detail below, and additional definitions may be provided throughout the specification.

Compounds

[0104] The compounds disclosed herein may comprise a structure of Formula (I):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

Y is $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^{\text{A}})(\text{R}^{\text{B}})-$ (e.g., $-\text{CH}_2-$);

Z is absent, alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, $-\text{NR}^1-$, $-\text{O}-$, or $-\text{S}-$, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

X is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, heterocyclylene-heteroalkyl, $-\text{OC}(\text{O})$ -alkyl, $-\text{C}(\text{O})\text{O}$ -alkyl, $-\text{OC}(\text{O})$ -heteroalkyl, $-\text{C}(\text{O})\text{O}$ -heteroalkyl, $-\text{N}_3$, $-\text{NR}^1\text{R}^2$, $-\text{OR}^3$, or $-\text{SR}^4$, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl,

heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R¹ and R², together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R³ is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R⁴ is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

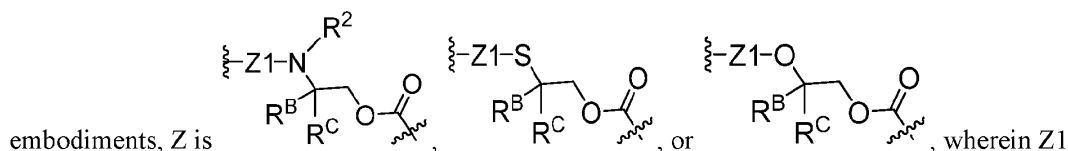
R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0105] Each optional substituent of a group in Formula (I) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidyl, or N-Boc-azetidyl), alkylaryl (e.g., benzyl), aryl (e.g., phenyl),

heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., methoxy (-OMe), ethoxy (-OEt), or benzyloxy (-OBn)), alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, -C(O)OH, -C(O)O-alkyl (e.g., -C(O)O-tBu or -C(O)OMe), -C(O)O-heteroalkyl, -C(O)O-alkylaryl, -OC(O)O-alkyl, -OC(O)O-heteroalkyl, -OC(O)O-alkylaryl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)NH-heteroalkyl, -C(O)NH-alkylaryl, -NHC(O)O-alkyl (e.g., -NHC(O)OtBu), -NHC(O)O-heteroalkyl, -NHC(O)O-alkylaryl (e.g., -NH-Cbz), -C(O)N(alkyl)₂, -C(O)N(alkyl)(heteroalkyl), -C(O)N(heteroalkyl)₂, -N(alkyl)C(O)O-alkyl (e.g., N(Me)C(O)OtBu), -N(alkyl)C(O)O-heteroalkyl, -N(alkyl)C(O)O-alkylaryl, -N(alkyl)C(O)N(alkyl)₂, -N(alkyl)C(O)N(alkyl)(heteroalkyl), -N(alkyl)C(O)N(heteroalkyl)₂, -N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

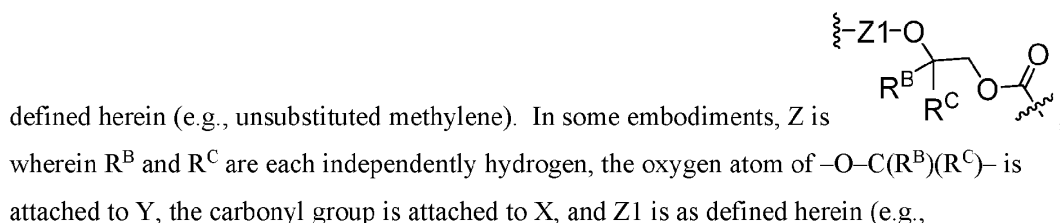
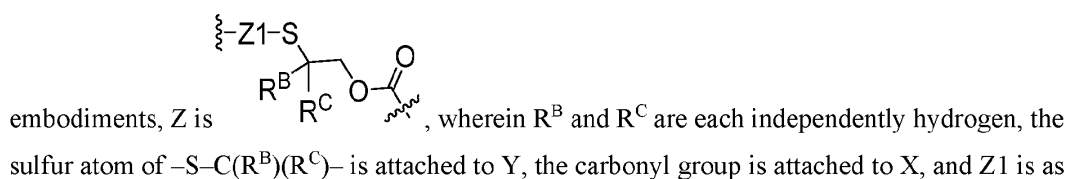
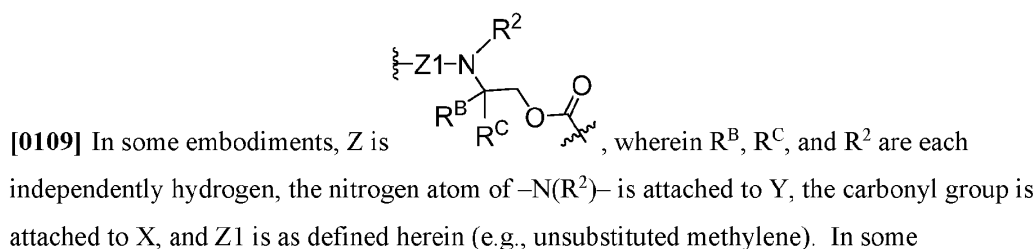
[0106] In some aspects, Y is -C(O)-, and X is -NR¹R², -OR³, or -SR⁴. For example, Y may be -C(O)- and X may be -NR¹R²; Y may be -C(O)- and X may be -OR³; or Y may be -C(O)- and X may be -SR⁴. In some aspects, Y is -C(O)-, and Z is optionally substituted alkylene. For example, Y may be -C(O)-, and Z may be unsubstituted methylene; or Y may be -C(O)-, and Z may be unsubstituted methylene. In some aspects, Y is -C(O)-; X is -NR¹R², -OR³, or -SR⁴; and Z is optionally substituted alkylene. For example Y may be -C(O)-, X may be -NR¹R², and Z may be unsubstituted methylene; Y may be -C(O)-, X may be -OR³, and Z may be unsubstituted methylene; Y may be -C(O)-, X may be -SR⁴, and Z may be unsubstituted methylene; Y may be -C(O)-, X may be -NR¹R², and Z may be substituted methylene; Y may be -C(O)-, X may be -OR³, and Z may be substituted methylene; Y may be -C(O)-, X may be -SR⁴, and Z may be substituted methylene.

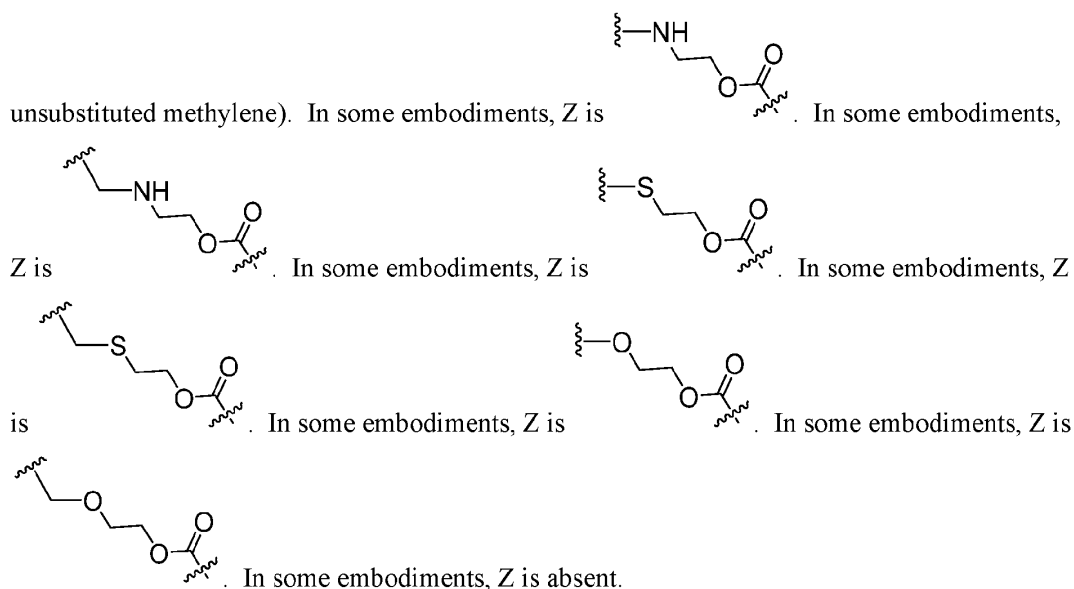
[0107] In some embodiments, Z is methylene (e.g., unsubstituted methylene). In some



is absent, alkylene (e.g., methylene, e.g., unsubstituted methylene), alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, or heteroarylene, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted (e.g., with a substituent described herein); R^2 is hydrogen or alkyl; and R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted (e.g., with a substituent described herein); and each $\sim$ denotes the point of attachment of Z to X or Y. In some embodiments, Z1 is absent.

[0108] In some embodiments, Z1 is optionally substituted alkylene (e.g., optionally substituted methylene), wherein the optional substituent is a substituent described herein. In some embodiments, Z is unsubstituted methylene. In some embodiments, Z1 is absent.





[0110] In some embodiments, R^1 is hydrogen, and R^2 is hydrogen. In some embodiments, one of R^1 and R^2 is hydrogen, and the other of R^1 and R^2 is optionally substituted alkyl. In some embodiments, one of R^1 and R^2 is hydrogen, and the other of R^1 and R^2 is optionally substituted heteroalkyl. The alkyl or heteroalkyl groups may be substituted with any suitable substituent, e.g., a substituent described herein. For example, the alkyl or heteroalkyl groups may be substituted with one or more of an alkyl, oxo, or hydroxyl group.

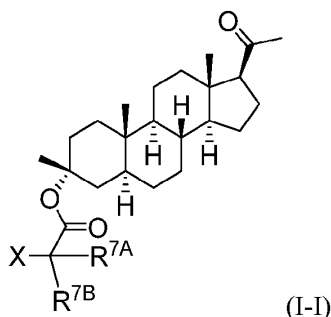
[0111] Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and each of R^1 and R^2 may be independently hydrogen; Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), R^1 may be hydrogen, and R^2 may be substituted alkyl (e.g., alkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups); or Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), R^1 may be hydrogen, and R^2 may be substituted heteroalkyl (e.g., heteroalkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups). For example, Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), R^1 may be hydrogen, and R^2 may be substituted tertiary-butyl (e.g., tertiary-butyl substituted with oxo and hydroxyl groups). For example, Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be unsubstituted methylene,

R^1 may be hydrogen, and R^2 may be tertiary-butyl substituted with oxo and hydroxyl groups; or Y may be $-C(O)-$, X may be $-NR^1R^2$, Z may be substituted methylene, R^1 may be hydrogen, and R^2 may be tertiary-butyl substituted with oxo and hydroxyl groups.

[0112] Y may be $-C(O)-$, X may be $-OR^3$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^3 may be hydrogen; Y may be $-C(O)-$, X may be $-OR^3$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^3 may be optionally substituted alkyl (e.g., alkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups); or Y may be $-C(O)-$, X may be $-OR^3$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^3 may be optionally substituted heteroalkyl (e.g., heteroalkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups). For example, Y may be $-C(O)-$, X may be $-OR^3$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^3 may be substituted tertiary-butyl (e.g., tertiary-butyl substituted with oxo, thiol, hydroxyl, and/or amino groups). For example, Y may be $-C(O)-$, X may be $-OR^3$, Z may be unsubstituted methylene, and R^3 may be tertiary-butyl substituted with oxo, thiol, hydroxyl, and/or amino groups; or Y may be $-C(O)-$, X may be $-OR^3$, Z may be substituted methylene, and R^3 may be tertiary-butyl substituted with oxo, hydroxyl, thiol, and/or amino groups.

[0113] Y may be $-C(O)-$, X may be $-SR^4$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^4 may be hydrogen; Y may be $-C(O)-$, X may be $-SR^4$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^4 may be optionally substituted alkyl (e.g., alkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups); or Y may be $-C(O)-$, X may be $-SR^4$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^4 may be optionally substituted heteroalkyl (e.g., heteroalkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups). For example, Y may be $-C(O)-$, X may be $-SR^4$, Z may be optionally substituted alkylene (e.g., optionally substituted methylene), and R^4 may be substituted tertiary-butyl (e.g., tertiary-butyl substituted with oxo, thiol, hydroxyl, and/or amino groups). For example, Y may be $-C(O)-$, X may be $-SR^4$, Z may be unsubstituted methylene, and R^4 may be tertiary-butyl substituted with oxo, thiol, hydroxyl, and/or amino groups; or Y may be $-C(O)-$, X may be $-SR^4$, Z may be substituted methylene, and R^4 may be tertiary-butyl substituted with oxo, hydroxyl, thiol, and/or amino groups.

[0114] The compound of Formula (I) may be a compound of Formula (I-I):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

X is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, heterocyclylene-heteroalkyl, $-\text{OC}(\text{O})\text{-alkyl}$, $-\text{C}(\text{O})\text{O-alkyl}$, $-\text{OC}(\text{O})\text{-heteroalkyl}$, $-\text{C}(\text{O})\text{O-heteroalkyl}$, $-\text{N}_3$, $-\text{NR}^1\text{R}^2$, $-\text{OR}^3$, or $-\text{SR}^4$, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-

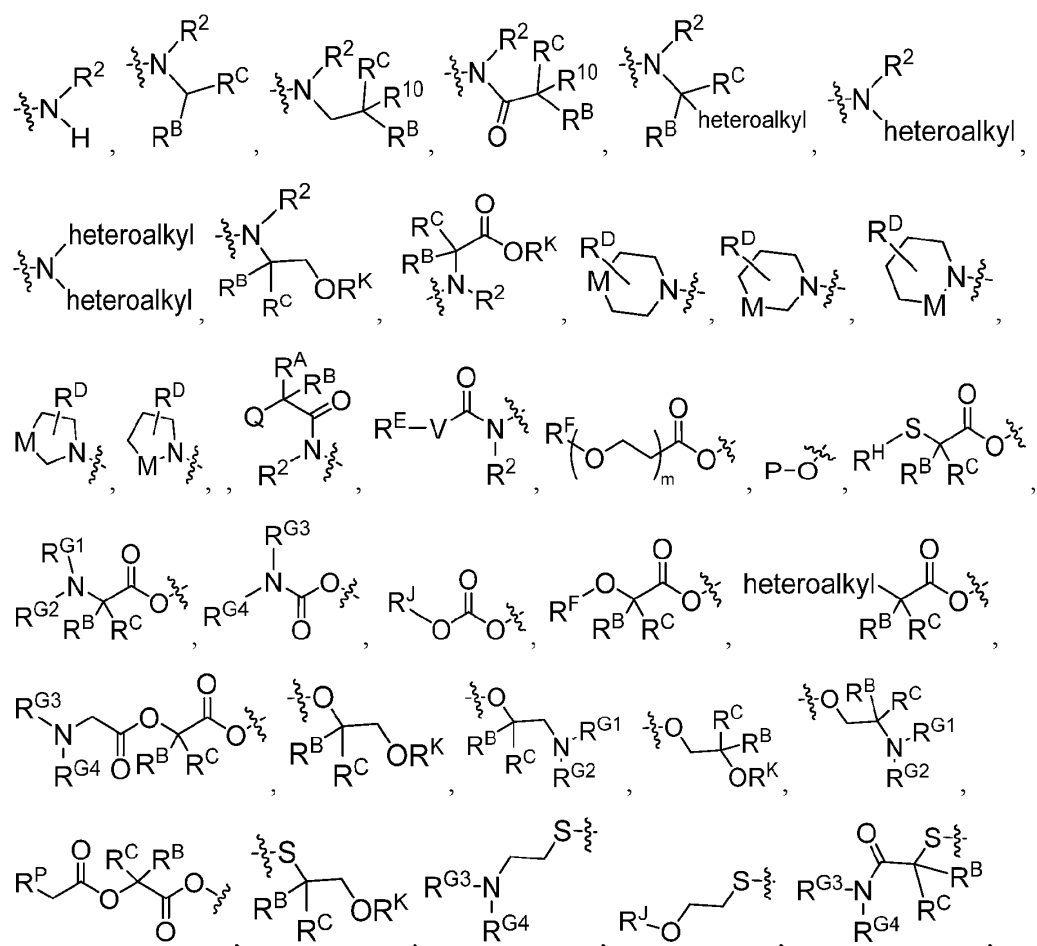
heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

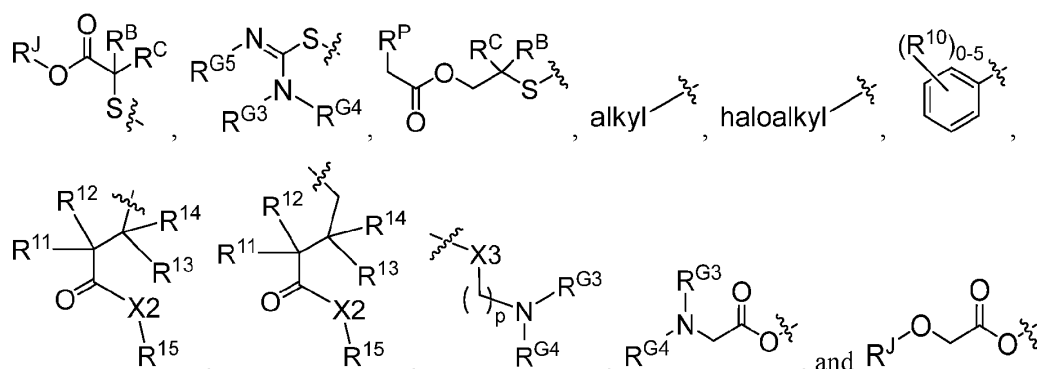
R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0115] Each optional substituent of a group in Formula (I-I) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, e.g., a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., -OMe, -OEt, or -OBn), alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonate, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, -C(O)OH, -C(O)O-alkyl (e.g., -C(O)O-tBu or -C(O)OMe), -C(O)O-heteroalkyl, -C(O)O-alkylaryl, -OC(O)O-alkyl, -OC(O)O-heteroalkyl, -OC(O)O-alkylaryl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)NH-heteroalkyl, -C(O)NH-alkylaryl, -NHC(O)O-alkyl (e.g., -NHC(O)OtBu), -NHC(O)O-heteroalkyl, -NHC(O)O-alkylaryl (e.g., -NH-Cbz), -C(O)N(alkyl)₂, -C(O)N(alkyl)(heteroalkyl), -C(O)N(heteroalkyl)₂, -N(alkyl)C(O)O-alkyl (e.g., N(Me)C(O)OtBu), -N(alkyl)C(O)O-heteroalkyl, -N(alkyl)C(O)O-alkylaryl, -N(alkyl)C(O)N(alkyl)₂, -N(alkyl)C(O)N(alkyl)(heteroalkyl), -N(alkyl)C(O)N(heteroalkyl)₂, -N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl,

aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0116] In a compound disclosed herein, e.g., a compound of Formula (I) or Formula (I-I), X may be a moiety selected from the group consisting of





wherein

R^2 is hydrogen or alkyl;

M is $-C(H)(R^D)-$ (e.g., $-CH_2-$), $-O-$, or $-N(R^D)-$ (e.g., $-N(Me)-$);

P is an amino acid residue (e.g., glycine, alanine, valine, leucine, or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

Q is heteroalkyl or heterocyclyl, wherein the heteroalkyl or heterocyclyl is optionally substituted;

V is $-O-$, $-N(H)-$, or $-N(Me)-$;

X2 and X3 are each independently $-CH_2-$, $-O-$, $-S-$, or $-N(R^{G3})-$ (e.g., $-NH-$);

R^A , R^B , R^C , R^D , R^E , and R^K are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R^P is halo (e.g., chloro), heterocyclyl (e.g., morpholinyl), $-NH$ -alkyl, $-NH$ -heteroalkyl, $-N$ -(alkyl)₂ (e.g., $-N(Me)_2$), or $-N$ -(heteroalkyl)₂ (e.g., $-N(CH_2CH_2OH)_2$);

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$; $-NO_2$, $-CN$, or $-NC$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-N(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{15} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted;

m is an integer of 1-5;

p is an integer between 0 and 4; and

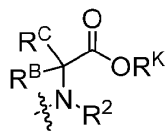
$\{$ denotes the point of attachment of X to another group of the compound, e.g., an attachment of X to Z, or X to Y when Z is absent in Formula (I), or an attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I).

[0117] Each optional substituent of a group described above (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable

substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (*e.g.*, C₁-C₆ alkyl), alkenyl (*e.g.*, C₂-C₆ alkenyl), alkynyl (*e.g.*, C₂-C₆ alkynyl), heteroalkyl (*e.g.*, C₁-C₆ heteroalkyl), haloalkyl (*e.g.*, C₁-C₆ haloalkyl, *e.g.*, -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (*e.g.*, C₃-C₈ cycloalkyl, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (*e.g.*, C₃-C₈ heterocyclyl, *e.g.*, morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (*e.g.*, benzyl), aryl (*e.g.*, phenyl), heteroaryl (*e.g.*, pyrrolyl, imidazolyl, or indolyl), halogen (*e.g.*, -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (*e.g.*, -OMe, -OEt, or -OBn), alkoxycarbonyloxy, aryloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (*e.g.*, -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, -C(O)OH, -C(O)O-alkyl (*e.g.*, -C(O)O-tBu or -C(O)OMe), -C(O)O-heteroalkyl, -C(O)O-alkylaryl, -OC(O)O-alkyl, -OC(O)O-heteroalkyl, -OC(O)O-alkylaryl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)NH-heteroalkyl, -C(O)NH-alkylaryl, -NHC(O)O-alkyl (*e.g.*, -NHC(O)OtBu), -NHC(O)O-heteroalkyl, -NHC(O)O-alkylaryl (*e.g.*, -NH-Cbz), -C(O)N(alkyl)₂, -C(O)N(alkyl)(heteroalkyl), -C(O)N(heteroalkyl)₂, -N(alkyl)C(O)O-alkyl (*e.g.*, N(Me)C(O)OtBu), -N(alkyl)C(O)O-heteroalkyl, -N(alkyl)C(O)O-alkylaryl, -N(alkyl)C(O)N(alkyl)₂, -N(alkyl)C(O)N(alkyl)(heteroalkyl), -N(alkyl)C(O)N(heteroalkyl)₂, -N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (*e.g.*, cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

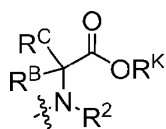
[0118] When P is an amino acid residue (*e.g.*, glycine, alanine, valine, leucine, or proline) or dipeptide moiety (*e.g.*, a leucine-leucine moiety), it may comprise one or more D-amino acids, L-amino acids, or a combination thereof. The amino acid residue or dipeptide moiety may be attached via its C-terminus, and may further comprise a free N-terminus or an N-terminus that is optionally substituted, *e.g.*, with a carboxybenzyl (Cbz) group). The amino acid residue or

dipeptide moiety may alternatively be attached via its N-terminus, and may further comprise a free C-terminus (e.g., $-\text{C}(\text{O})\text{OH}$), a C-terminus that is optionally substituted.



[0119] In some embodiments, X is $-\text{NR}^1\text{R}^2$, R^2 is H, R^B and R^C are each independently alkyl (e.g., methyl), and R^K is hydrogen.

[0120] In some embodiments, Y is $-\text{C}(\text{O})-$ and Z is alkylene (e.g., methylene), and X is

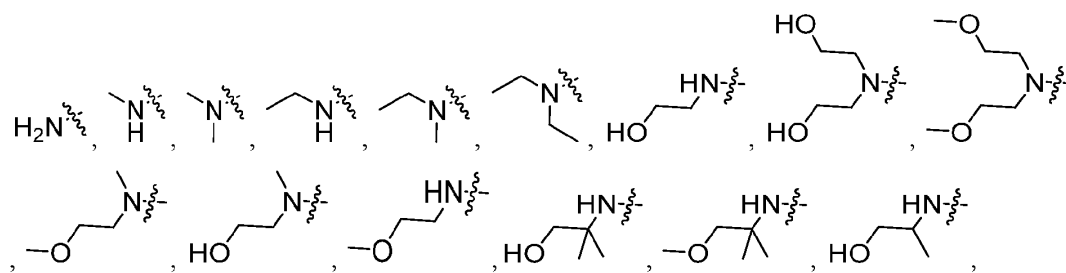


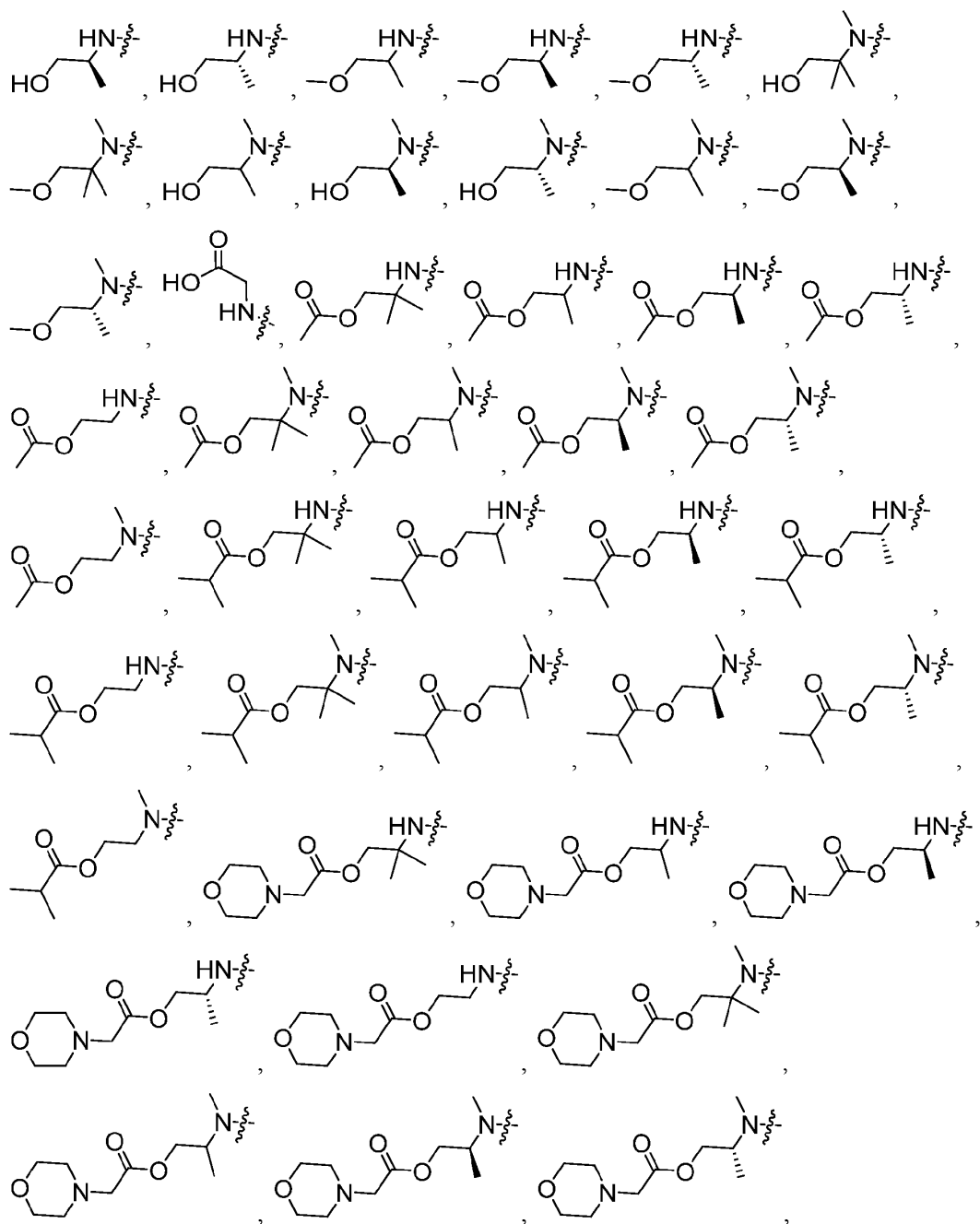
[0121] In some embodiments, when X is $-\text{NR}^1\text{R}^2$, R^1 and R^2 are not both hydrogen. In some embodiments, when X is $-\text{NR}^1\text{R}^2$, and R^1 is hydrogen, R^2 is not unsubstituted alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl). In some embodiments, when X is $-\text{NR}^1\text{R}^2$, and R^1 is alkyl (e.g., methyl), R^2 is not unsubstituted alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl).

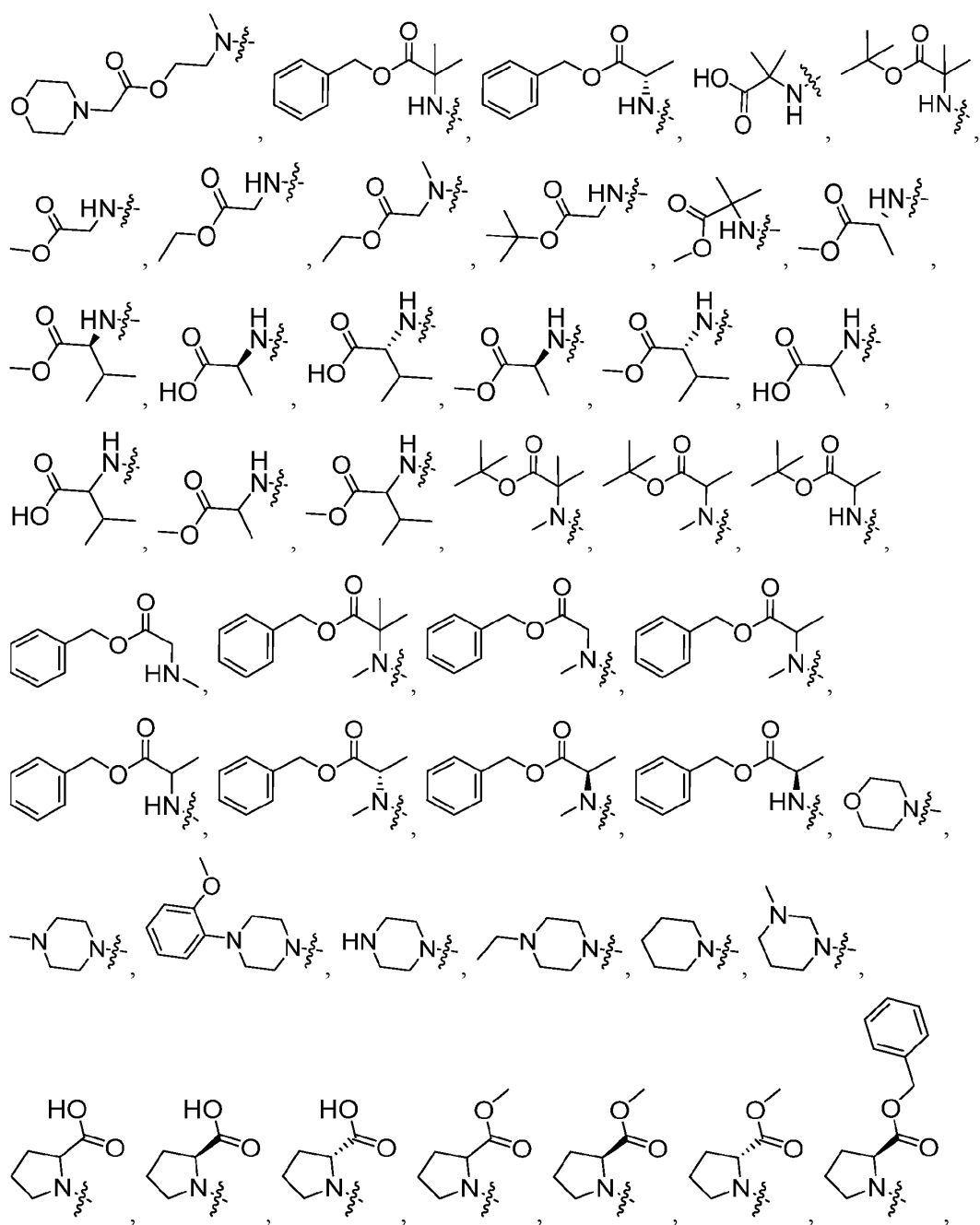
[0122] In some embodiments, when X is $-\text{OR}^3$, R^3 is not hydrogen. In some embodiments, when X is $-\text{OR}^3$, R^3 is not unsubstituted alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl).

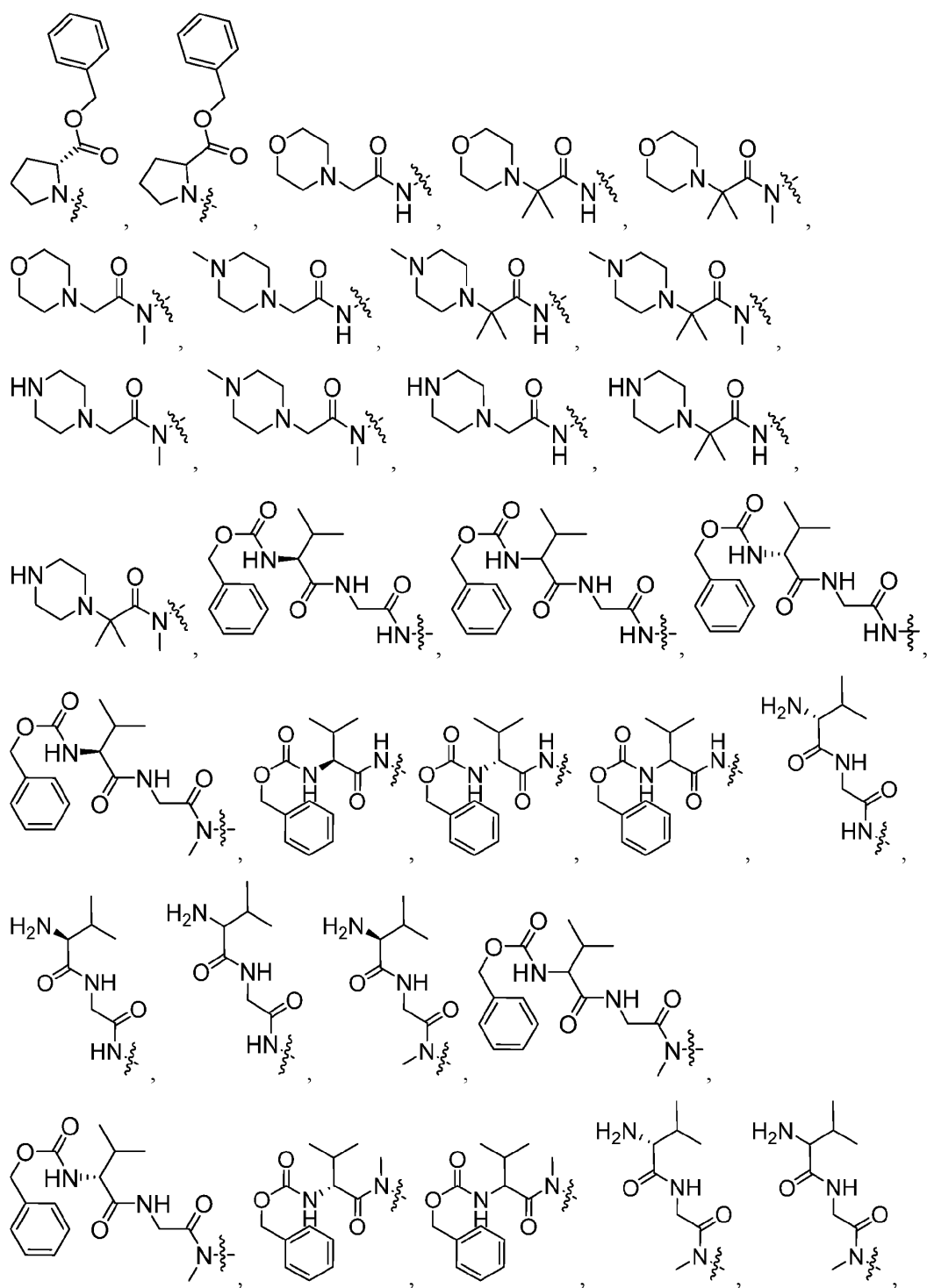
[0123] In some embodiments, when X is $-\text{SR}^4$, R^4 is not hydrogen. In some embodiments, when X is $-\text{SR}^4$, R^4 is not unsubstituted alkyl (e.g., methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, or dodecyl).

[0124] In a compound disclosed herein, e.g. a compound of Formula (I) or Formula (I-I), X may be a moiety selected from the group consisting of



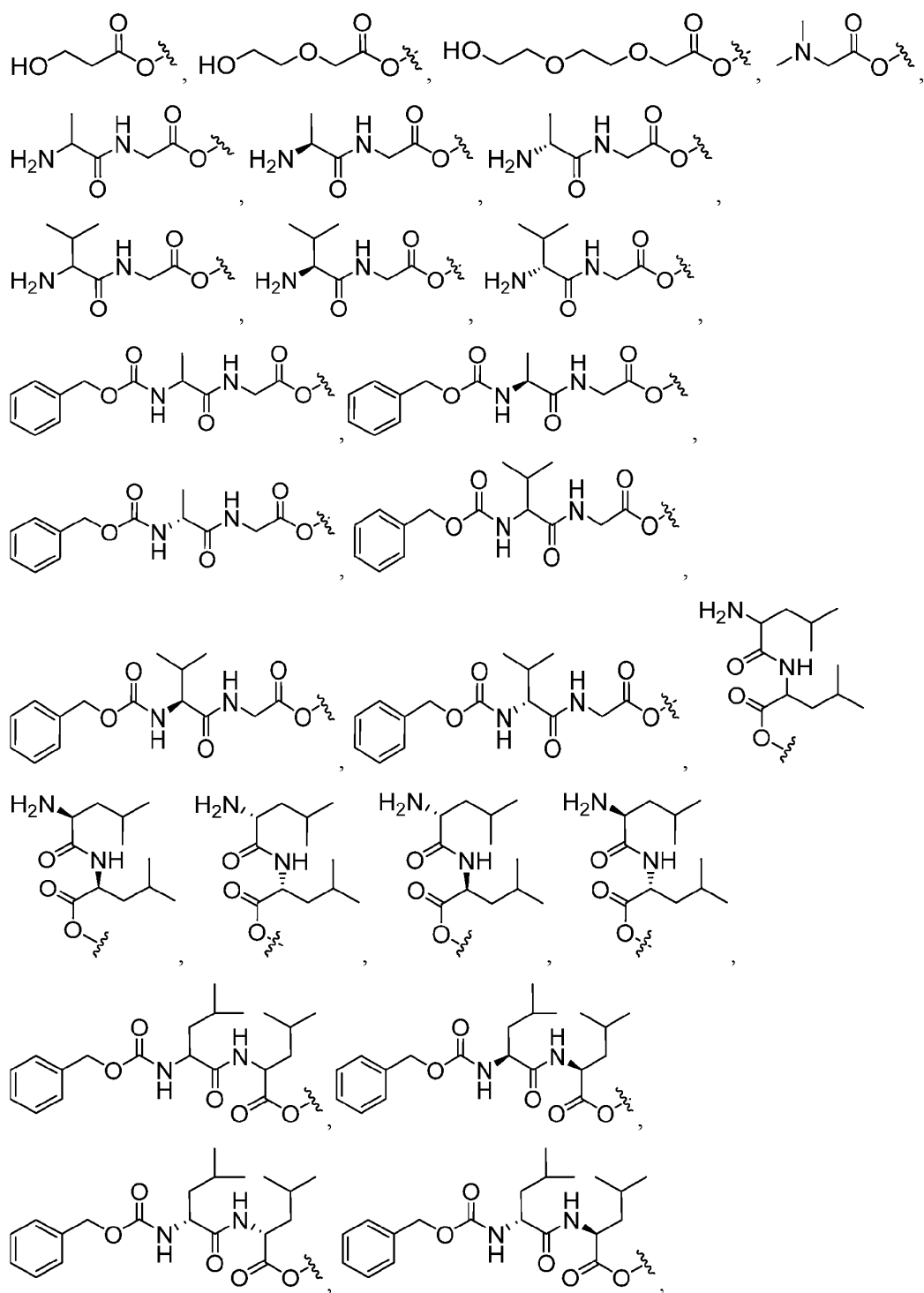




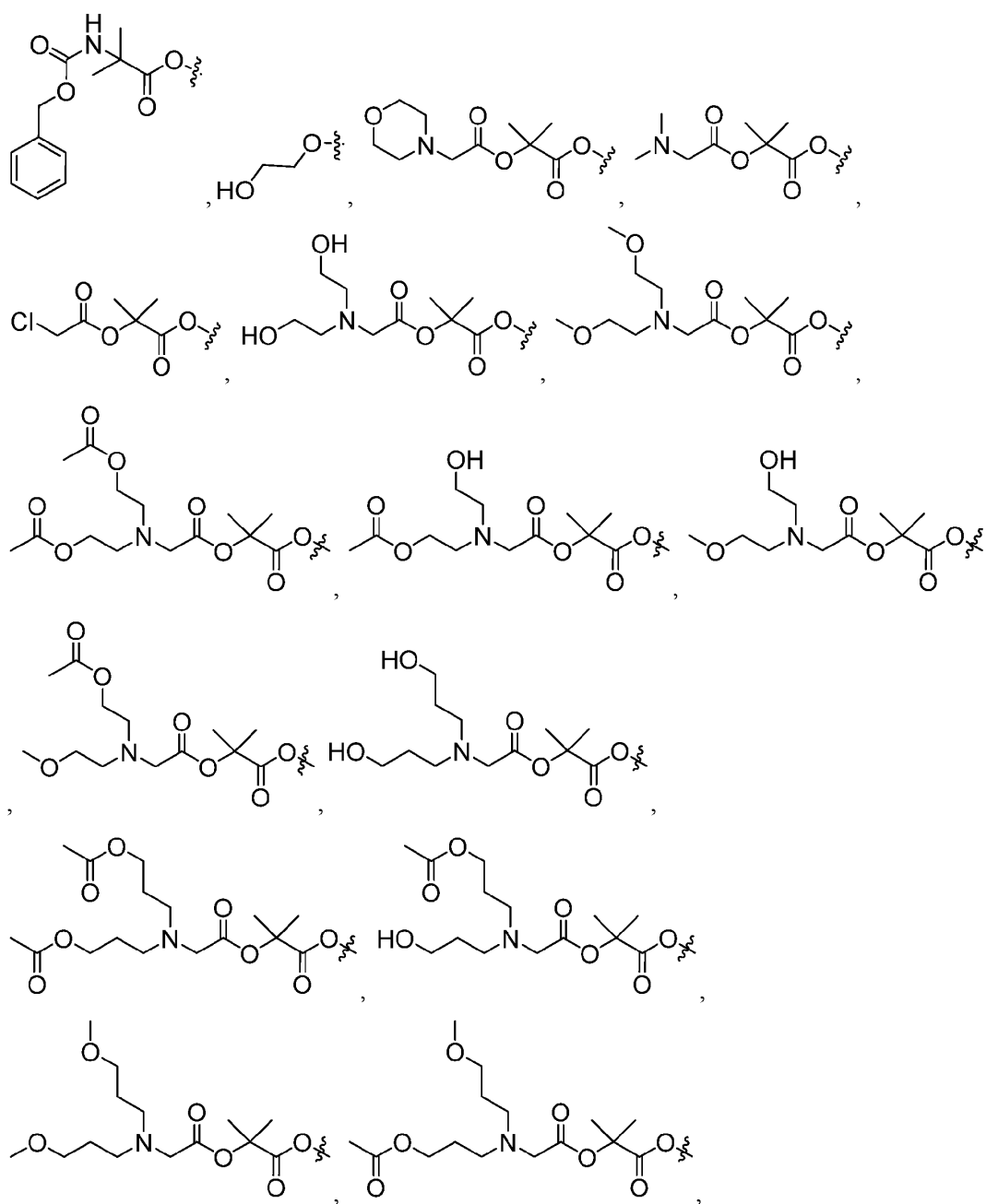


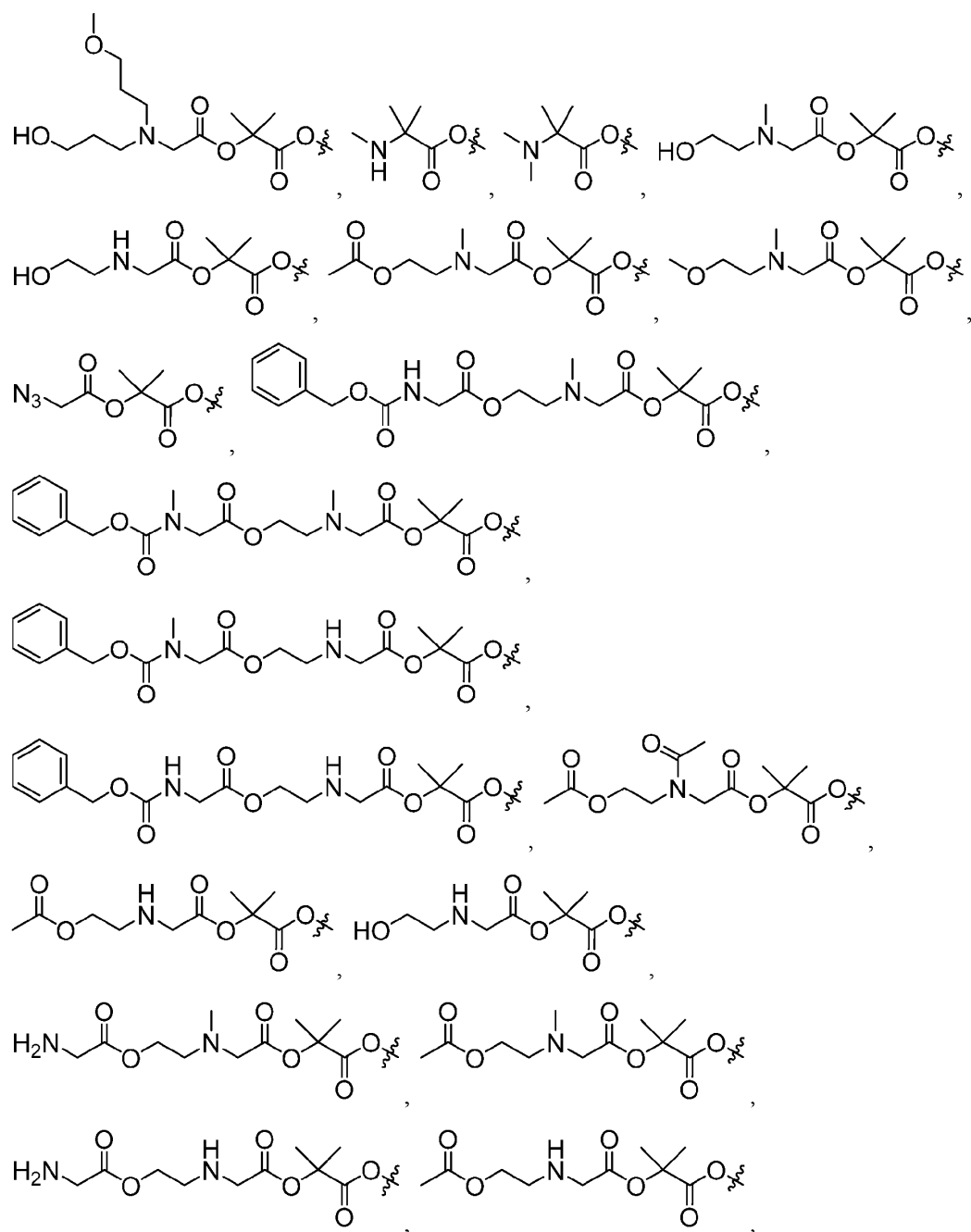


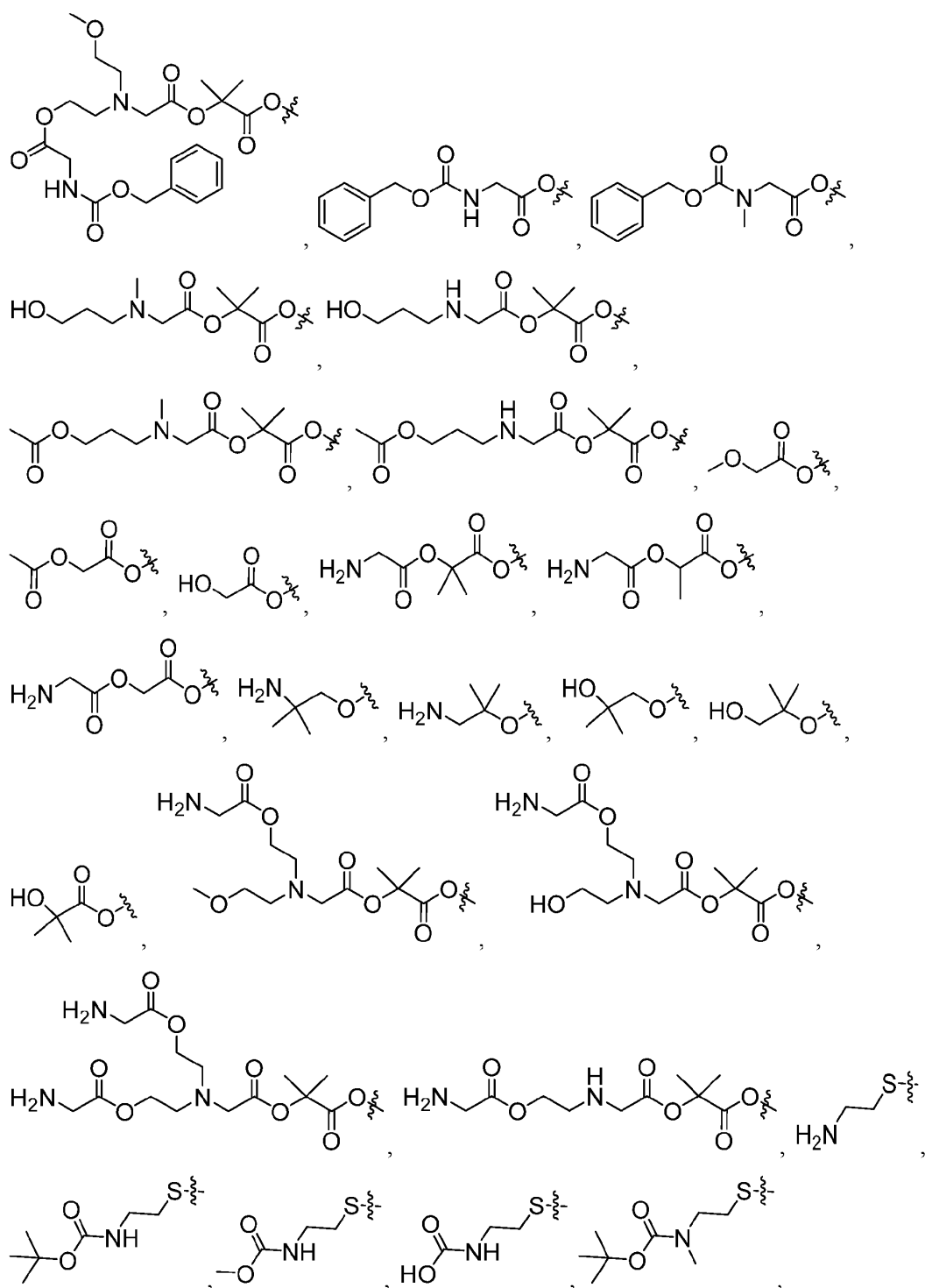




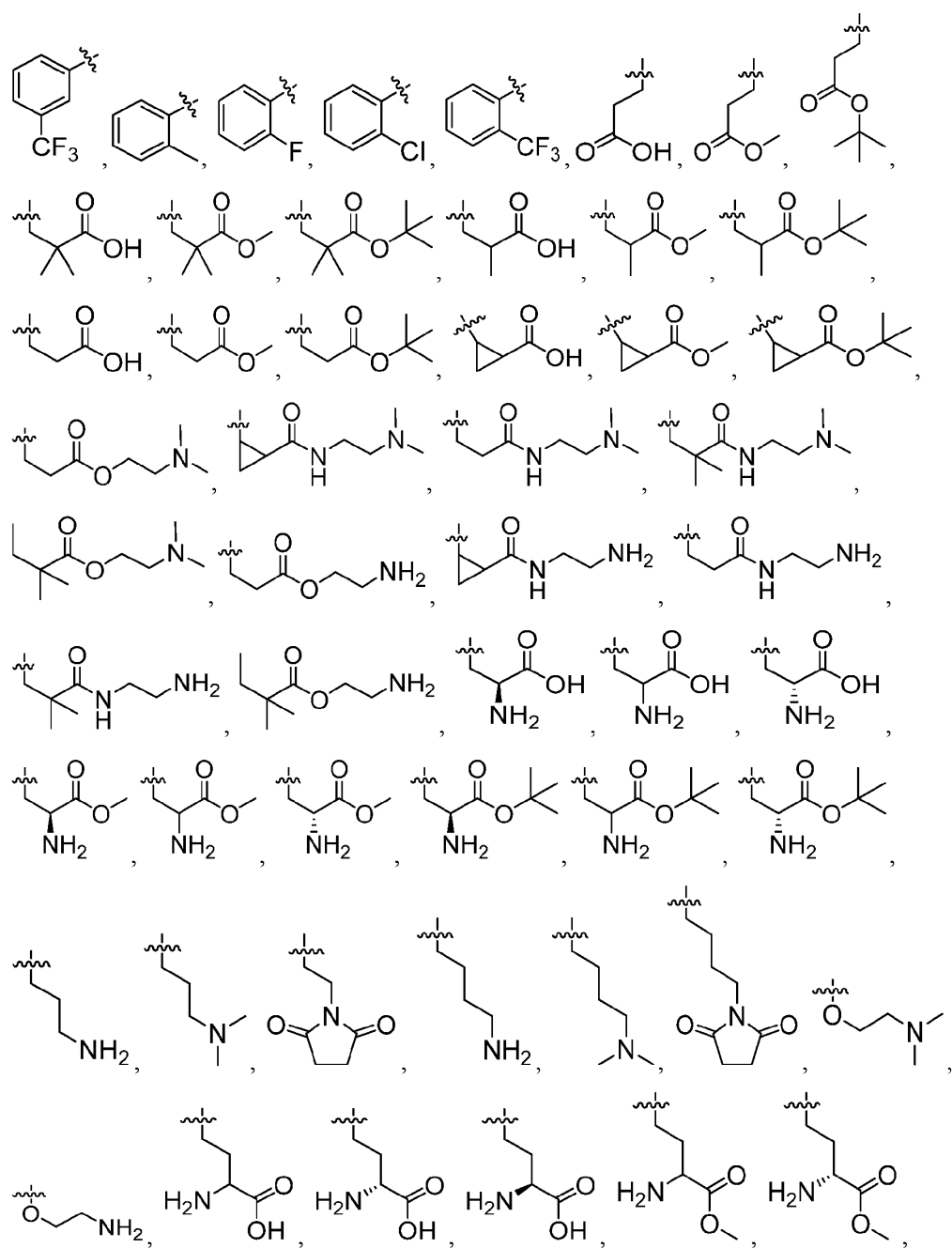


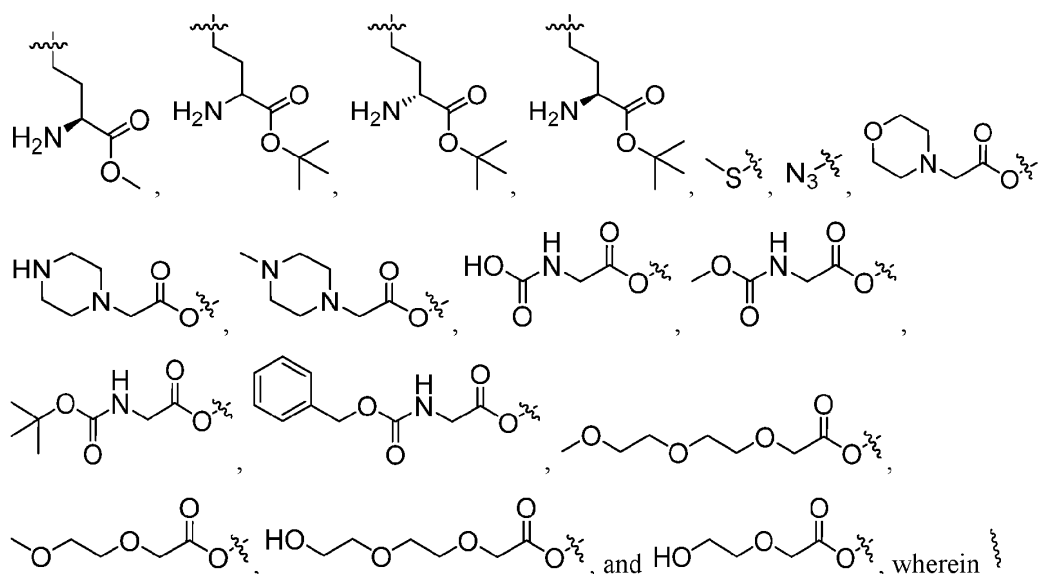






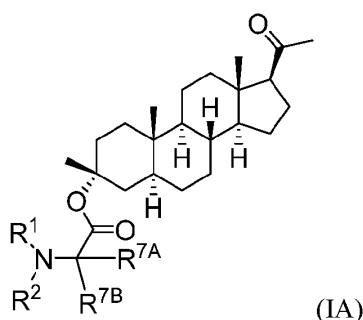






denotes the point of attachment of X to another group of the compound, e.g., an attachment of X to Z, or X to Y when Z is absent in Formula (I), or an attachment of X to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (I-I).

[0125] The compound of Formula (I) or Formula (I-I) may be a compound of Formula (IA):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R¹ and R² are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl,

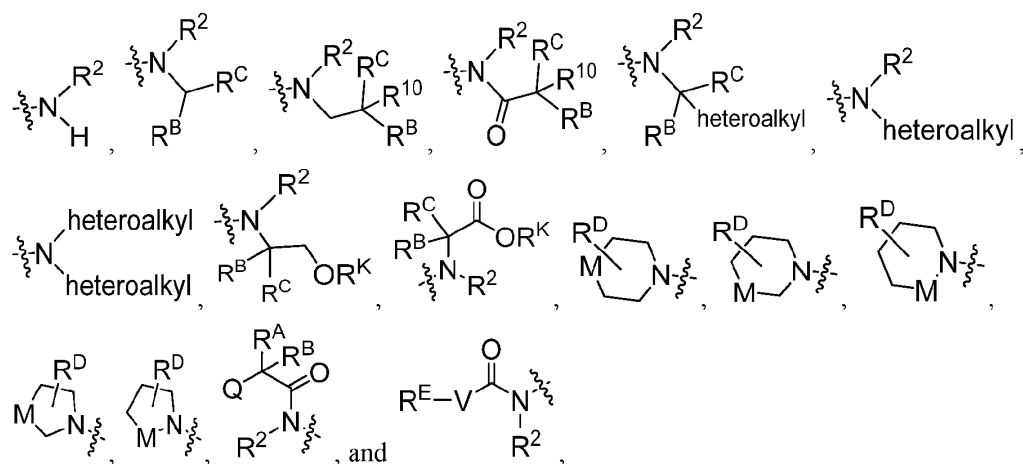
alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0126] In some embodiments, R^1 and R^2 are each independently hydrogen. In some embodiments, R^1 is hydrogen, and R^2 is optionally substituted alkyl (e.g., alkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups). In some embodiments, R^1 is hydrogen, and R^2 is optionally substituted heteroalkyl (e.g., heteroalkyl substituted with one or more alkyl, oxo, thiol, amino, hydroxyl, heterocyclyl, aryl, or heteroaryl groups). In some embodiments, R^{7A} and R^{7B} are each independently hydrogen. For example, R^1 , R^{7A} and R^{7B} may each independently be hydrogen, and R^2 may be tertiary-butyl substituted with oxo and hydroxyl groups.

[0127] The $-N(R^1)(R^2)$ group of Formula (IA) may be a moiety selected from the group consisting of



wherein

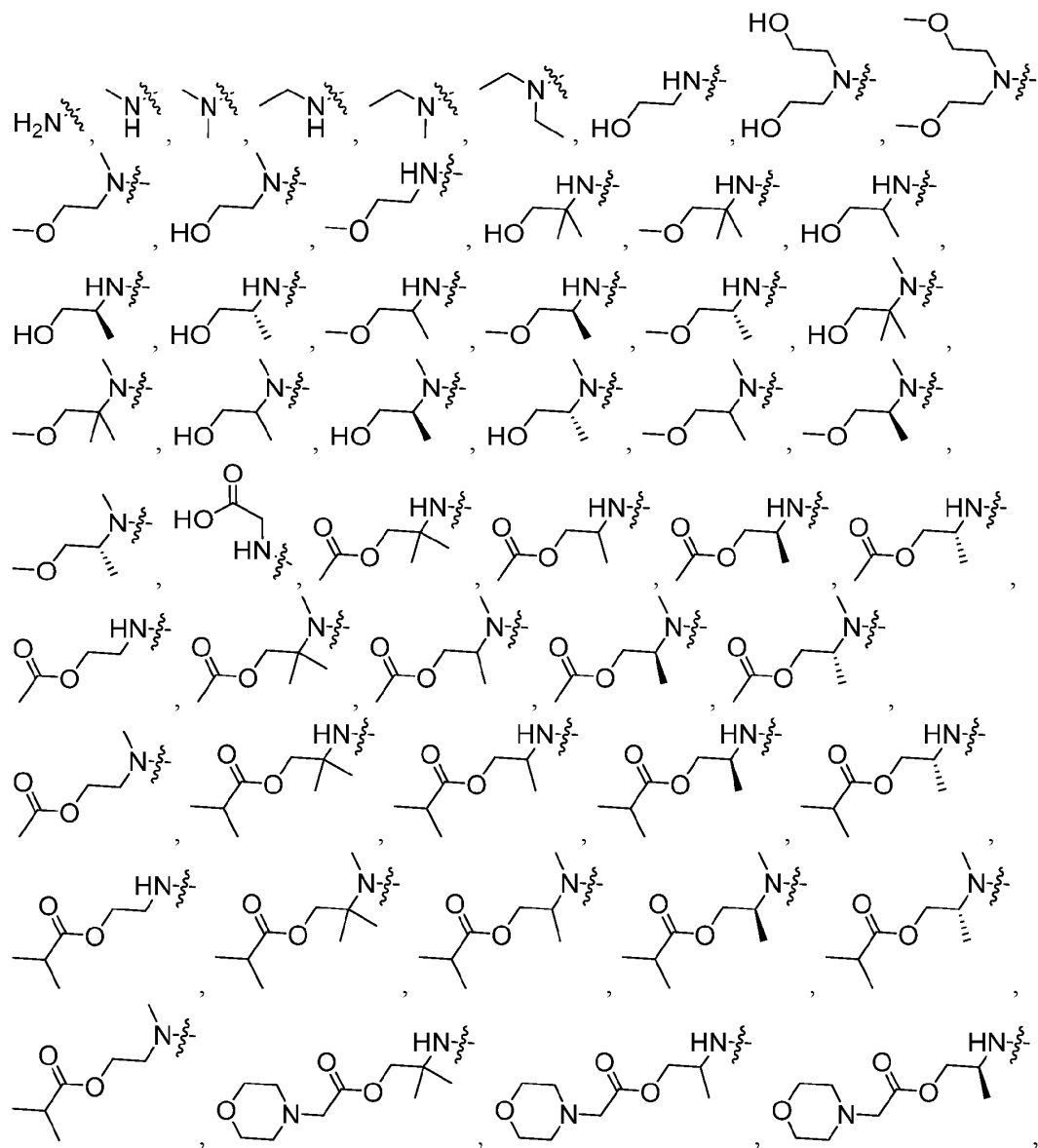
R^2 is hydrogen or alkyl;

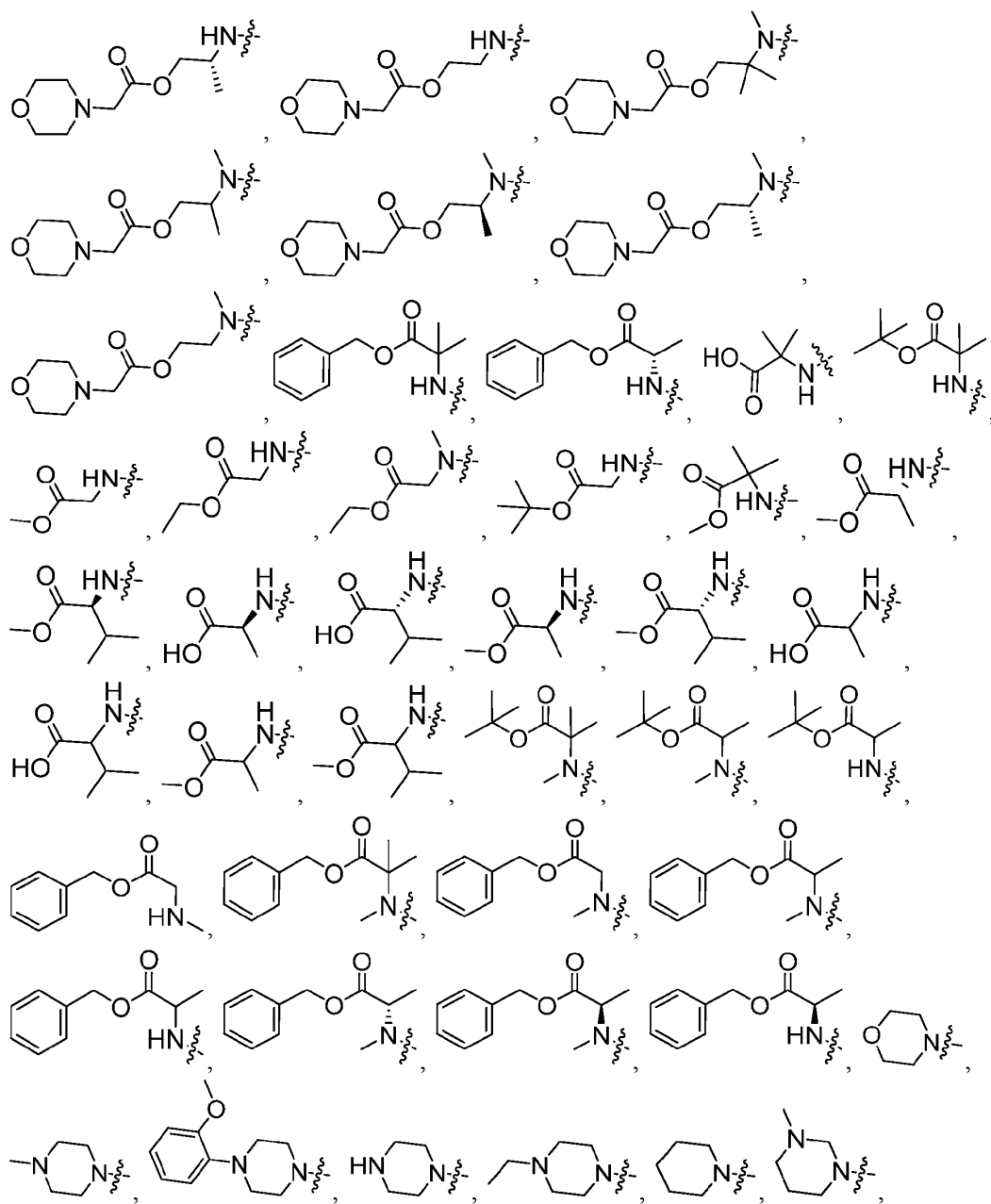
M is $-C(H)(R^D)-$ (e.g., $-CH_2-$), $-O-$, or $-N(R^D)-$ (e.g., $-N(Me)-$);

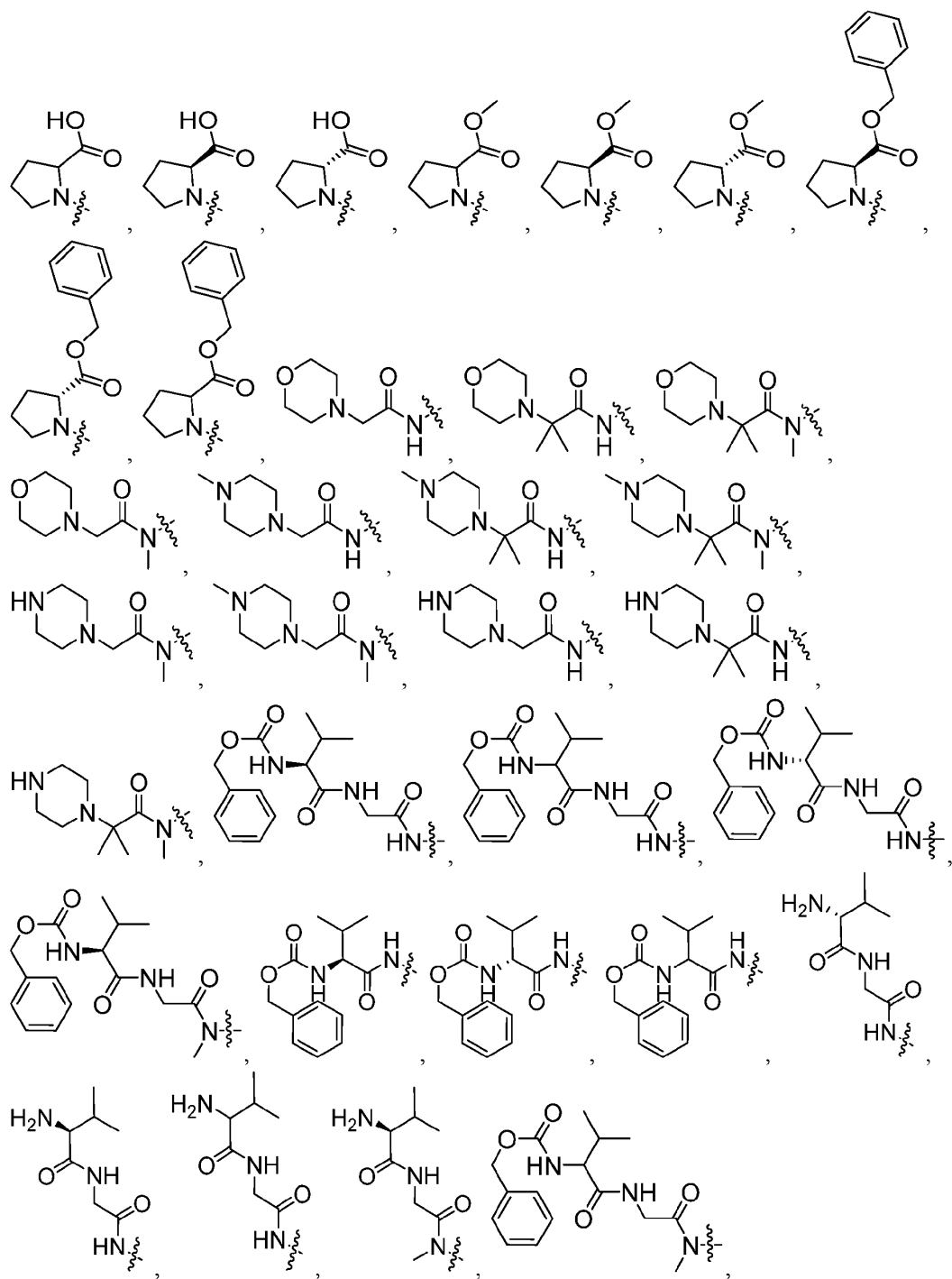
Q is heteroalkyl or heterocyclyl, wherein the heteroalkyl or heterocyclyl is optionally substituted;

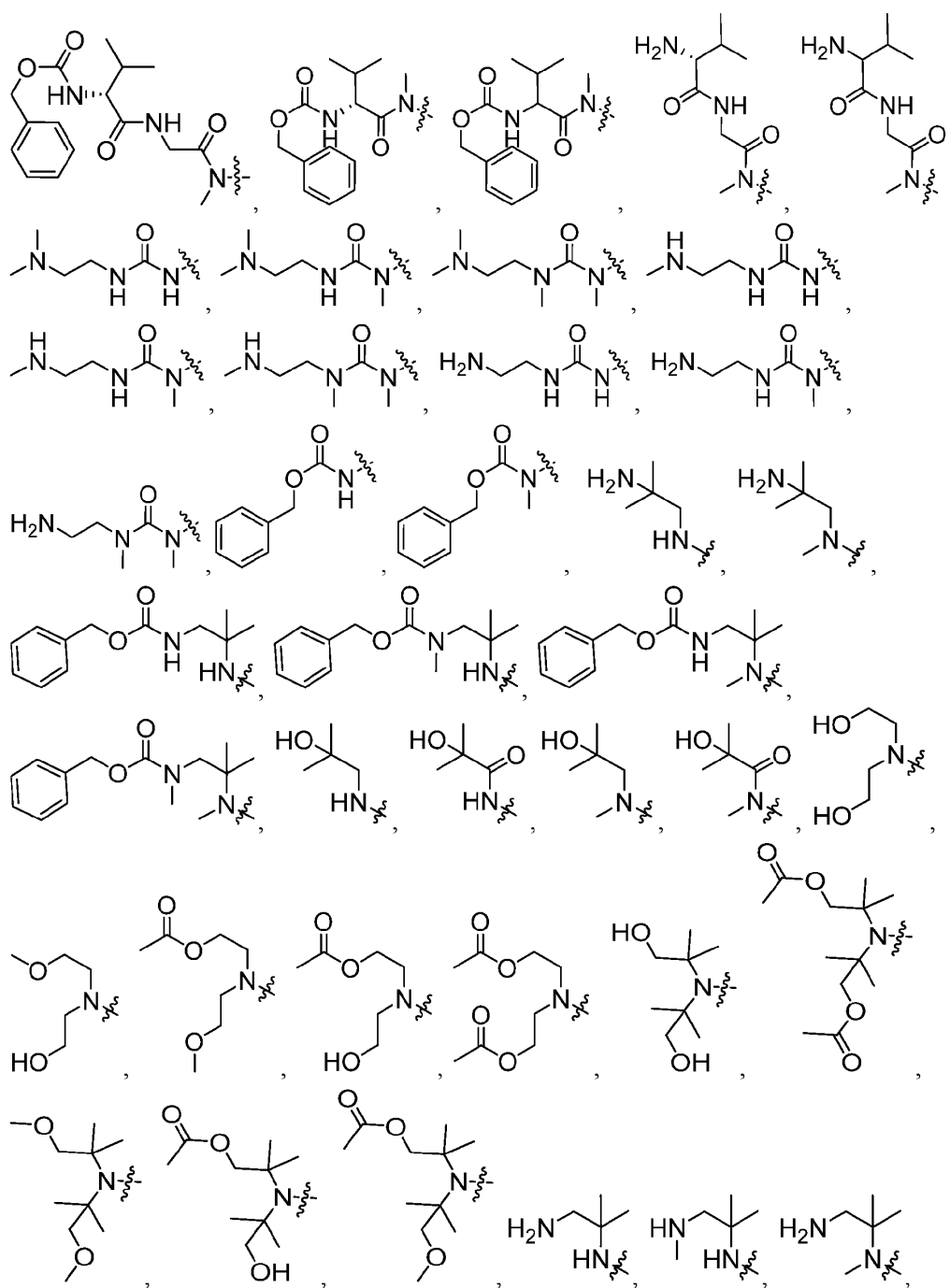
N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

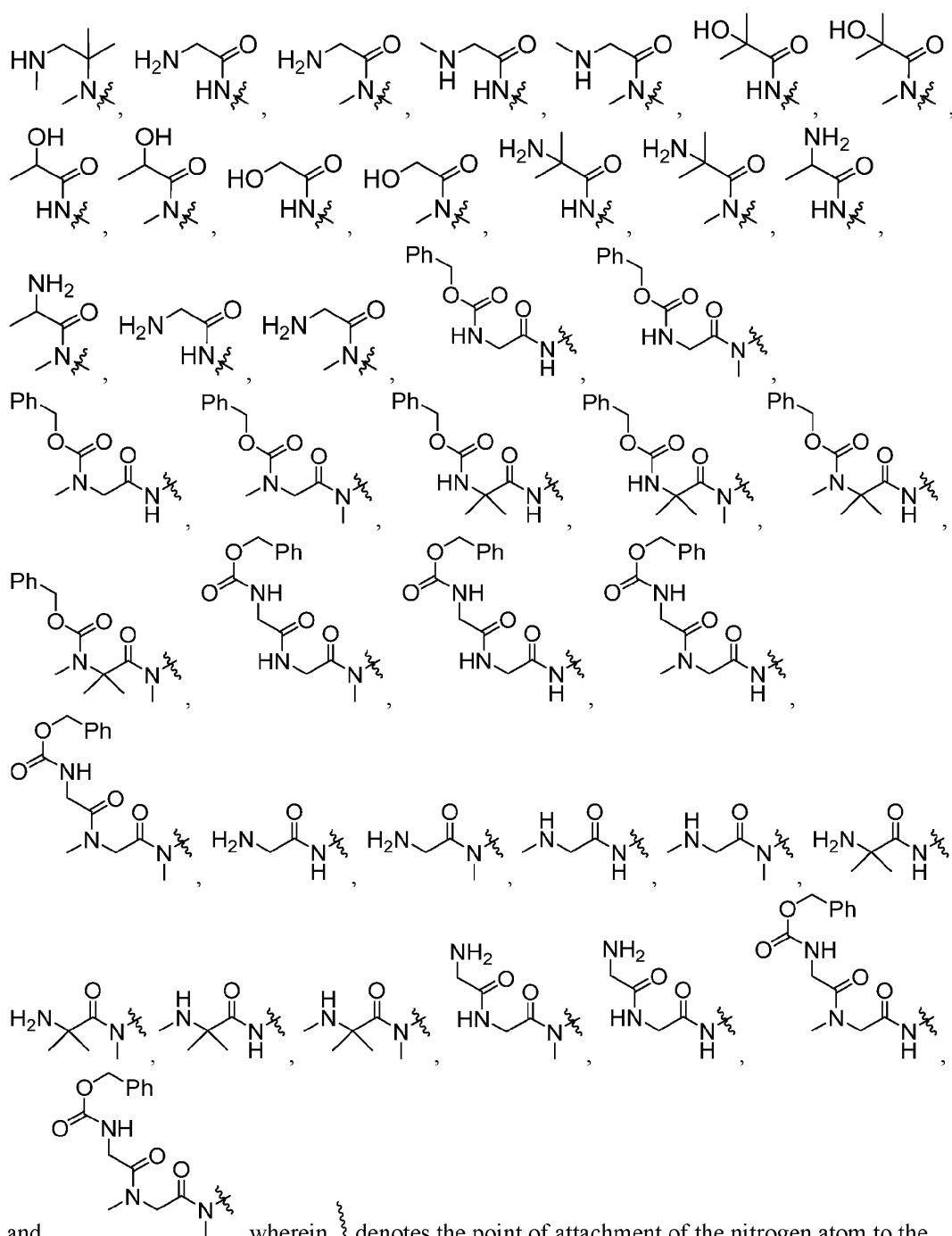
[0129] The $-N(R^1)(R^2)$ group of Formula (IA) may be a moiety selected from the group consisting of





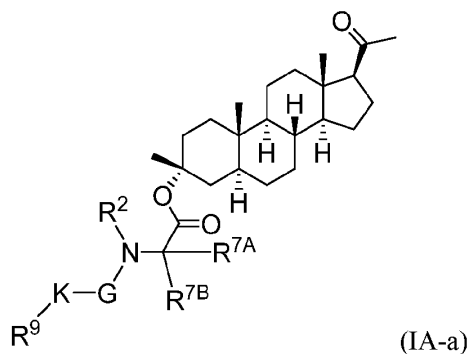






and $\text{N}(\text{R}')-\text{CH}(\text{R}'')-\text{C}(=\text{O})-\text{N}(\text{R}''')$, wherein $\text{N}(\text{R}')-\text{CH}(\text{R}'')-\text{C}(=\text{O})-\text{N}(\text{R}''')$ denotes the point of attachment of the nitrogen atom to the carbon atom of the $-\text{C}(\text{R}^{\text{7A}})(\text{R}^{\text{7B}})$ group.

[0130] The compound of Formula (I), Formula (I-I), or Formula (IA) may be a compound of Formula (IA-a):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

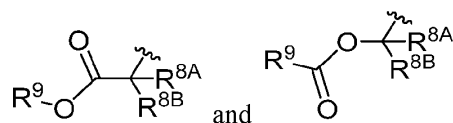
G is absent, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$ (e.g., $-\text{CH}_2-$),

K is alkylene, heteroalkylene, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{O}-(\text{CH}_2)-$, or $-(\text{CH}_2)-\text{O}-$, wherein the alkylene or heteroalkylene is optionally substituted;

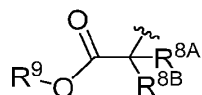
R^2 , $\text{R}^{7\text{A}}$, $\text{R}^{7\text{B}}$, $\text{R}^{8\text{A}}$, and $\text{R}^{8\text{B}}$ are each independently hydrogen or optionally substituted alkyl; and

R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0131] It will be understood that when K is $-\text{OC}(\text{O})-$ or $-(\text{CH}_2)-\text{O}-$, the $-\text{OC}(\text{O})-$ or $-(\text{CH}_2)-\text{O}-$ group may be connected to G and R^9 groups in either orientation (in other words, these groups may be thought of as being equivalent to $-\text{C}(\text{O})\text{O}-$ and $-\text{O}-(\text{CH}_2)-$, respectively). For example, when G is $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$ and K is $-\text{OC}(\text{O})-$, it will be understood that both



are described. In some embodiments, G is $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$ and K is $-\text{OC}(\text{O})-$, and the carbonyl group in $-\text{OC}(\text{O})-$ is bonded to G, i.e.,

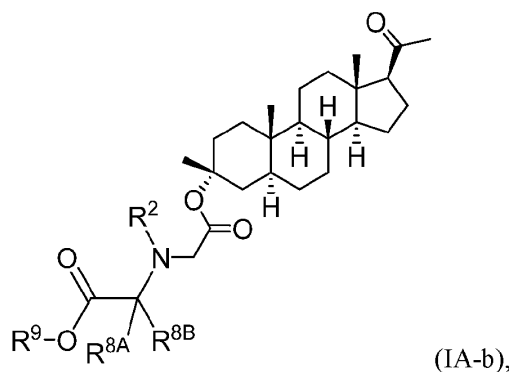


[0132] Each optional substituent of a group in Formula (IA-a) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidyl, or N-Boc-azetidyl), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., -OMe, -OEt, or -OBn), alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, -C(O)OH, -C(O)O-alkyl (e.g., -C(O)O-tBu or -C(O)OMe), -C(O)O-heteroalkyl, -C(O)O-alkylaryl, -OC(O)O-alkyl, -OC(O)O-heteroalkyl, -OC(O)O-alkylaryl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)NH-heteroalkyl, -C(O)NH-alkylaryl, -NHC(O)O-alkyl (e.g., -NHC(O)OtBu), -NHC(O)O-heteroalkyl, -NHC(O)O-alkylaryl (e.g., -NH-Cbz), -C(O)N(alkyl)₂, -C(O)N(alkyl)(heteroalkyl), -C(O)N(heteroalkyl)₂, -N(alkyl)C(O)O-alkyl (e.g., N(Me)C(O)OtBu), -N(alkyl)C(O)O-heteroalkyl, -N(alkyl)C(O)O-alkylaryl, -N(alkyl)C(O)N(alkyl)₂, -N(alkyl)C(O)N(alkyl)(heteroalkyl), -N(alkyl)C(O)N(heteroalkyl)₂, -N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0133] In some embodiments G is -C(R^{8A})(R^{8B})-, e.g., -C(CH₃)₂-. In some embodiments, K is -OC(O)-. In some embodiments, R² is hydrogen. In some embodiments, R^{7A} and R^{7B} are each independently hydrogen. In some embodiments, R⁹ is hydrogen. In some embodiments, R^{8A} and

R^{8B} are each independently alkyl (e.g., methyl). For example, G may be $-C(CH_3)_2-$. In some embodiments, G is $-C(CH_3)_2-$, K is $-OC(O)-$, and R^2 , R^{7A} and R^{7B} are each independently hydrogen.

[0134] The compound of Formula (I), Formula (I-I), Formula (IA), or Formula (IA-a) may be a compound of Formula (IA-b):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

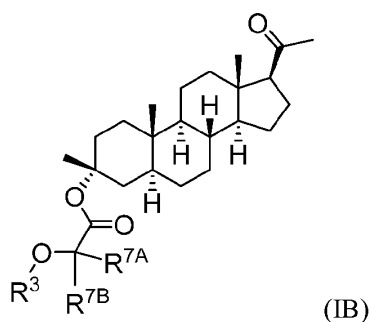
R^2 , R^{8A} , and R^{8B} are each independently hydrogen or optionally substituted alkyl; and

R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0135] In some embodiments, R^2 is hydrogen. In some embodiments, R^{8A} and R^{8B} are each independently alkyl (e.g., methyl). In some embodiments, R^{8A} and R^{8B} are each independently methyl. For example, R^2 may be hydrogen and R^{8A} and R^{8B} may each be independently methyl. In some embodiments, R^9 is hydrogen.

[0136] In some embodiments, R^2 is hydrogen, R^{8A} and R^{8B} are each independently methyl, and R^9 is hydrogen.

[0137] The compound of Formula (I) or Formula (I-I) may be a compound of Formula (IB):

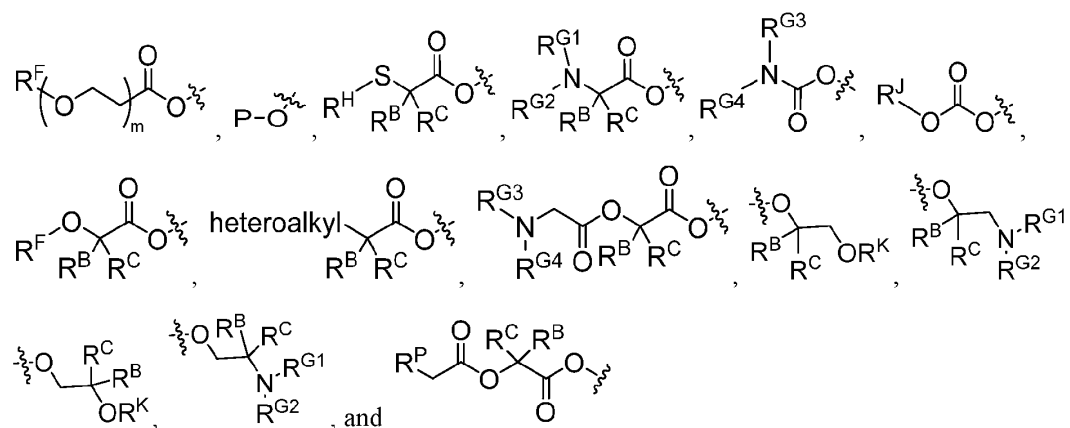


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0138] The $-O-(R^3)$ group of Formula (IB) may be a moiety selected from the group consisting of



wherein

P is an amino acid residue (e.g., glycine, alanine, valine, leucine, or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^I is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

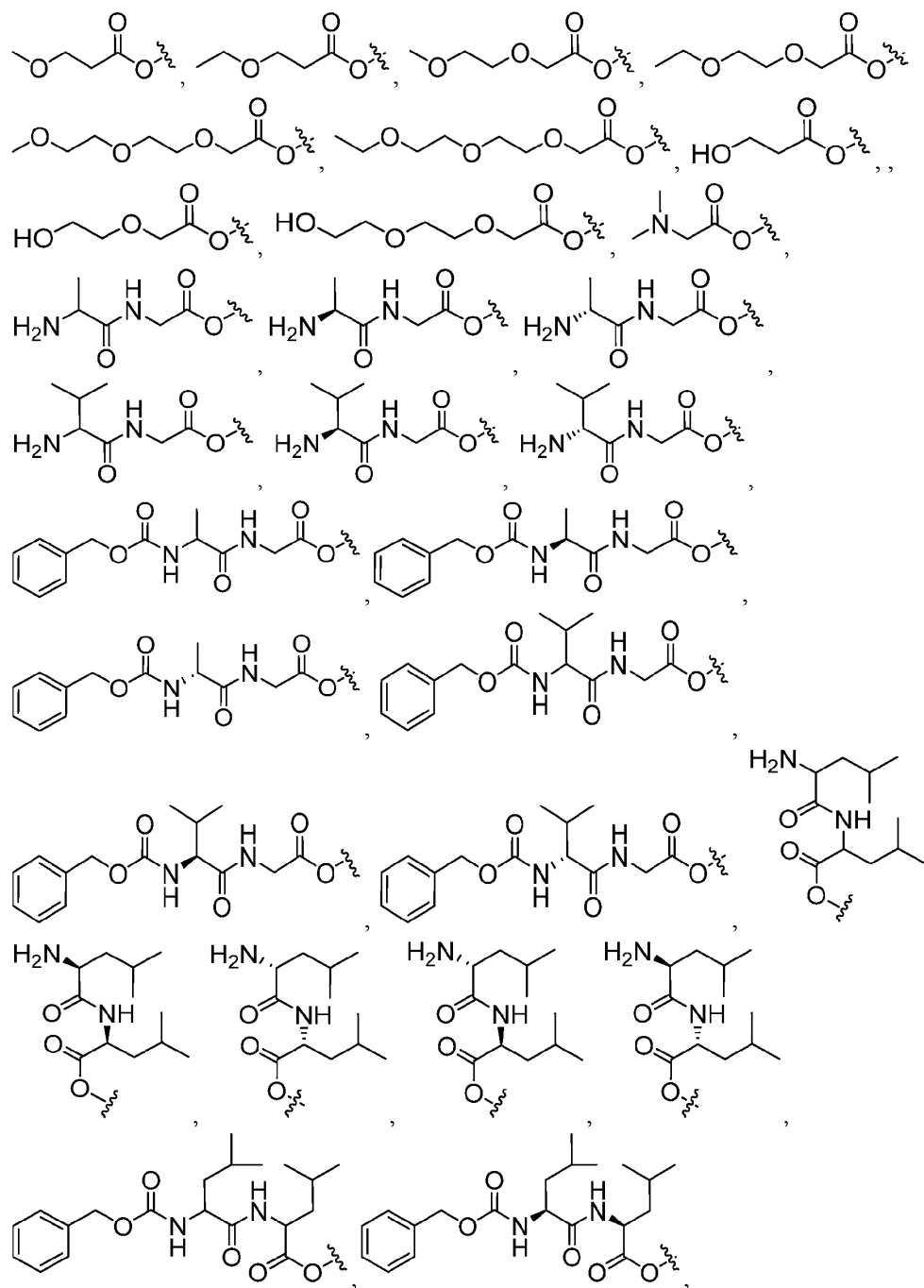
R^P is halo, -NH-alkyl, -NH-heteroalkyl, -N-(alkyl)₂ (e.g., -N(Me)₂), -N-(heteroalkyl)₂ (e.g., -N(CH₂CH₂OH)₂), or heterocyclyl (e.g., morpholinyl);

m is an integer of 1-5; and

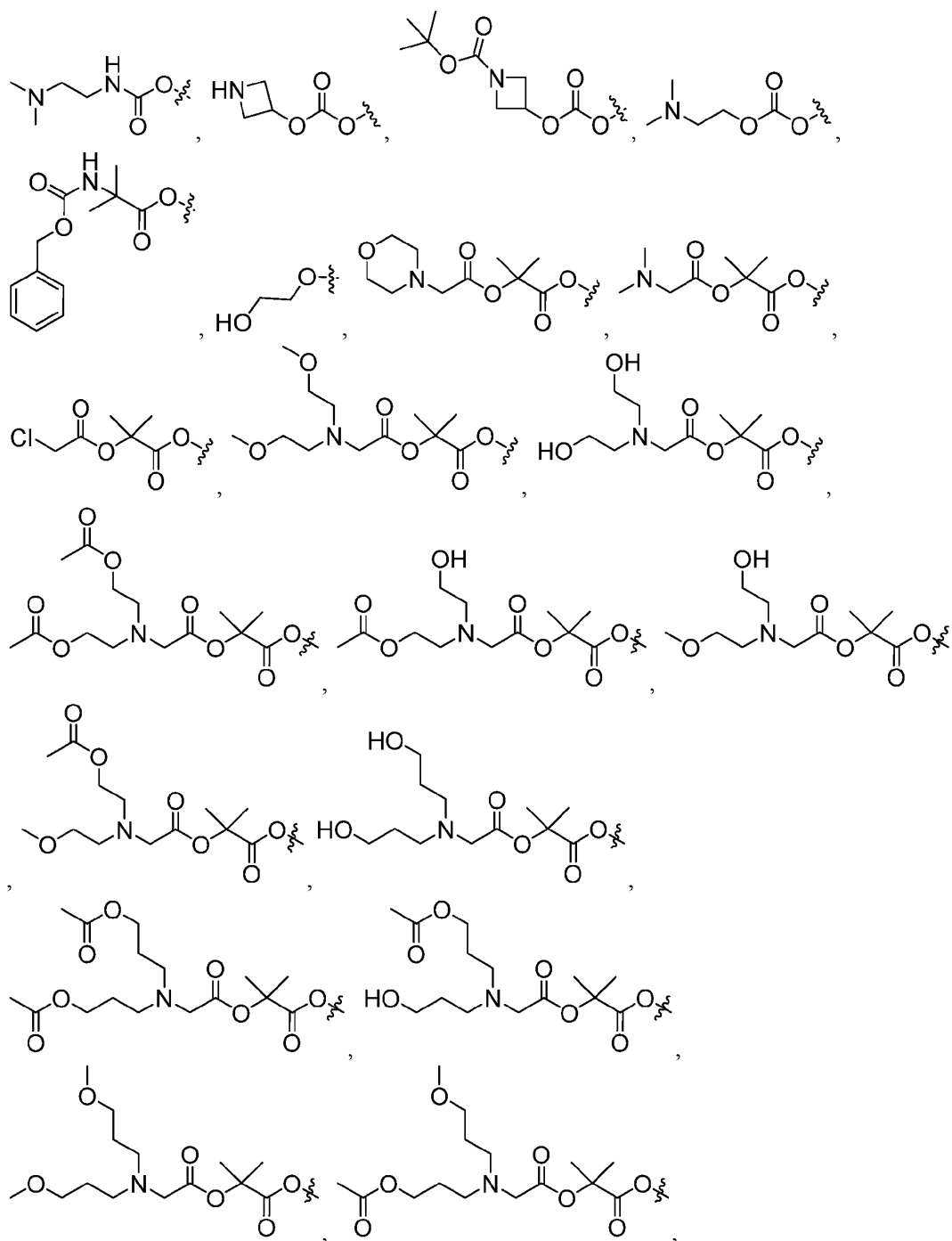
 denotes the point of attachment of the oxygen atom to the carbon atom of the –C(R^{7A})(R^{7B}) group.

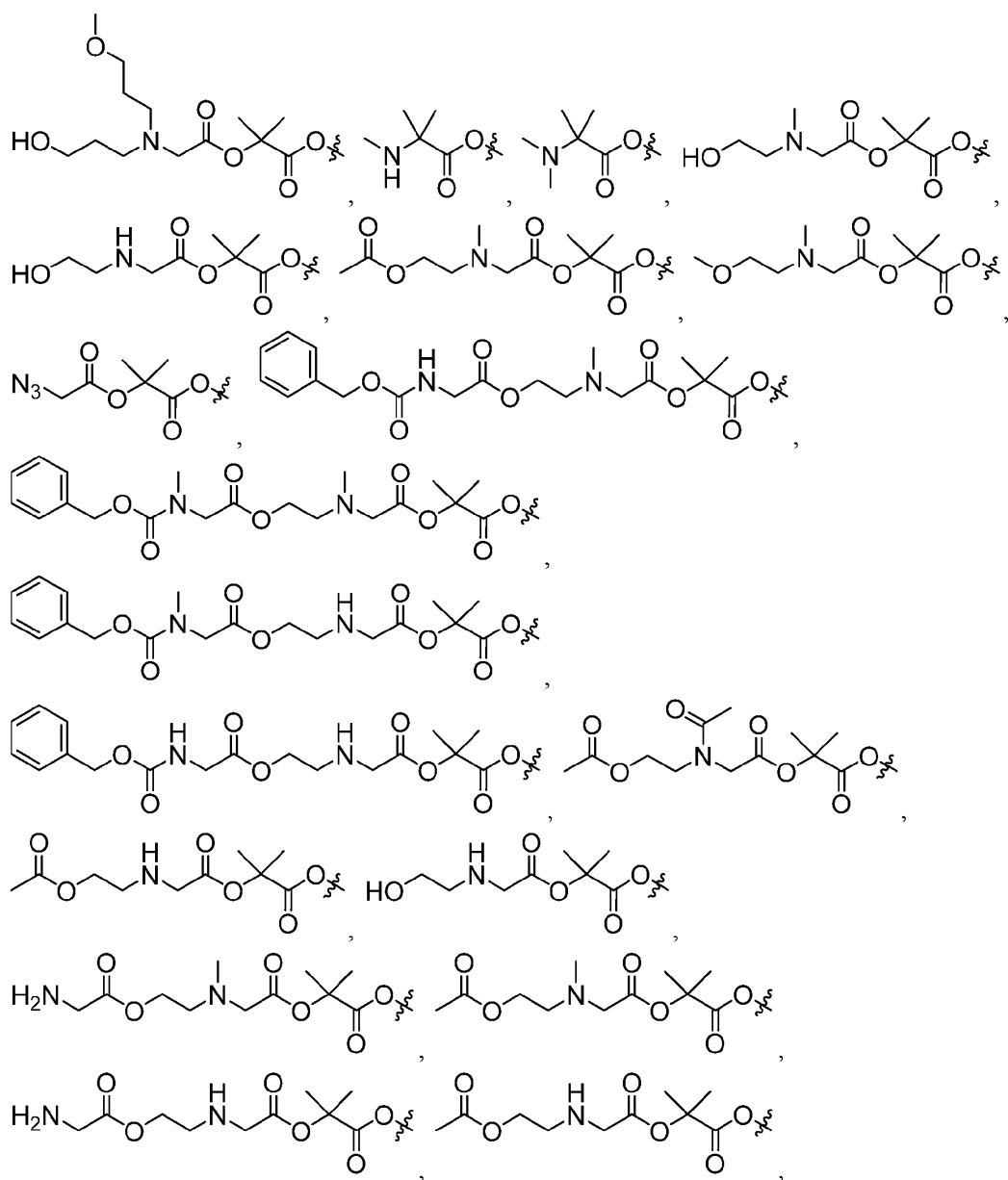
[0139] Each optional substituent of a group in Formula (IB) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, e.g., a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., –CH₂Cl, –CH₂I, –(CH₂)₂Cl, –(CH₂)₂I, or –CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., –F, –Cl, –Br, or –I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., –OMe, –OEt, or –OBn), alkoxy carbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxy carbonyl, amino (e.g., –NH₂, –NHMe, or –NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, –C(O)OH, –C(O)O-alkyl (e.g., –C(O)O-tBu or –C(O)OMe), –C(O)O-heteroalkyl, –C(O)O-alkylaryl, –OC(O)O-alkyl, –OC(O)O-heteroalkyl, –OC(O)O-alkylaryl, –C(O)NH₂, –C(O)NH-alkyl, –C(O)NH-heteroalkyl, –C(O)NH-alkylaryl, –NHC(O)O-alkyl (e.g., –NHC(O)OtBu), –NHC(O)O-heteroalkyl, –NHC(O)O-alkylaryl (e.g., –NH-Cbz), –C(O)N(alkyl)₂, –C(O)N(alkyl)(heteroalkyl), –C(O)N(heteroalkyl)₂, –N(alkyl)C(O)O-alkyl (e.g., N(Me)C(O)OtBu), –N(alkyl)C(O)O-heteroalkyl, –N(alkyl)C(O)O-alkylaryl, –N(alkyl)C(O)N(alkyl)₂, –N(alkyl)C(O)N(alkyl)(heteroalkyl), –N(alkyl)C(O)N(heteroalkyl)₂, –N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

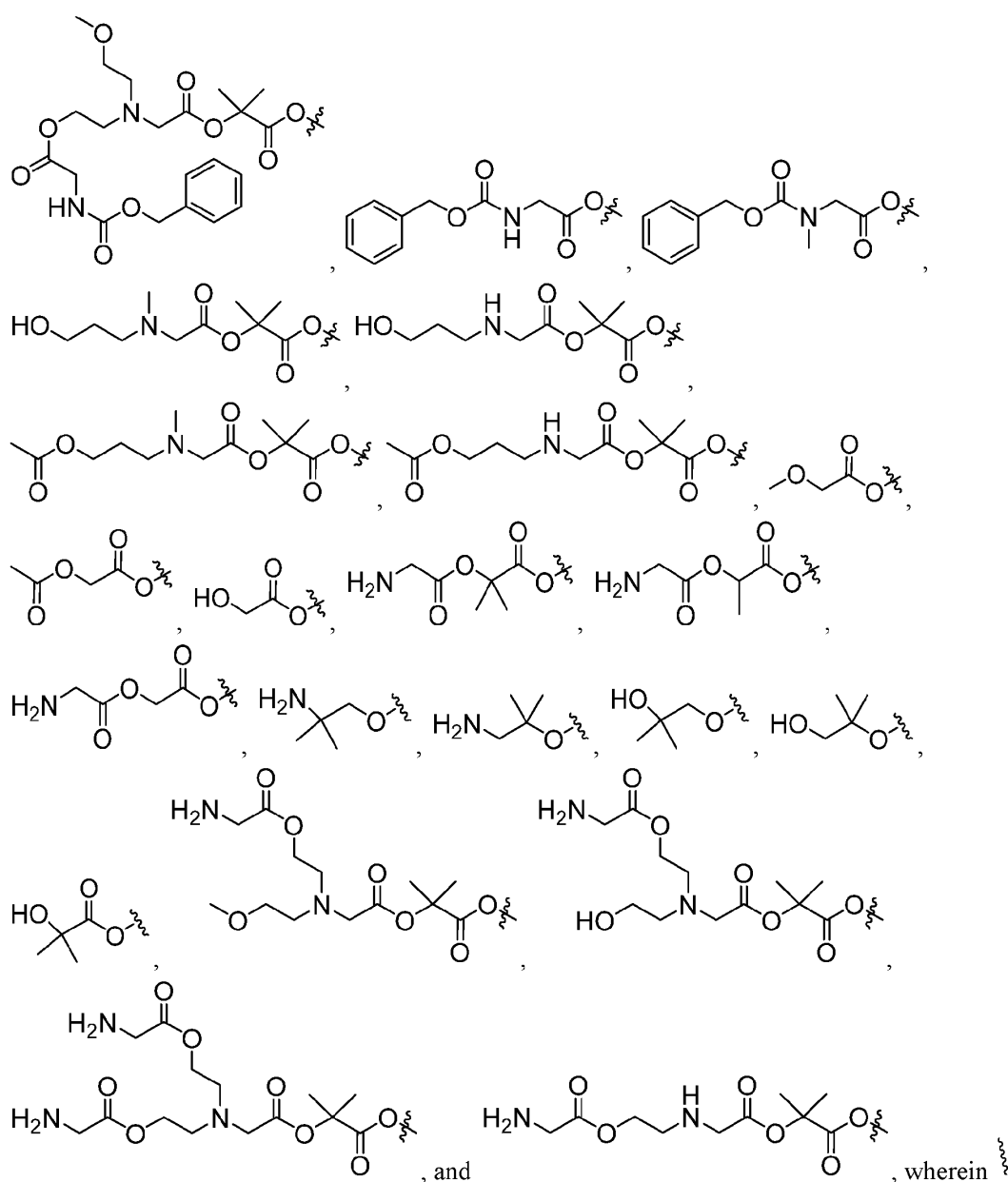
[0140] The $-O-(R^3)$ group of Formula (IB) may be a moiety selected from the group consisting of





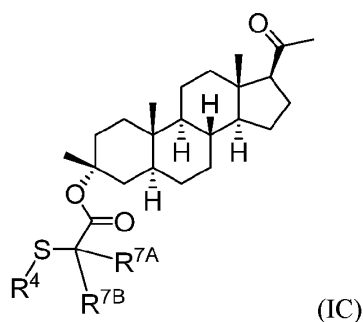






denotes the point of attachment of the oxygen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group.

[0141] The compound of Formula (I) or Formula (I-I) may be a compound of Formula (IC):

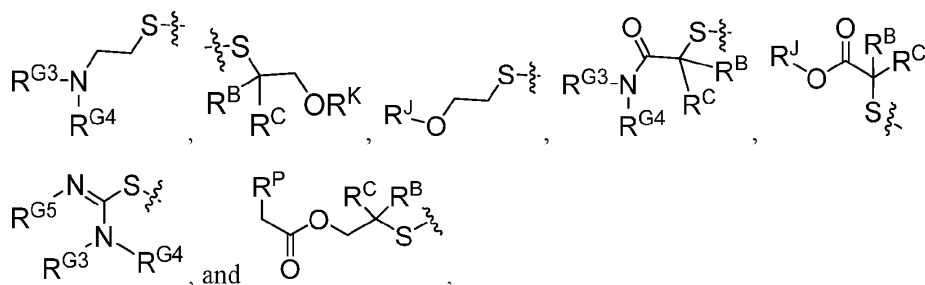


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R⁴ is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, or heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

[0142] The $-S-(R^4)$ group in Formula (IC) may be a moiety selected from the group consisting of



wherein

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4}, together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

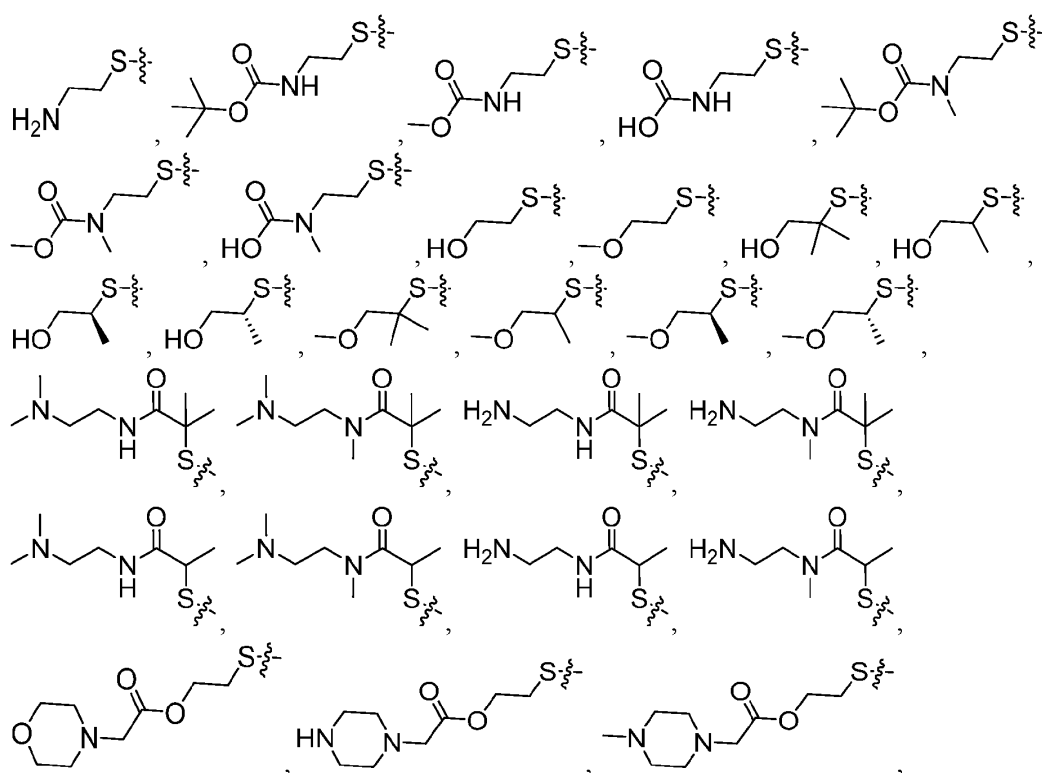
R^P is halo, -NH-alkyl, -NH-heteroalkyl, -N-(alkyl)₂ (e.g., -N(Me)₂), -N-(heteroalkyl)₂ (e.g., -N(CH₂CH₂OH)₂), or heterocyclyl (e.g., morpholinyl); and

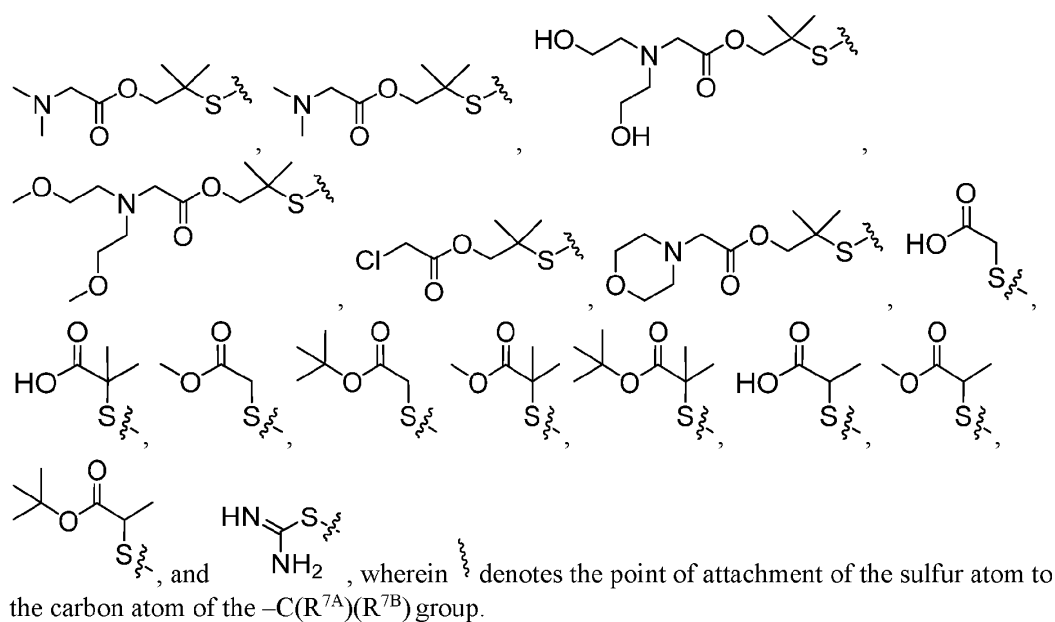
 denotes the point of attachment of the sulfur atom to the carbon atom of the -C(R^{7A})(R^{7B}) group.

[0143] Each optional substituent of a group in Formula (IC) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., -OMe, -OEt, or -OBn), alkoxycarbonyloxy, aryloxy carbonyloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylaryl amino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl,

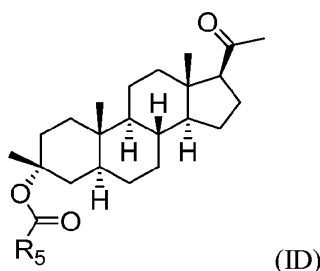
alkylheteroaryl, $-\text{C}(\text{O})\text{OH}$, $-\text{C}(\text{O})\text{O-alkyl}$ (e.g., $-\text{C}(\text{O})\text{O-tBu}$ or $-\text{C}(\text{O})\text{OMe}$), $-\text{C}(\text{O})\text{O-heteroalkyl}$, $-\text{C}(\text{O})\text{O-alkylaryl}$, $-\text{OC}(\text{O})\text{O-alkyl}$, $-\text{OC}(\text{O})\text{O-heteroalkyl}$, $-\text{OC}(\text{O})\text{O-alkylaryl}$, $-\text{C}(\text{O})\text{NH}_2$, $-\text{C}(\text{O})\text{NH-alkyl}$, $-\text{C}(\text{O})\text{NH-heteroalkyl}$, $-\text{C}(\text{O})\text{NH-alkylaryl}$, $-\text{NHC}(\text{O})\text{O-alkyl}$ (e.g., $-\text{NHC}(\text{O})\text{OtBu}$), $-\text{NHC}(\text{O})\text{O-heteroalkyl}$, $-\text{NHC}(\text{O})\text{O-alkylaryl}$ (e.g., $-\text{NH-Cbz}$), $-\text{C}(\text{O})\text{N(alkyl)}_2$, $-\text{C}(\text{O})\text{N(alkyl)(heteroalkyl)}$, $-\text{C}(\text{O})\text{N(heteroalkyl)}_2$, $-\text{N(alkyl)C}(\text{O})\text{O-alkyl}$ (e.g., $\text{N(Me)C}(\text{O})\text{OtBu}$), $-\text{N(alkyl)C}(\text{O})\text{O-heteroalkyl}$, $-\text{N(alkyl)C}(\text{O})\text{O-alkylaryl}$, $-\text{N(alkyl)C}(\text{O})\text{N(alkyl)}_2$, $-\text{N(alkyl)C}(\text{O})\text{N(alkyl)(heteroalkyl)}$, $-\text{N(alkyl)C}(\text{O})\text{N(heteroalkyl)}_2$, $-\text{N(alkyl)C}(\text{O})\text{NH-alkylaryl}$, $=\text{NH}$, or $=\text{N-alkyl}$. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0144] The $-\text{S}(\text{R}^4)$ group in Formula (IC) may be a moiety selected from the group consisting of





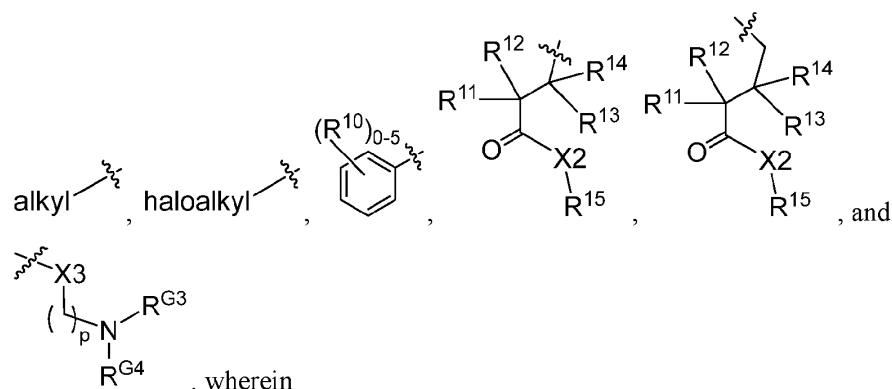
[0145] The compound of Formula (I) or Formula (I-I) may be a compound of Formula (ID):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,
wherein

R⁵ is alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted.

[0146] The $-R^5$ group in Formula (ID) may be a moiety selected from the group consisting of



X_2 and X_3 are each independently $-\text{CH}_2-$, $-\text{O}-$, $-\text{S}-$, or $-\text{N}(R^{G3})-$ (e.g., $-\text{NH}-$);

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-\text{OR}^J$, $-\text{N}(R^{G3})(R^{G4})$; $-\text{NO}_2$, $-\text{CN}$, or $-\text{NC}$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-\text{N}(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{15} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

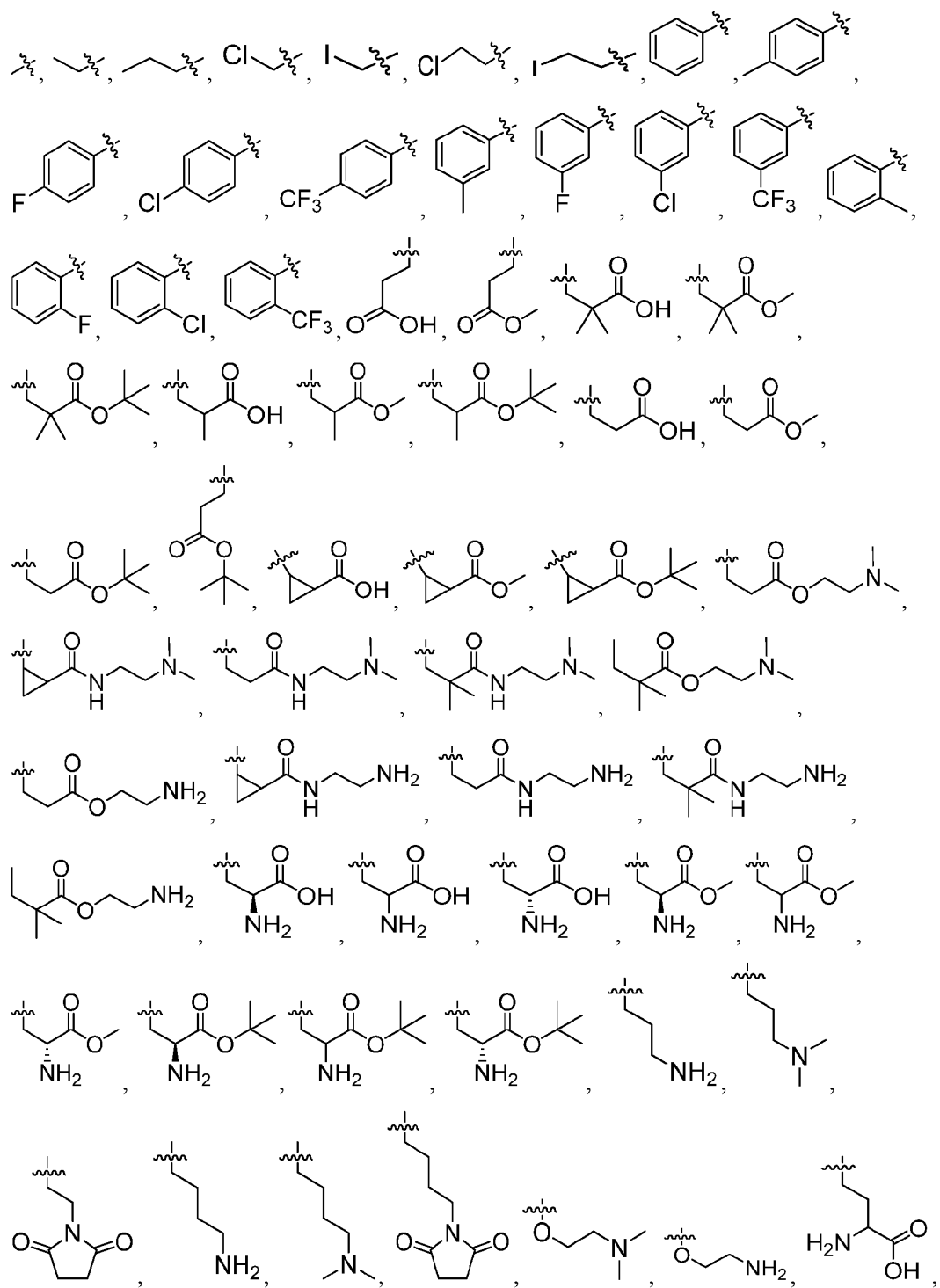
and

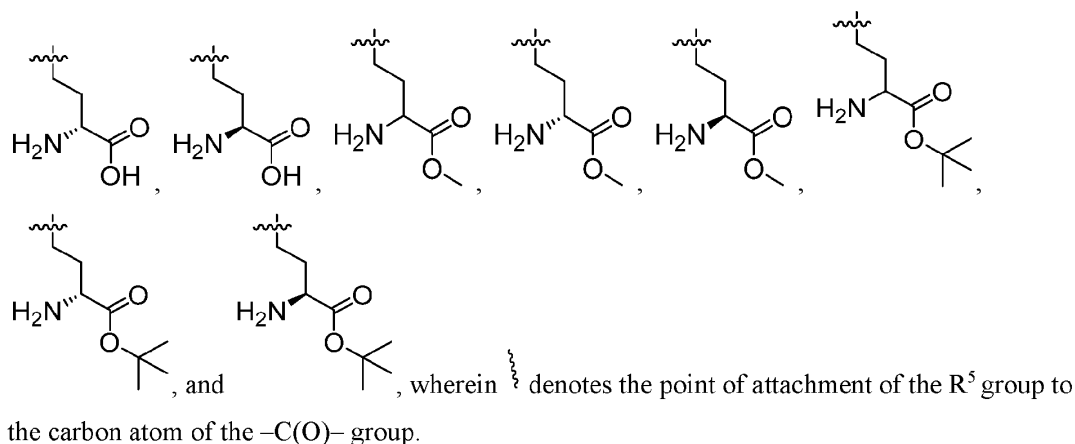
p is an integer between 0 and 4; and

--- denotes the point of attachment of the R^5 group to the carbon atom of the $-\text{C}(\text{O})-$ group.

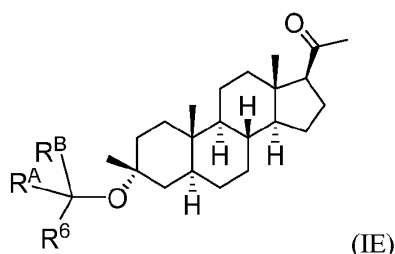
[0147] Each optional substituent of a group in Formula (ID) (e.g., an optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (e.g., C₁-C₆ alkyl), alkenyl (e.g., C₂-C₆ alkenyl), alkynyl (e.g., C₂-C₆ alkynyl), heteroalkyl (e.g., C₁-C₆ heteroalkyl), haloalkyl (e.g., C₁-C₆ haloalkyl, e.g., -CH₂Cl, -CH₂I, -(CH₂)₂Cl, -(CH₂)₂I, or -CF₃), cycloalkyl (e.g., C₃-C₈ cycloalkyl, e.g., cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (e.g., C₃-C₈ heterocyclyl, e.g., morpholinyl, piperazinyl, N-methylpiperazinyl, azetidyl, or N-Boc-azetidyl), alkylaryl (e.g., benzyl), aryl (e.g., phenyl), heteroaryl (e.g., pyrrolyl, imidazolyl, or indolyl), halogen (e.g., -F, -Cl, -Br, or -I), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (e.g., -OMe, -OEt, or -OBn), alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (e.g., -NH₂, -NHMe, or -NMe₂), aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxy, phosphate, phosphonate, phosphinate, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonate, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, -C(O)OH, -C(O)O-alkyl (e.g., -C(O)O-tBu or -C(O)OMe), -C(O)O-heteroalkyl, -C(O)O-alkylaryl, -OC(O)O-alkyl, -OC(O)O-heteroalkyl, -OC(O)O-alkylaryl, -C(O)NH₂, -C(O)NH-alkyl, -C(O)NH-heteroalkyl, -C(O)NH-alkylaryl, -NHC(O)O-alkyl (e.g., -NHC(O)OtBu), -NHC(O)O-heteroalkyl, -NHC(O)O-alkylaryl (e.g., -NH-Cbz), -C(O)N(alkyl)₂, -C(O)N(alkyl)(heteroalkyl), -C(O)N(heteroalkyl)₂, -N(alkyl)C(O)O-alkyl (e.g., N(Me)C(O)OtBu), -N(alkyl)C(O)O-heteroalkyl, -N(alkyl)C(O)O-alkylaryl, -N(alkyl)C(O)N(alkyl)₂, -N(alkyl)C(O)N(alkyl)(heteroalkyl), -N(alkyl)C(O)N(heteroalkyl)₂, -N(alkyl)C(O)NH-alkylaryl, =NH, or =N-alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0148] The -R⁵ group in Formula (ID) may be a moiety selected from the group consisting of





[0149] The compound of Formula (I) or Formula (I-I) may be a compound of Formula (IE):

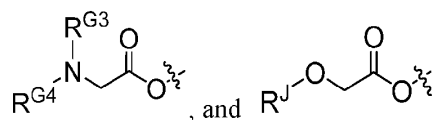


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R⁶ is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, -OC(O)-alkyl, -C(O)O-alkyl, -OC(O)-heteroalkyl, -C(O)O-heteroalkyl, -N₃, -SH, or -S-alkyl (e.g., -S-Me), wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

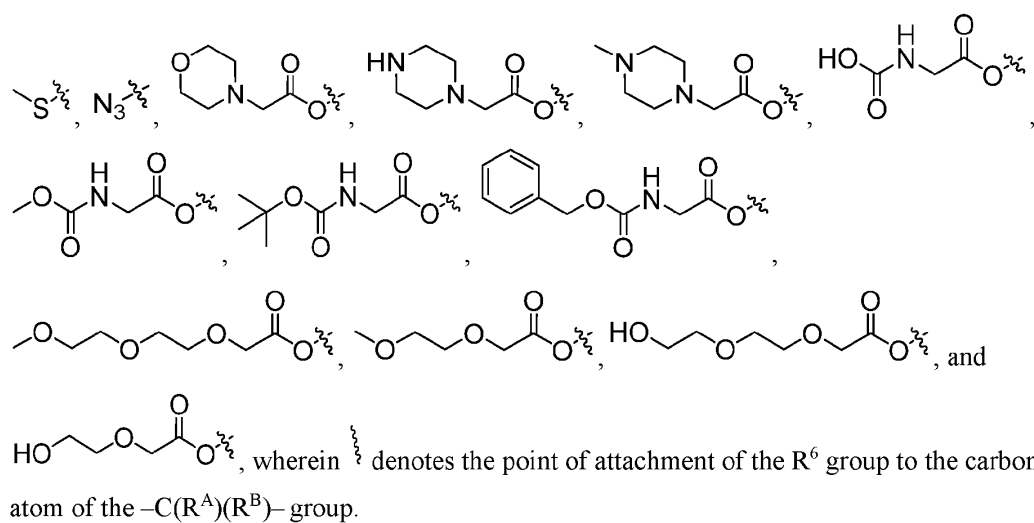
R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

[0150] The R⁶ group in Formula (IE) may be a moiety selected from the group consisting of

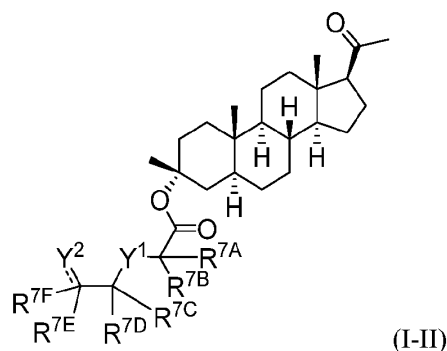


NHC(O)OtBu), $\text{NHC(O)O-heteroalkyl}$, NHC(O)O-alkylaryl (e.g., NH-Cbz), C(O)N(alkyl)_2 , $\text{C(O)N(alkyl)(heteroalkyl)}$, $\text{C(O)N(heteroalkyl)}_2$, $\text{N(alkyl)C(O)O-alkyl}$ (e.g., N(Me)C(O)OtBu), $\text{N(alkyl)C(O)O-heteroalkyl}$, $\text{N(alkyl)C(O)O-alkylaryl}$, $\text{N(alkyl)C(O)N(alkyl)}_2$, $\text{N(alkyl)C(O)N(alkyl)(heteroalkyl)}$, $\text{N(alkyl)C(O)N(heteroalkyl)}_2$, $\text{N(alkyl)C(O)NH-alkylaryl}$, $=\text{NH}$, or $=\text{N-alkyl}$. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

[0152] The R^6 group in Formula (IE) may be a moiety selected from the group consisting of



[0153] A compound of the present disclosure may be a compound of Formula (I-II):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

$\parallel$ denotes a single bond or a double bond;

Y^1 is alkylene (e.g., methylene), alkenylene, alkynylene, heteroalkylene, $-C(O)-$, $-OC(O)-$, $-C(O)O-$, $-NR^1-$, $-O-$, or $-S-$, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

Y^2 is heteroalkyl, heterocyclyl, heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, $-NR^1R^2$, $-OR^3$, $-SR^4$, $=NR^1$, or $=O$, wherein the heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl, or one of R^{7A} and R^{7B} is bonded to Y^1 through one or more carbon atoms or heteroatoms to form a cyclic

moiety (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl, e.g., pyrrole), and the other of the R^{7A} and R^{7B} groups is hydrogen or optionally substituted alkyl;

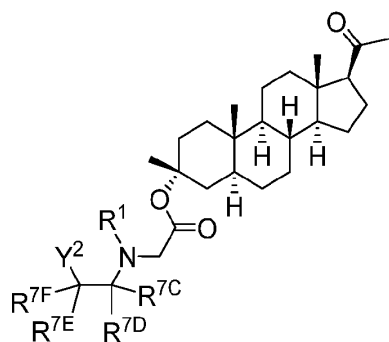
R^{7C} and R^{7D} are each independently hydrogen or optionally substituted alkyl, or R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group; and

R^{7E} and R^{7F} are each independently absent, hydrogen, alkyl, heteroalkyl, $-NR^1R^2$, $-OR^3$, or $-SR^4$, wherein the alkyl or heteroalkyl is optionally substituted, with the proviso that when

 is a double bond, one of R^{7E} and R^{7F} is absent, or R^{7E} and R^{7F} are each bonded to the same oxygen to form an oxo group.

[0154] In some embodiments Y^1 of Formula (I-II) is $-O-$ or $-N(R^1)-$ (e.g., $-N(H)-$, $-N(alkyl)-$, or $-N(heteroalkyl)-$). For example, Y^1 of Formula (I-II) may be $-O-$ or $-N(H)-$. Alternatively, Y^1 of Formula (I-II) may be $-N(Me)-$, $-N(Et)-$, $-N(EtOH)-$, or $-N(^nPrOH)-$.

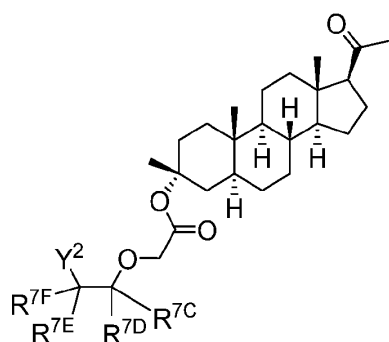
[0155] The compound of Formula (I-II) may be a compound of Formula (I-IIa):



(I-IIa), or a pharmaceutically acceptable salt, solvate,

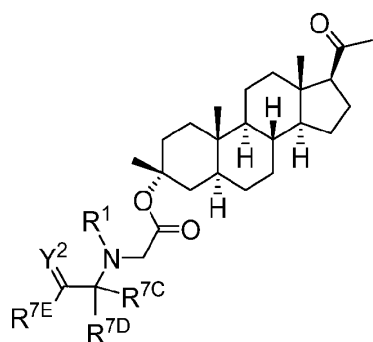
hydrate, tautomer, or stereoisomer thereof, wherein Y^2 , R^1 , R^{7C} , R^{7D} , R^{7E} , and R^{7F} are as defined above.

[0156] The compound of Formula (I-II) may be a compound of Formula (I-IIb):



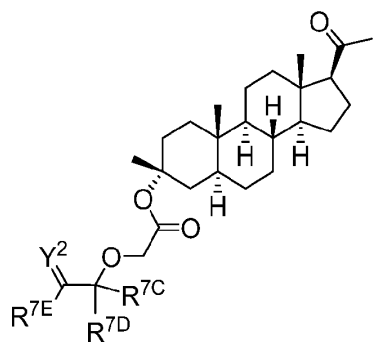
(I-IIb), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Y^2 , R^{7C} , R^{7D} , R^{7E} , and R^{7F} are as defined above.

[0157] The compound of Formula (I-II) may be a compound of Formula (I-IIc):



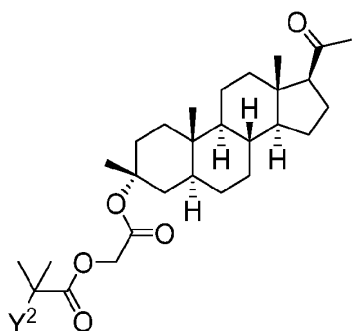
(I-IIc), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Y^2 , R^1 , R^{7C} , R^{7D} , and R^{7E} are as defined above.

[0158] The compound of Formula (I-II) may be a compound of Formula (I-IId):



(I-IId), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Y^2 , R^{7C} , R^{7D} , and R^{7E} are as defined above.

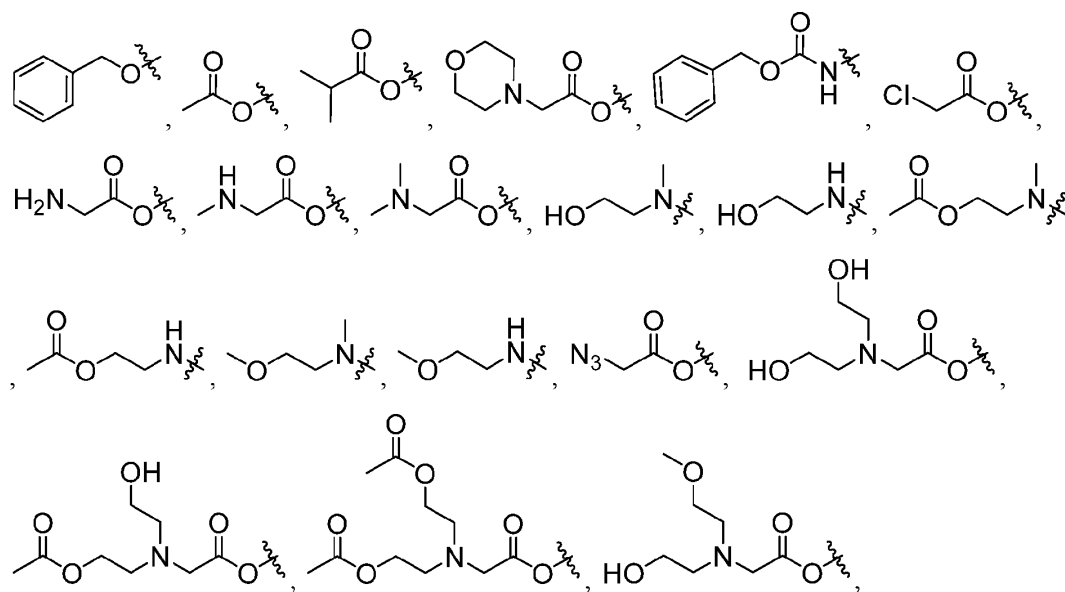
[0159] The compound of Formula (I-II) may be a compound of Formula (I-IIe):

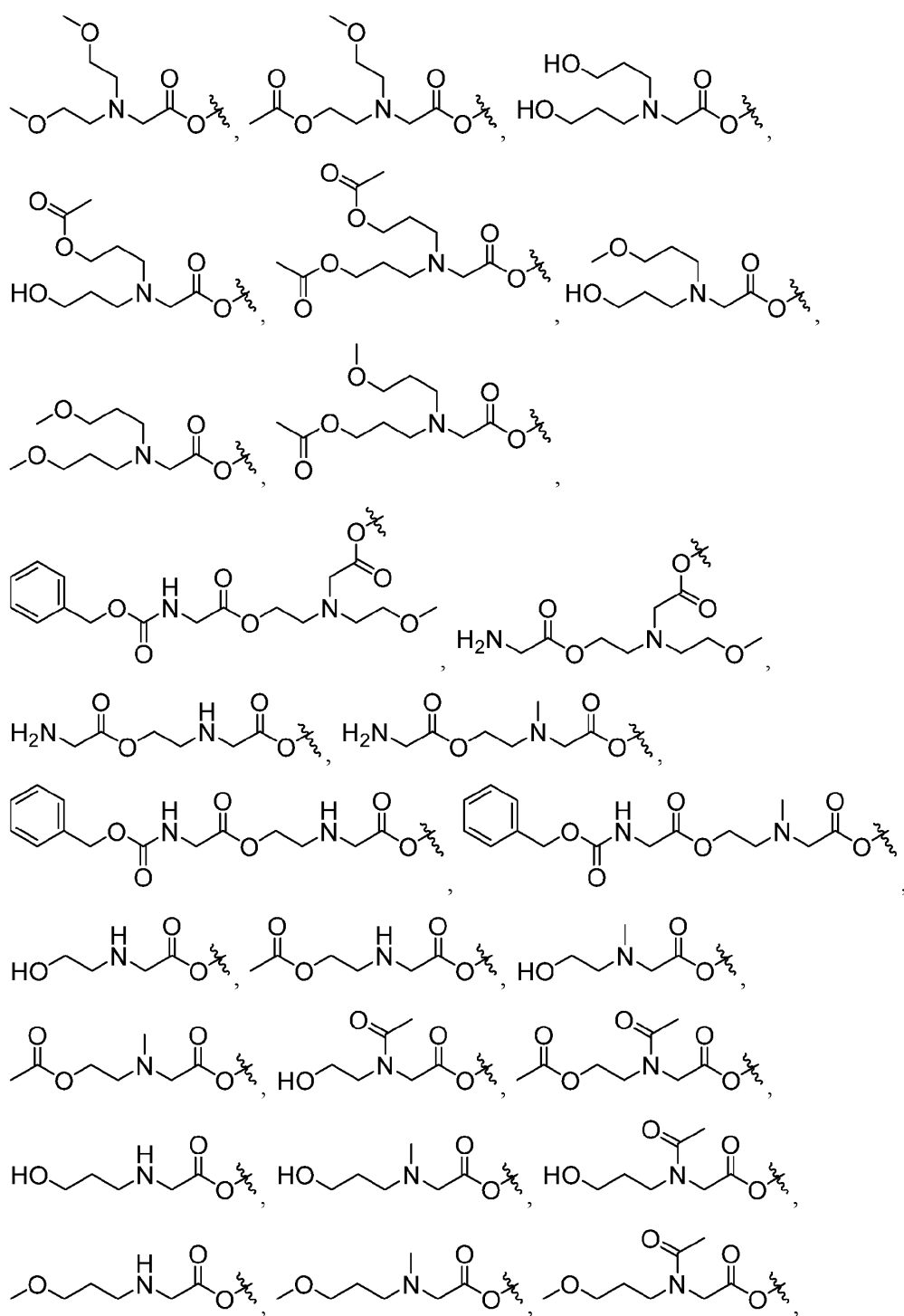


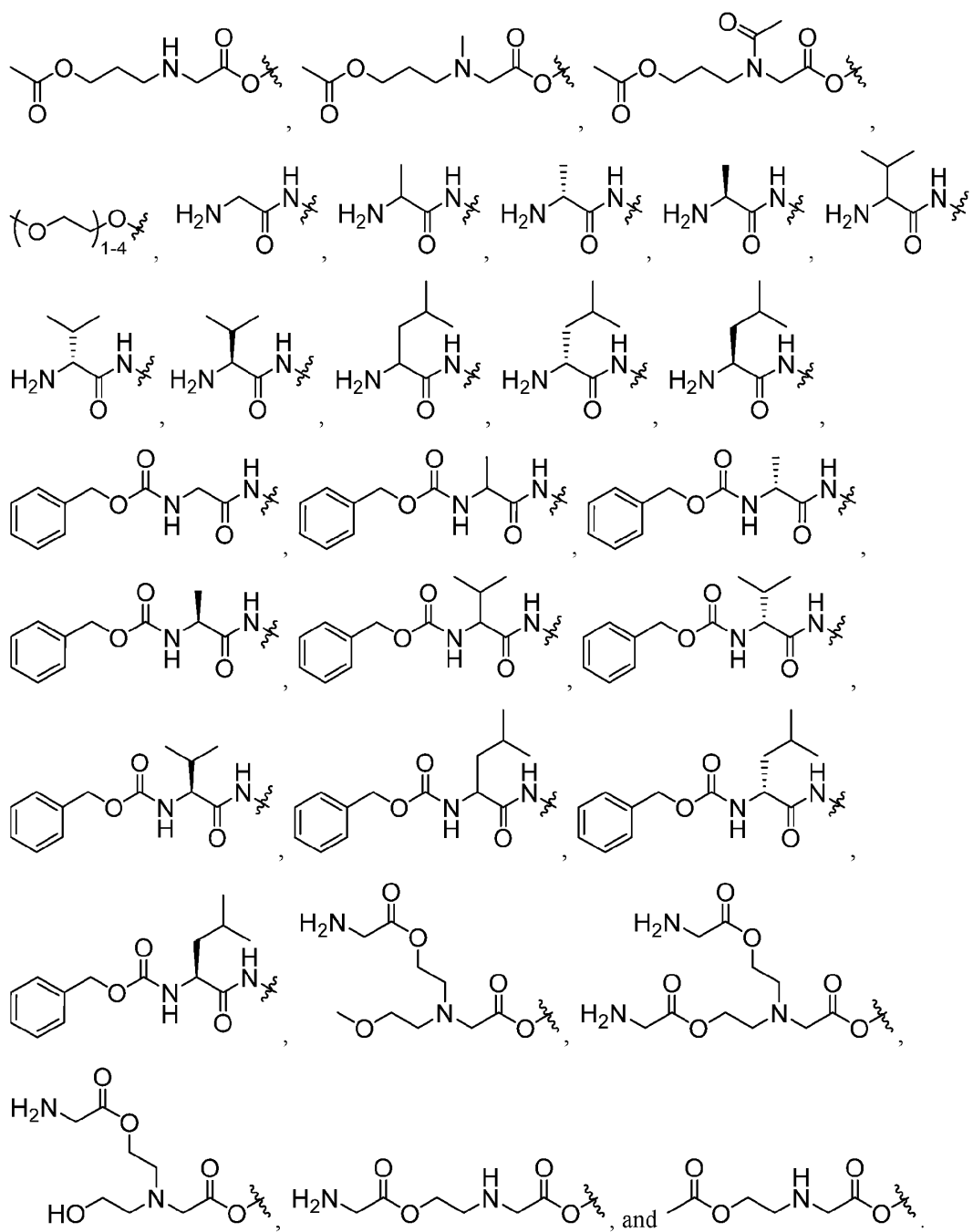
Y²  (I-IIe), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein Y² is as defined above.

[0160] Y² of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or R^{7E} when  is a double bond, may be optionally substituted heteroalkyl, -NR¹R² (e.g., -NH₂, -NHMe, or -NMe₂), -OR³ (e.g., -OH, -OMe, -OEt, or -O^tBu), or =O. For example, Y² of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or R^{7E} when  is a double bond, may be -NH₂, -NHMe, or -OH.

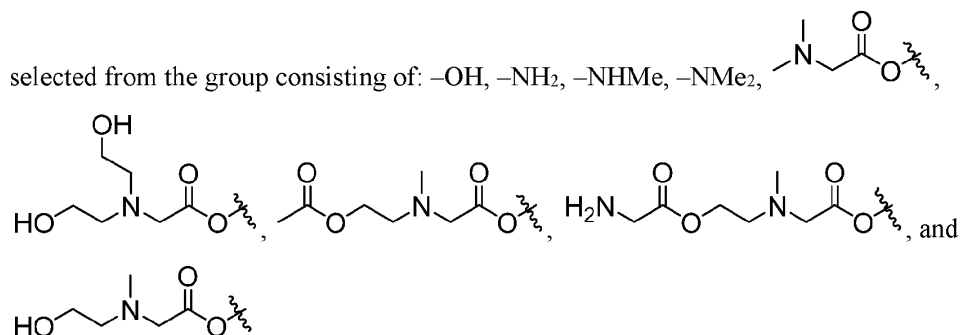
[0161] Alternatively, Y² of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), or R^{7E} when  is a double bond, may be optionally substituted heteroalkyl, for example a substituted or unsubstituted heteroalkyl selected from the group consisting of:







[0162] For example, Y^2 of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe) may be



[0163] R^{7A} and R^{7B} of Formula (I-II) may each be independently hydrogen.

[0164] R^{7C} and R^{7D} of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), or (I-IId) may each be independently hydrogen or methyl, or R^{7C} and R^{7D} of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), or (I-IId) may each be bonded to the same oxygen atom to form an oxo group.

[0165] R^{7E} and R^{7F} of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), or (I-IId) may each be independently hydrogen or methyl, or R^{7C} and R^{7D} of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), or (I-IId) may each be bonded to the same oxygen atom to form an oxo group.

[0166] R^1 of Formulae (I-II), (I-IIa), and (I-IIc) may be hydrogen, alkyl, or heteroalkyl. For example, R^1 of Formulae (I-II), (I-IIa), and (I-IIc) may be hydrogen, methyl, ethyl, $-MeOH$, $-EtOH$, or $-nPrOH$.

[0167] Each optional substituent of a group in one of Formulae (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe), such as optional substituent on an alkyl, alkylene, alkenyl, alkenylene, alkynyl, alkynylene, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl group) may be any suitable substituent, *e.g.*, a substituent described herein. For example, the optional substituent can be alkyl (*e.g.*, C_1 - C_6 alkyl), alkenyl (*e.g.*, C_2 - C_6 alkenyl), alkynyl (*e.g.*, C_2 - C_6 alkynyl), heteroalkyl (*e.g.*, C_1 - C_6 heteroalkyl), haloalkyl (*e.g.*, C_1 - C_6 haloalkyl, *e.g.*, $-CH_2Cl$, $-CH_2I$, $-(CH_2)_2Cl$, $-(CH_2)_2I$, or $-CF_3$), cycloalkyl (*e.g.*, C_3 - C_8 cycloalkyl, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl), heterocyclyl (*e.g.*, C_3 - C_8 heterocyclyl, *e.g.*, morpholinyl, piperazinyl, N-methylpiperazinyl, azetidiny, or N-Boc-azetidiny), alkylaryl (*e.g.*, benzyl), aryl (*e.g.*, phenyl), heteroaryl (*e.g.*, pyrrolyl, imidazolyl, or indolyl), halogen (*e.g.*, $-F$, $-Cl$, $-Br$, or $-I$), hydroxyl, alkylcarbonyloxy, arylcarbonyloxy, alkoxy (*e.g.*, $-OMe$, $-OEt$, or $-OBn$), alkoxycarbonyloxy, aryloxy, carboxylate, alkylcarbonyl, arylcarbonyl, alkoxycarbonyl, amino (*e.g.*, $-NH_2$, $-NHMe$, or $-NMe_2$),

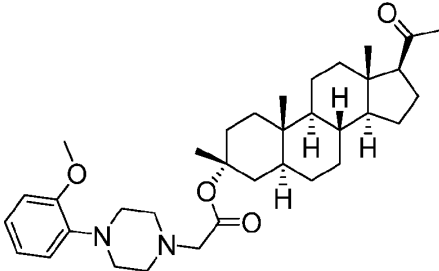
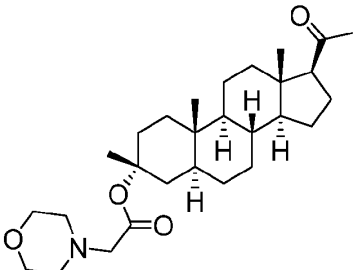
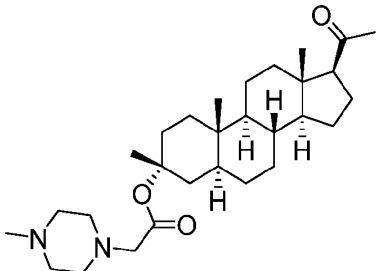
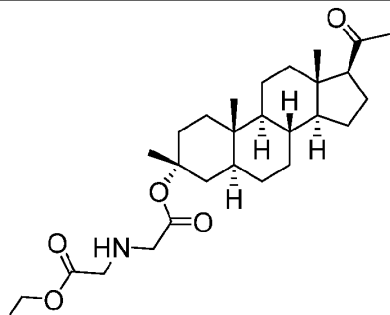
aminocarbonyl, alkylaminocarbonyl, dialkylaminocarbonyl, alkylthiocarbonyl, alkoxyl, phosphate, phosphonato, phosphinato, amino (including alkylamino, dialkylamino, arylamino, diarylamino and alkylarylamino), acylamino (including alkylcarbonylamino, arylcarbonylamino, carbamoyl, and ureido), amidino, imino, sulfhydryl, alkylthio, arylthio, thiocarboxylate, sulfate, sulfinyl, sulfonyl, alkylsulfinyl, sulfonato, sulfamoyl, sulfonamido, oxo, nitro, trifluoromethyl, cyano, azido, alkyl-cycloalkyl, alkyl-heterocyclyl, alkylheteroaryl, $-C(O)OH$, $-C(O)O$ -alkyl (e.g., $-C(O)O$ -tBu or $-C(O)OMe$), $-C(O)O$ -heteroalkyl, $-C(O)O$ -alkylaryl, $-OC(O)O$ -alkyl, $-OC(O)O$ -heteroalkyl, $-OC(O)O$ -alkylaryl, $-C(O)NH_2$, $-C(O)NH$ -alkyl, $-C(O)NH$ -heteroalkyl, $-C(O)NH$ -alkylaryl, $-NHC(O)O$ -alkyl (e.g., $-NHC(O)OtBu$), $-NHC(O)O$ -heteroalkyl, $-NHC(O)O$ -alkylaryl (e.g., $-NH$ -Cbz), $-C(O)N(alkyl)_2$, $-C(O)N(alkyl)(heteroalkyl)$, $-C(O)N(heteroalkyl)_2$, $-N(alkyl)C(O)O$ -alkyl (e.g., $N(Me)C(O)OtBu$), $-N(alkyl)C(O)O$ -heteroalkyl, $-N(alkyl)C(O)O$ -alkylaryl, $-N(alkyl)C(O)N(alkyl)_2$, $-N(alkyl)C(O)N(alkyl)(heteroalkyl)$, $-N(alkyl)C(O)N(heteroalkyl)_2$, $-N(alkyl)C(O)NH$ -alkylaryl, $=NH$, or $=N$ -alkyl. Cyclic groups (e.g., cycloalkyl, heterocyclyl, aryl, and heteroaryl) can be substituted at one or more ring positions with any suitable substituent, such as one of the substituents listed above.

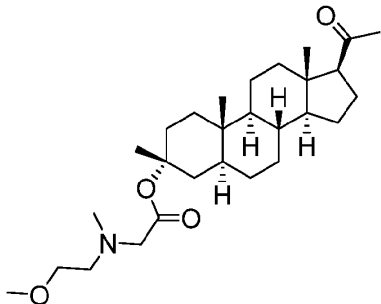
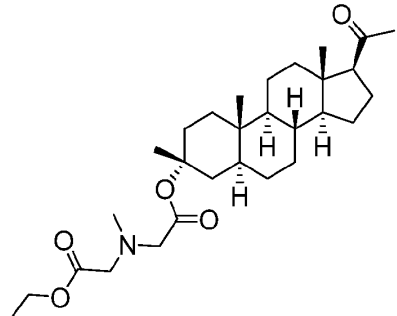
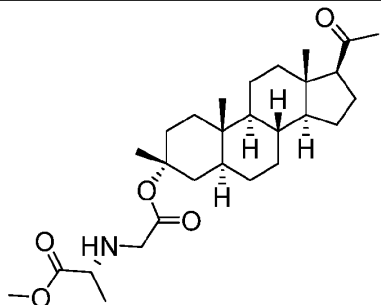
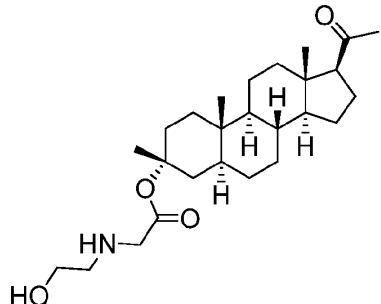
[0168] A compound disclosed herein, e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe) may have a structure provided in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe) is a hydrochloride (HCl) salt. In some embodiments, a compound disclosed herein is a hydrochloride (HCl) salt of a compound provided in Table 1. In some embodiments, a compound disclosed herein (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), or (I-IIe) is a trifluoroacetate (TFA) salt. In some embodiments, a compound disclosed herein is a trifluoroacetate (TFA) salt of a compound provided in Table 1.

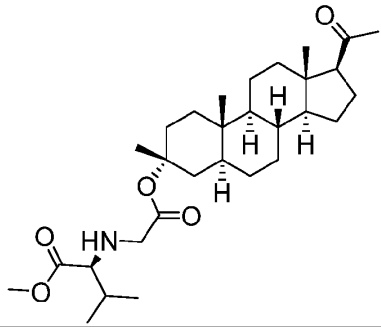
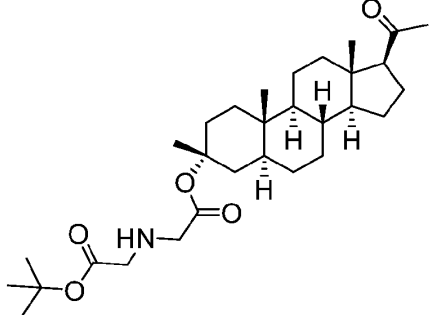
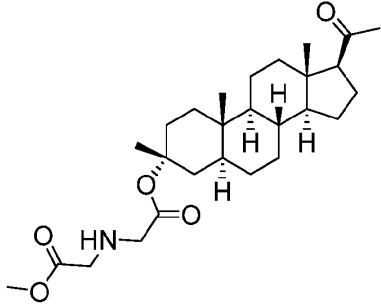
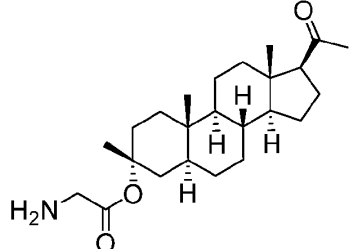
[0169] It will be appreciated that certain compounds may form a salt with more than one counterion, for example, two chloride ions to form a bis-HCl salt. Therefore, it will be appreciated that reference to an HCl salt herein may refer to a monohydrochloride salt or a bis-

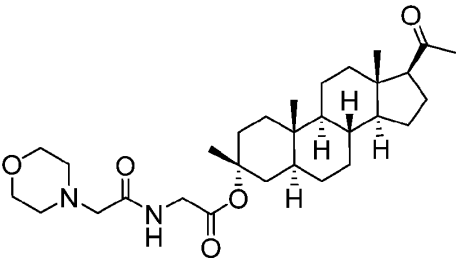
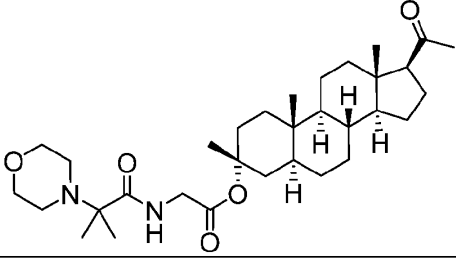
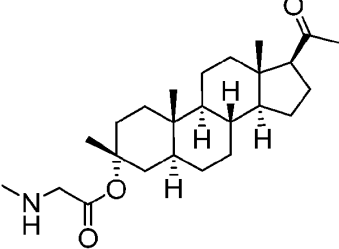
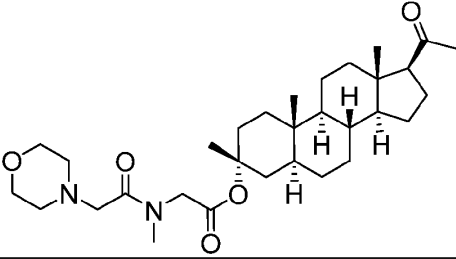
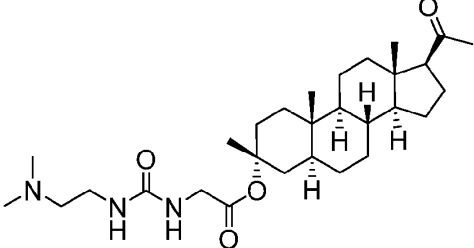
hydrochloride salt. Similarly, it will be appreciated that reference to a TFA salt herein may refer to a monotrifluoroacetate salt, or a bis-trifluoroacetate salt.

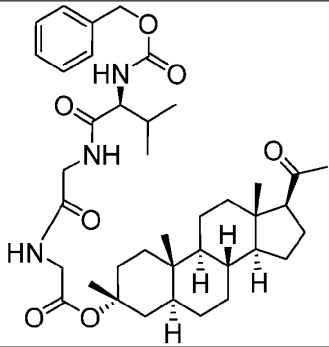
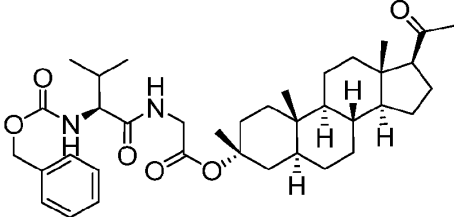
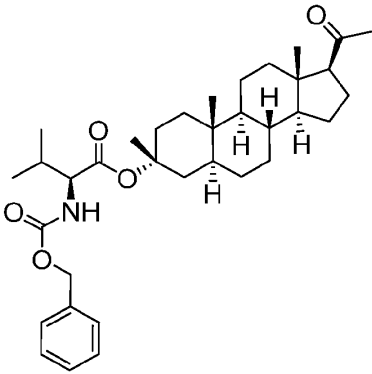
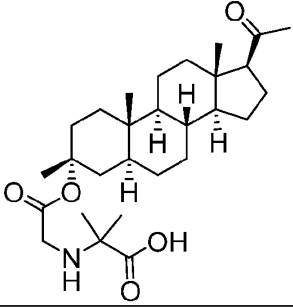
[0170] **Table 1.** Exemplary compounds.

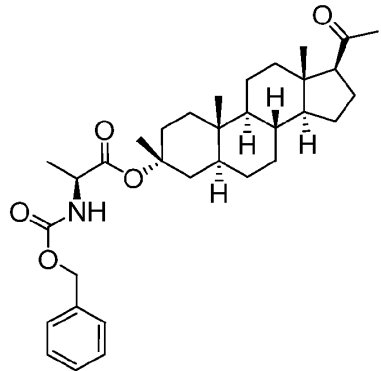
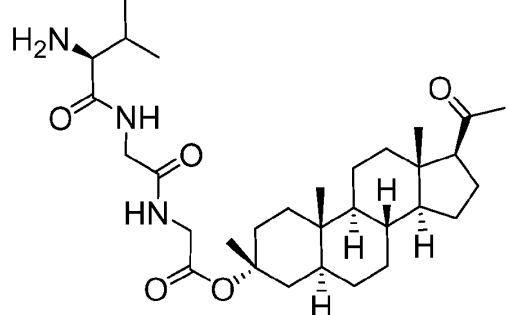
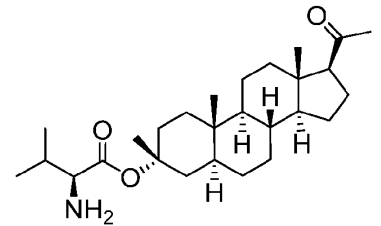
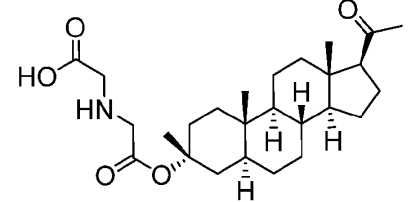
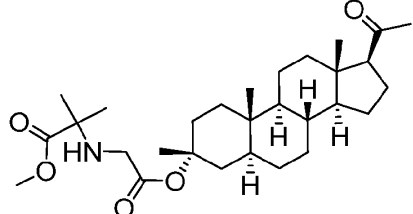
Compound No.	Structure
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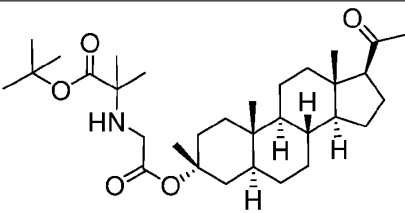
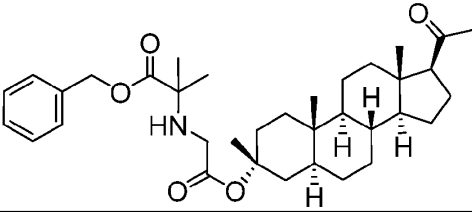
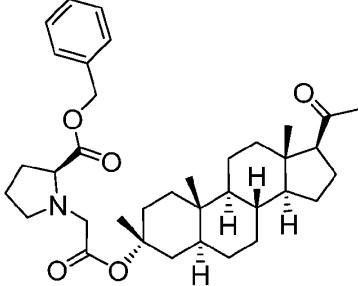
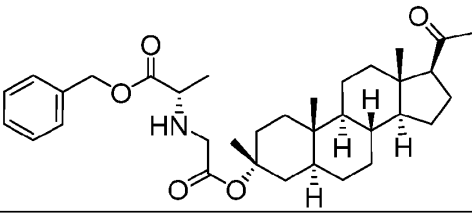
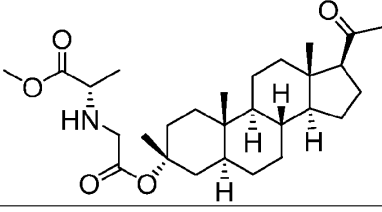
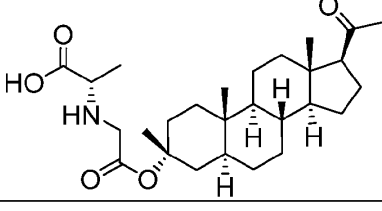
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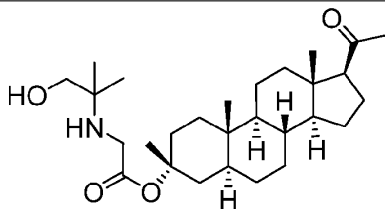
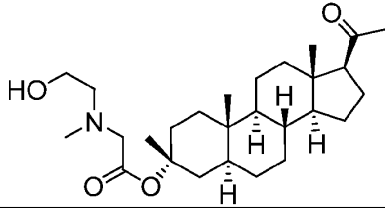
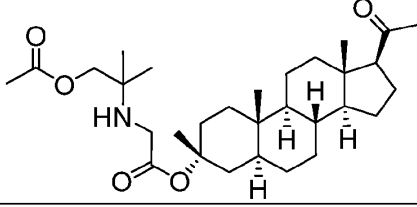
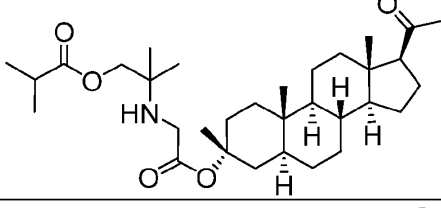
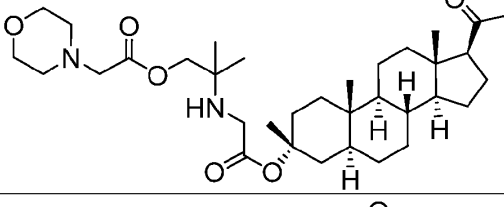
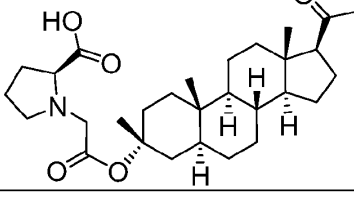
108	 <chem>CC(=O)O[C@@H](CNC(=O)OC(C)C)C[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C)C)C</chem>
109	 <chem>CC(=O)O[C@@H](CNC(=O)OC(C)(C)C(C)C)C[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C)C)C</chem>
110	 <chem>CC(=O)O[C@@H](CNC(=O)OC(C)C)C[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C)C)C</chem>
111	 <chem>CC(=O)O[C@@H](CNC(=O)N)C[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)C)C)C</chem>

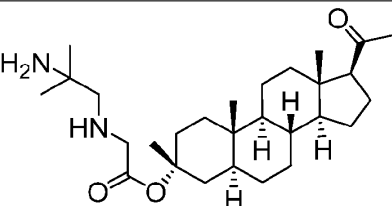
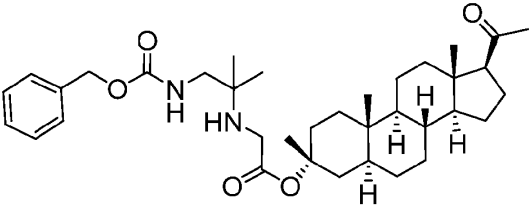
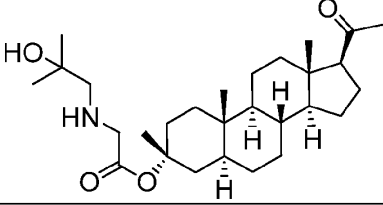
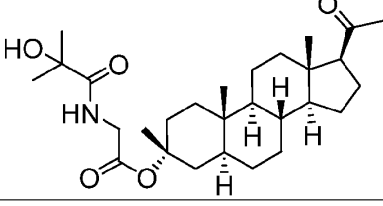
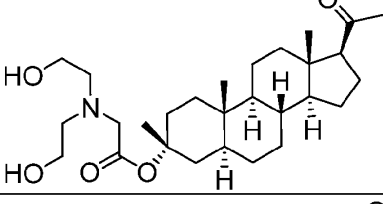
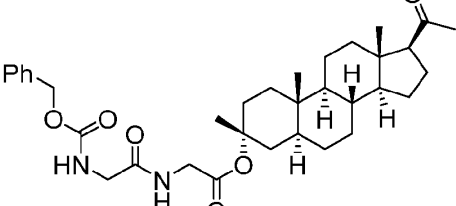
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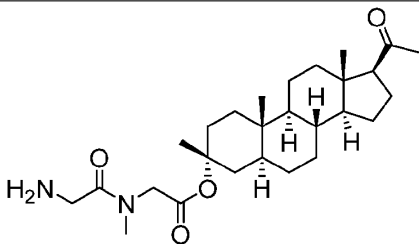
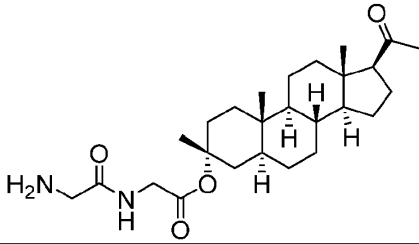
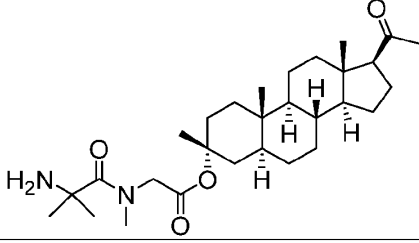
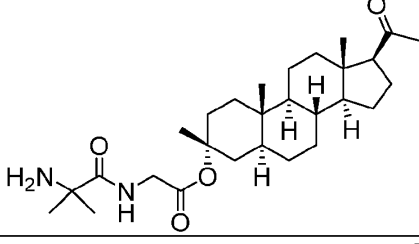
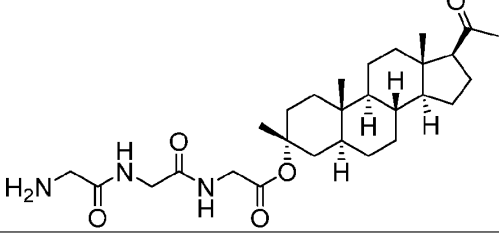
121	 <chem>CC(=O)C1CCC2[C@H]3[C@@H]([C@H]1CC[C@@H]2[C@H]([C@@H]3OC(=O)C(C)NC(=O)OCc4ccccc4)C)C</chem>
122	 <chem>CC(=O)C1CCC2[C@H]3[C@@H]([C@H]1CC[C@@H]2[C@H]([C@@H]3OC(=O)CCNC(=O)CCNC(=O)C(C)N)C)C</chem>
123	 <chem>CC(=O)C1CCC2[C@H]3[C@@H]([C@H]1CC[C@@H]2[C@H]([C@@H]3OC(=O)C(C)N)C)C</chem>
124	 <chem>CC(=O)C1CCC2[C@H]3[C@@H]([C@H]1CC[C@@H]2[C@H]([C@@H]3OC(=O)CCNC(=O)CC(=O)O)C)C</chem>
125	 <chem>CC(=O)C1CCC2[C@H]3[C@@H]([C@H]1CC[C@@H]2[C@H]([C@@H]3OC(=O)CCNC(=O)C(C)(C)OC(=O)C)C)C</chem>

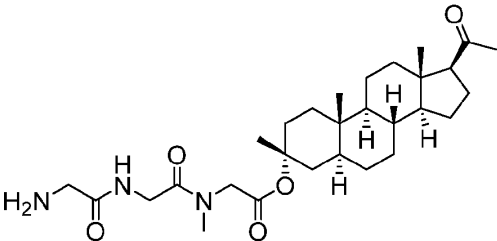
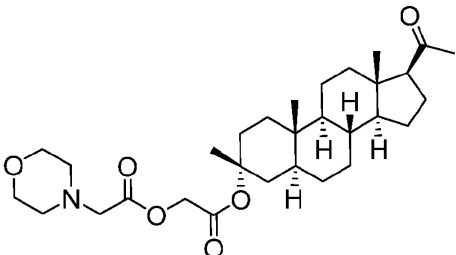
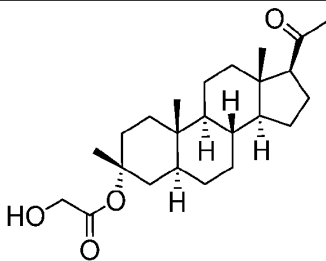
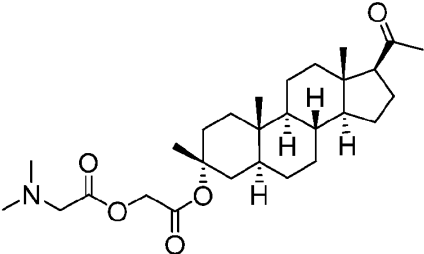
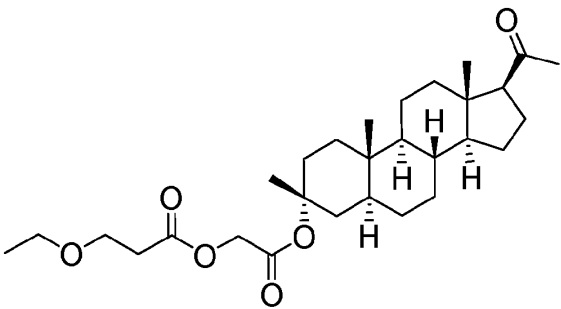
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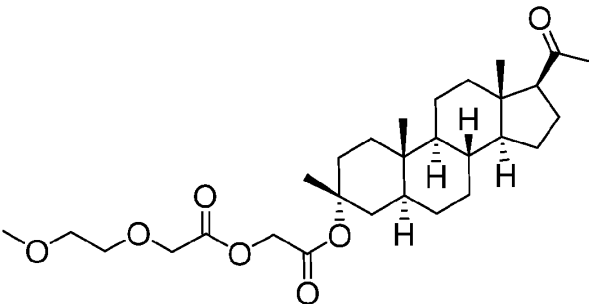
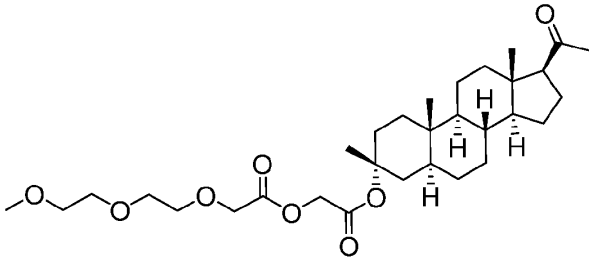
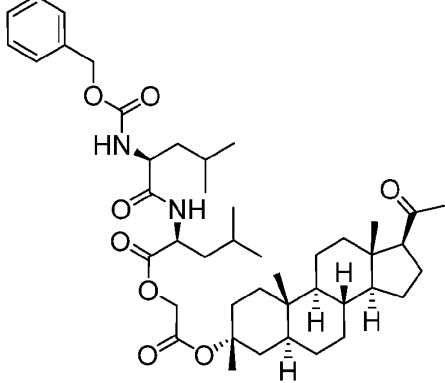
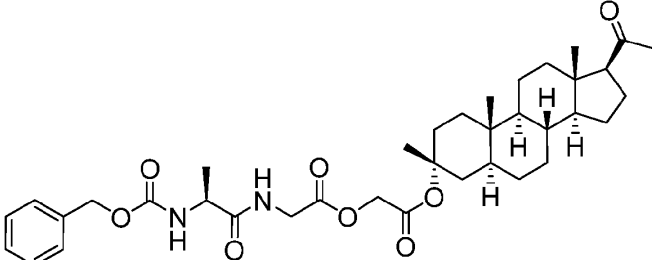
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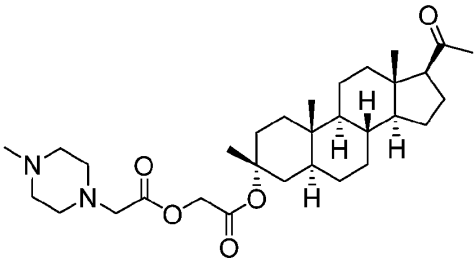
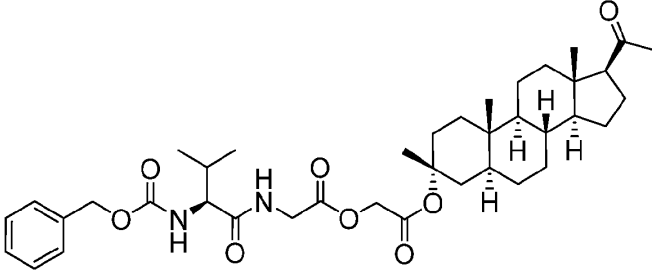
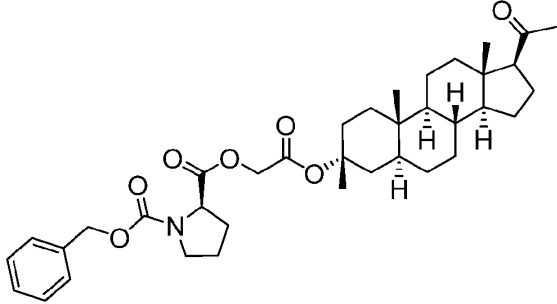
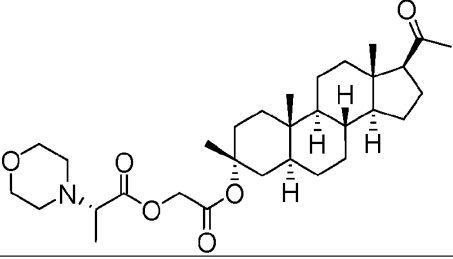
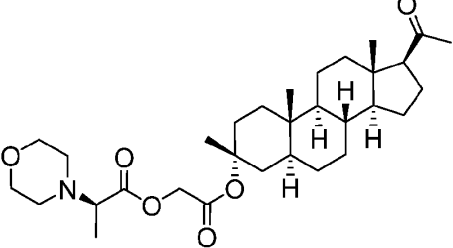
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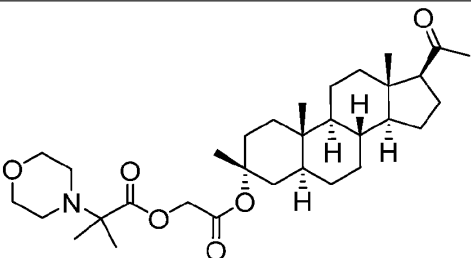
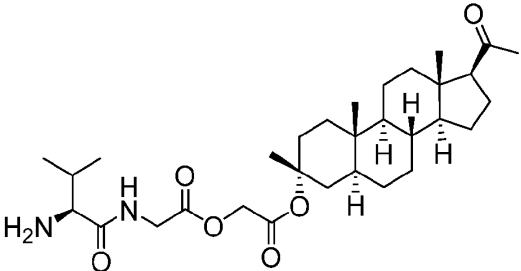
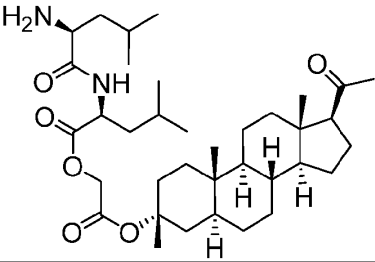
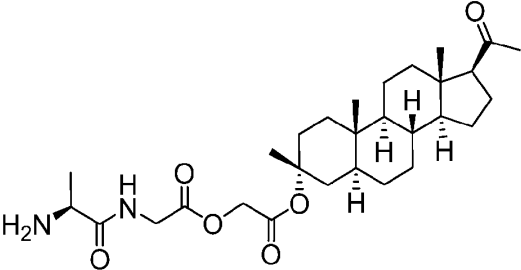
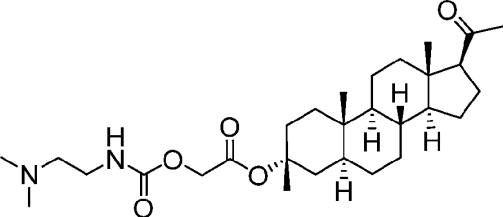
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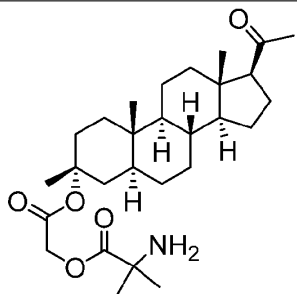
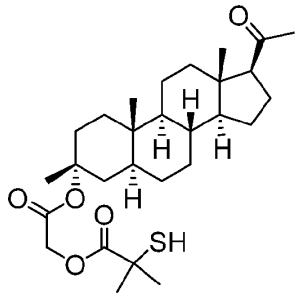
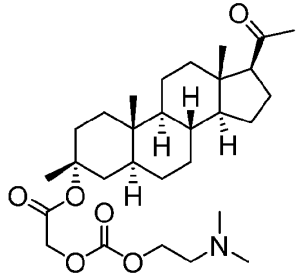
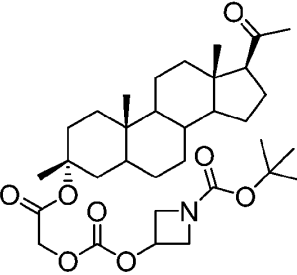
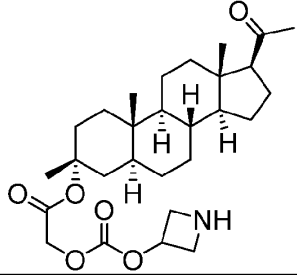
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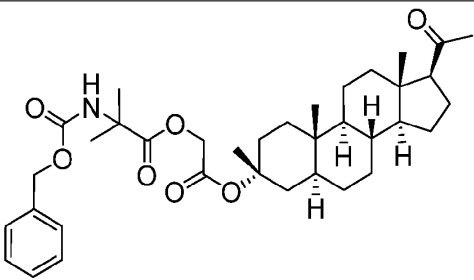
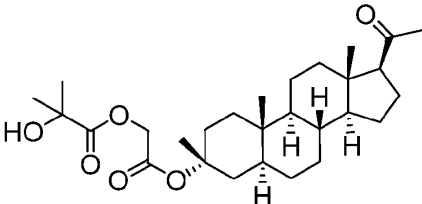
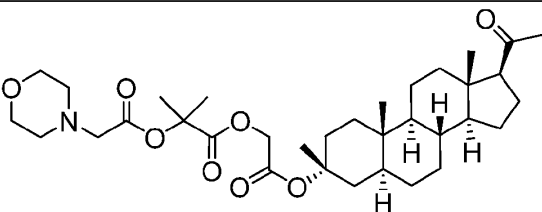
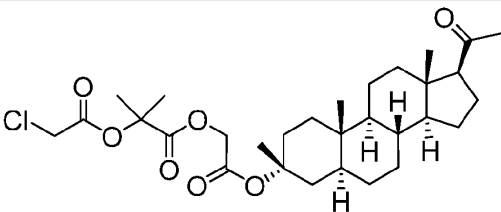
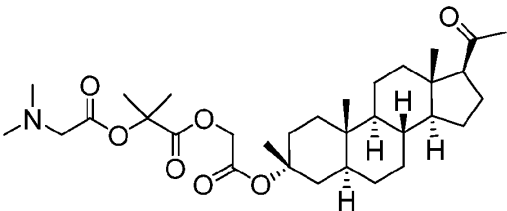
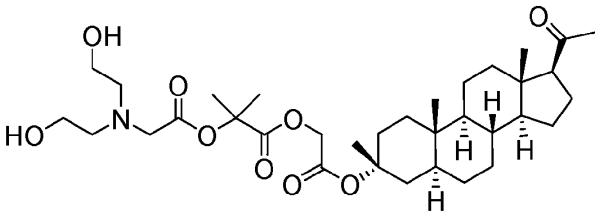
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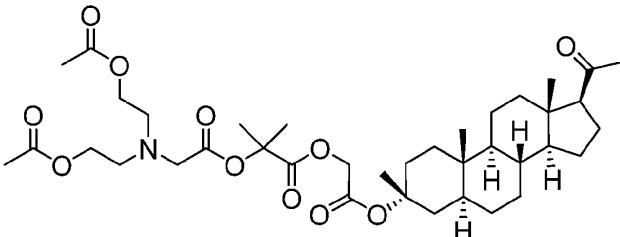
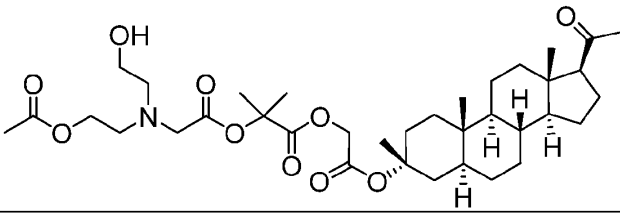
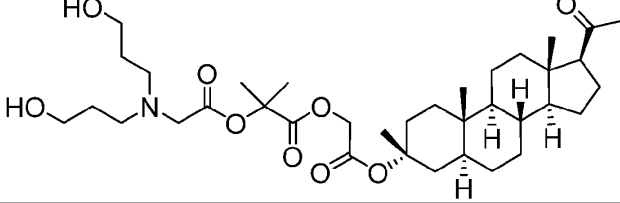
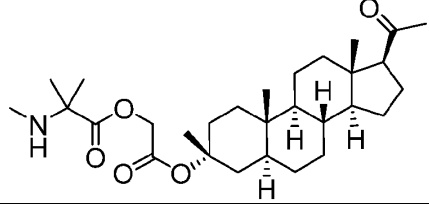
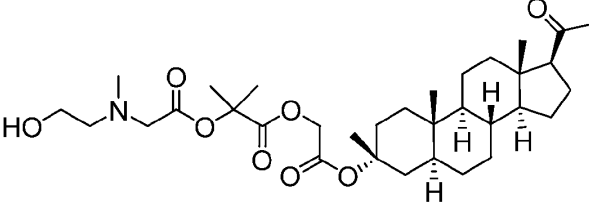
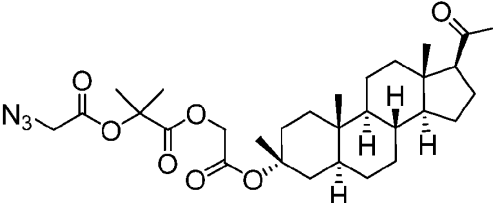
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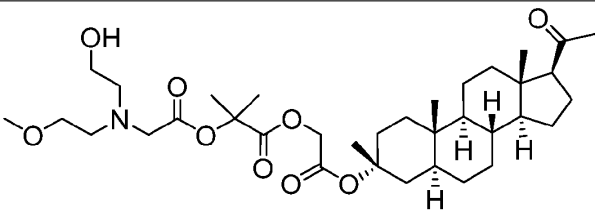
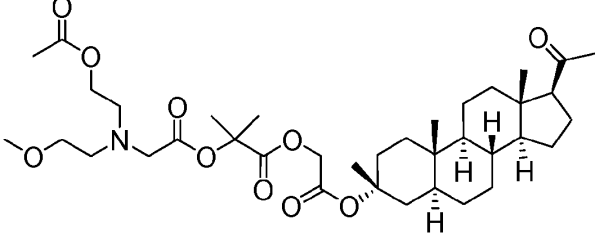
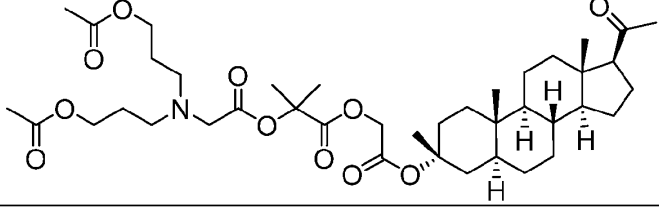
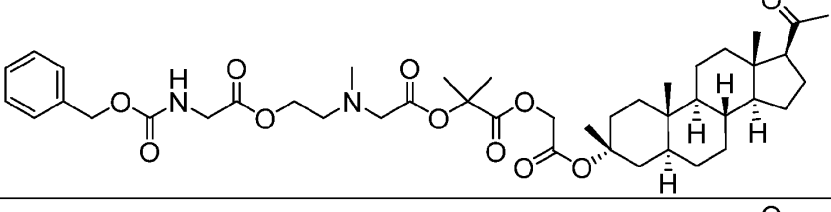
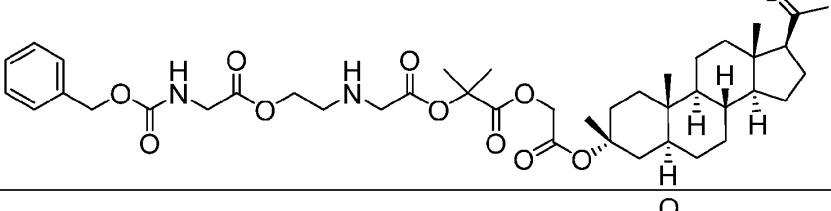
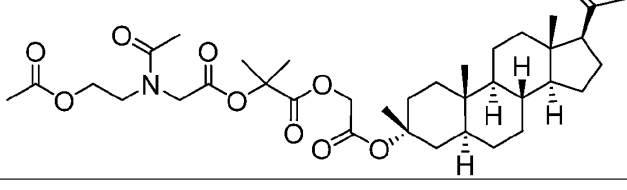
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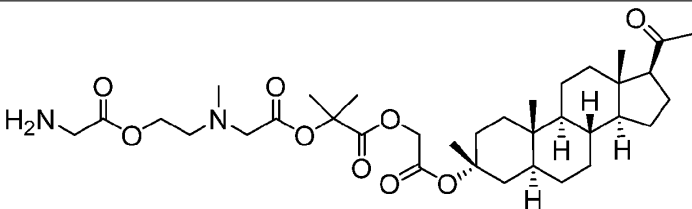
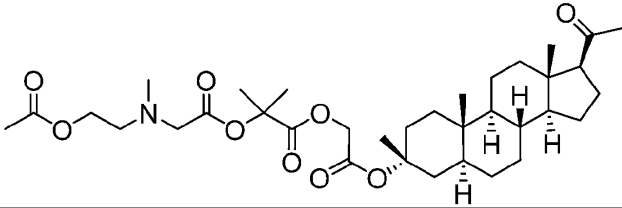
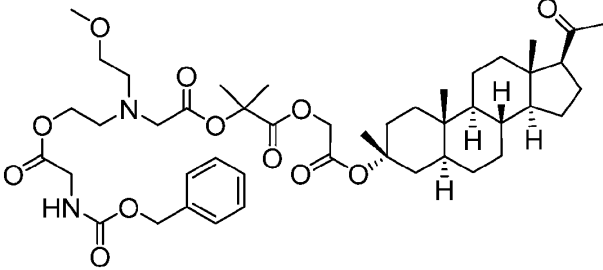
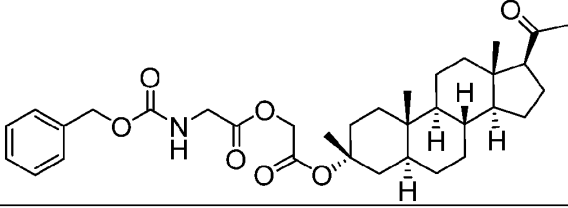
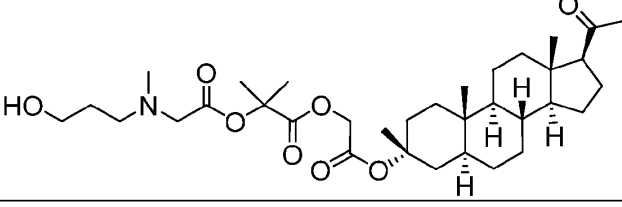
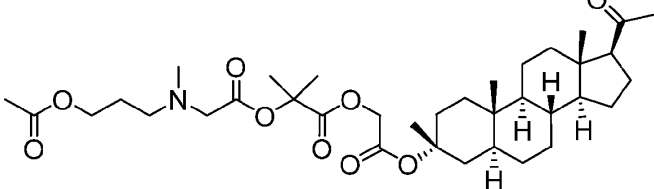
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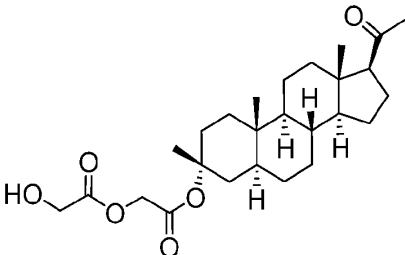
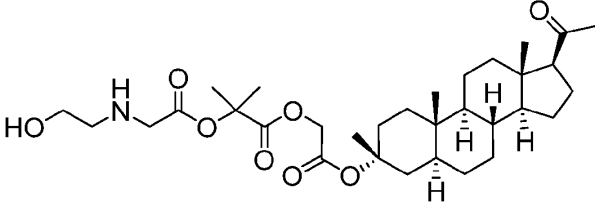
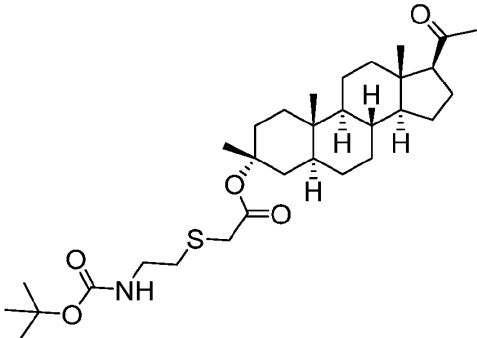
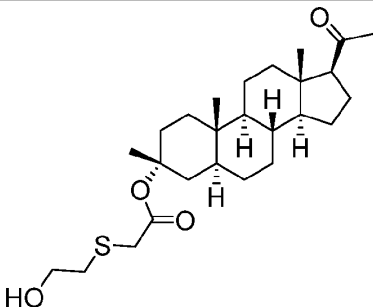
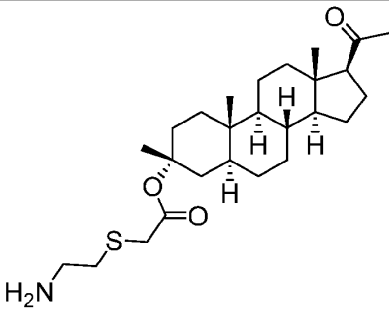
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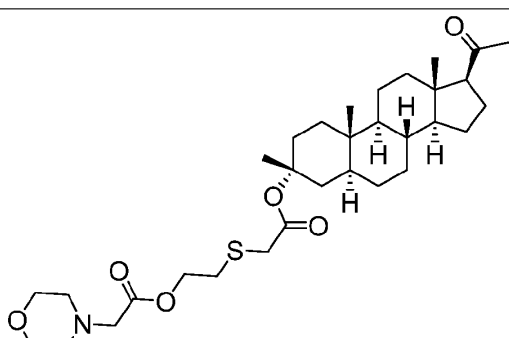
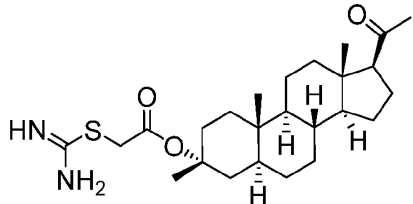
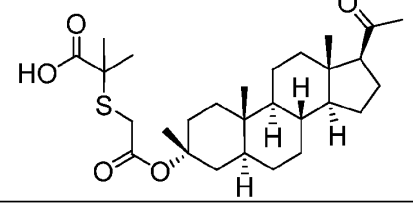
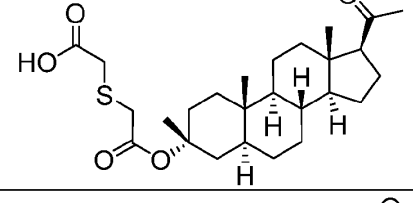
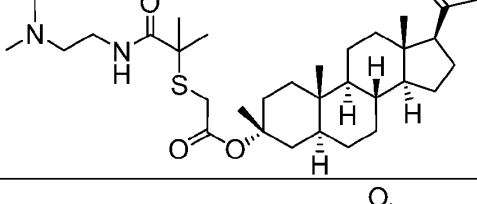
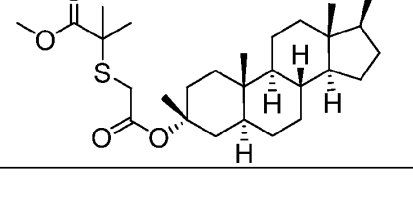
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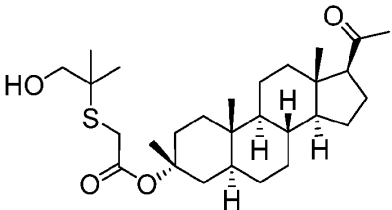
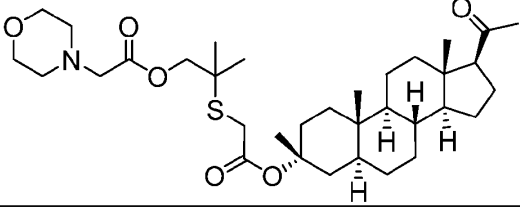
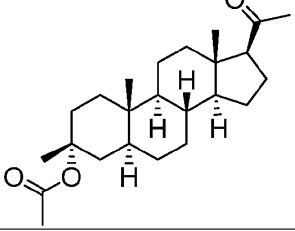
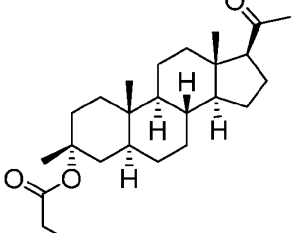
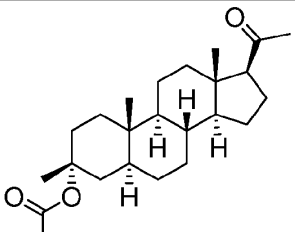
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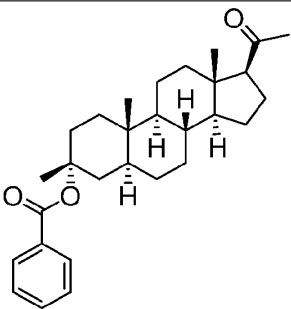
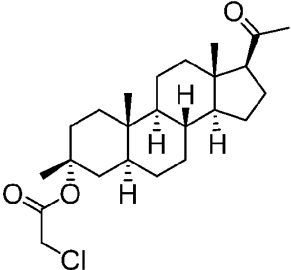
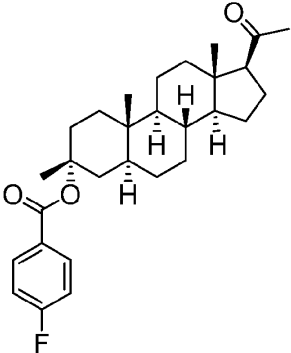
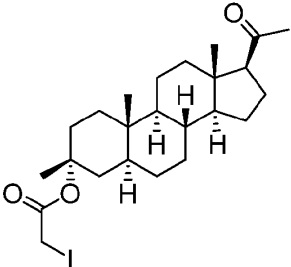
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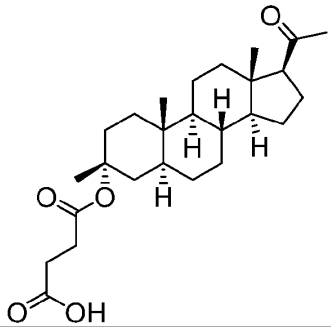
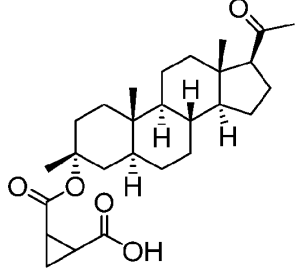
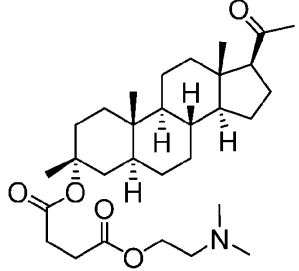
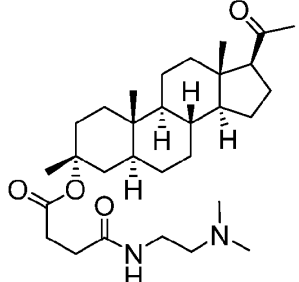
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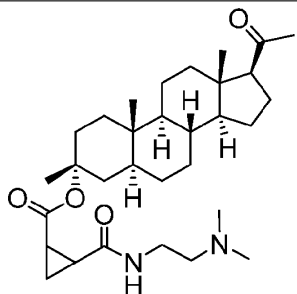
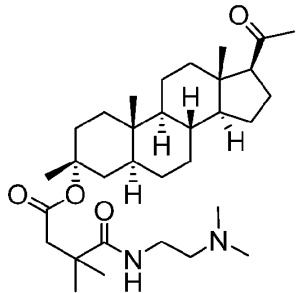
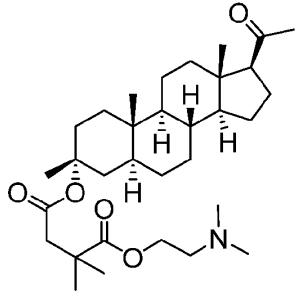
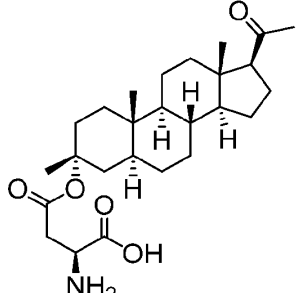
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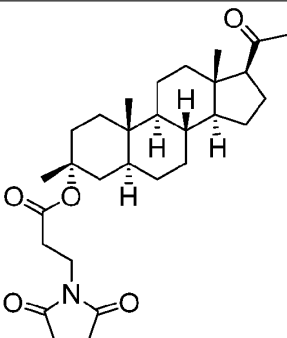
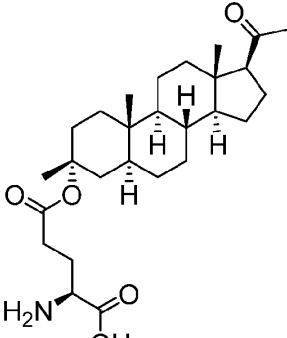
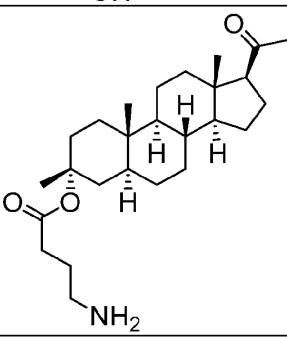
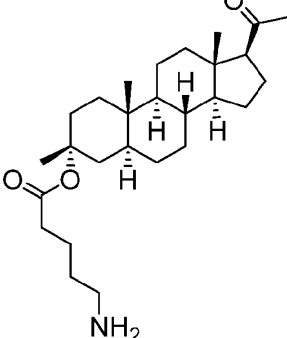
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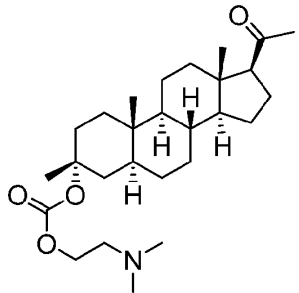
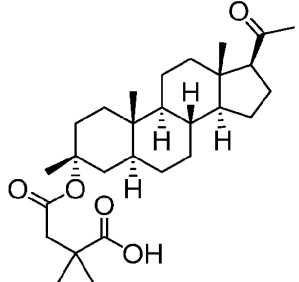
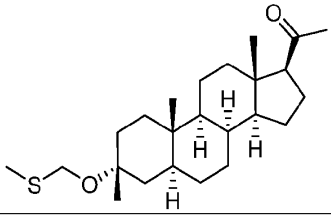
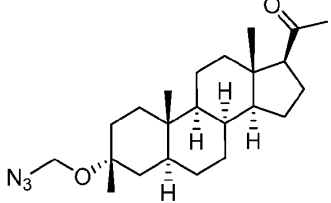
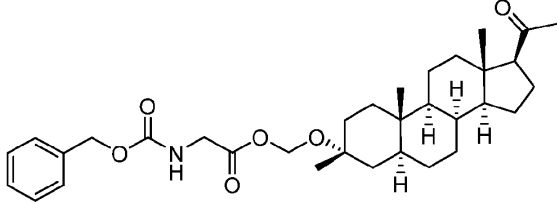
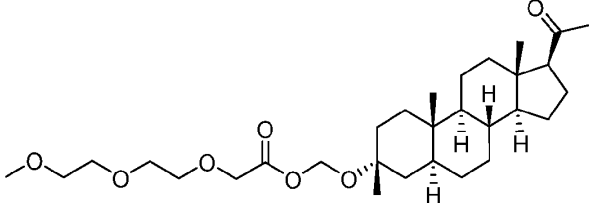
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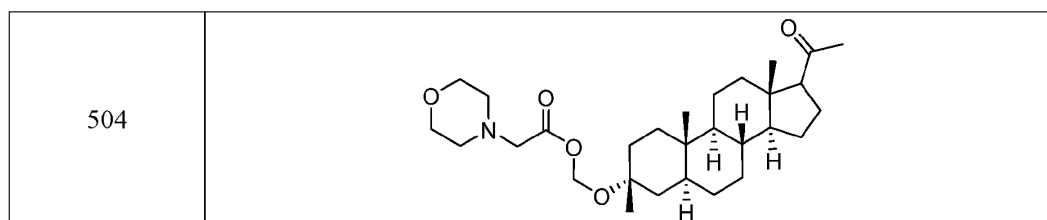
403	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)OC(=O)c5ccccc5)C)C</chem>
404	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)OC(=O)CCl)C)C</chem>
405	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)OC(=O)c5ccc(F)cc5)C)C</chem>
406	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)OC(=O)CCI)C)C</chem>

407	 Chemical structure of a steroid derivative. The steroid nucleus is shown with a 3-acetyl group (CH₃CO-) and a 20-(3-oxopropyl) ester group (-COOCH₂CH₂COOH). The stereochemistry is indicated with wedges and dashes.
408	 Chemical structure of a steroid derivative. The steroid nucleus is shown with a 3-acetyl group (CH₃CO-) and a 20-(3-oxopropyl) ester group (-COOCH₂CH₂COOH). The stereochemistry is indicated with wedges and dashes.
409	 Chemical structure of a steroid derivative. The steroid nucleus is shown with a 3-acetyl group (CH₃CO-) and a 20-(3-oxopropyl) ester group (-COOCH₂CH₂COOH). The stereochemistry is indicated with wedges and dashes.
410	 Chemical structure of a steroid derivative. The steroid nucleus is shown with a 3-acetyl group (CH₃CO-) and a 20-(3-oxopropyl) ester group (-COOCH₂CH₂COOH). The stereochemistry is indicated with wedges and dashes.

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415	 Chemical structure of a steroid derivative. The steroid nucleus is shown with stereochemistry. At C3, there is a succinimide group (a five-membered ring with one nitrogen and two carbonyl groups). At C17, there is an acetyl group (a two-carbon chain with a terminal carbonyl group).
416	 Chemical structure of a steroid derivative. The steroid nucleus is shown with stereochemistry. At C3, there is a 2-amino-3-hydroxypropyl group (a three-carbon chain with an amino group at C2 and a hydroxyl group at C3). At C17, there is an acetyl group (a two-carbon chain with a terminal carbonyl group).
417	 Chemical structure of a steroid derivative. The steroid nucleus is shown with stereochemistry. At C3, there is a 3-aminopropyl group (a three-carbon chain with an amino group at the terminal carbon). At C17, there is an acetyl group (a two-carbon chain with a terminal carbonyl group).
418	 Chemical structure of a steroid derivative. The steroid nucleus is shown with stereochemistry. At C3, there is a 4-aminobutyl group (a four-carbon chain with an amino group at the terminal carbon). At C17, there is an acetyl group (a two-carbon chain with a terminal carbonyl group).

419	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)COCN(C)C)C)C</chem>
420	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)C(=O)C(C)(C)O)C)C</chem>
500	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)CSC)C)C</chem>
501	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)C[N+]=[N-])C)C</chem>
502	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)COC(=O)NCC(=O)OC(=O)COC6=CC=CC=C6)C)C</chem>
503	 <chem>CC(=O)[C@H]1CC[C@@H]2[C@@]1(CC[C@H]3[C@H]2CC=C4[C@@]3(CC[C@@H](C4)O[C@]5(C[C@@H](O5)COC(=O)COCCOC)C)C</chem>



[0171] In some embodiments, the compound of Formulae (I), (I-I), and (IA) is Compound 100, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), and (IA) is Compound 101, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), and (IA) is Compound 102, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 103, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 104, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 105, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 106, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 107, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 108, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 109, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulae (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 110, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some

embodiments, the compound of Formulas (I), (I-I), (IA), and (IA-a) is Compound 111, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 112, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 113, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IA) is Compound 114, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 115, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IA) is Compound 116, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 117, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 118, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IA) is Compound 119, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (IA-b), (I-II), (I-IIa), and (I-IIc) is Compound 120, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IA) is Compound 121, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 122, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IA) is Compound 123, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 124, or a

pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 125, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 126, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 127, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 128, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 129, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (IA-b), (I-II), (I-IIa), and (I-IIc) is Compound 130, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (IA-b), (I-II), (I-IIa), and (I-IIc) is Compound 131, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 132, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 133, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 134, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 135, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 136, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas

(I), (I-I), (IA), (I-II), (I-IIa), and (I-IIc) is Compound 137, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 138, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 139, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 140, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (IA-a), (I-II), and (I-IIa) is Compound 141, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 142, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 143, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 144, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 145, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 146, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 147, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 148, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 149, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II),

and (I-IIa) is Compound 150, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 151, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 152, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 153, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IA), (I-II), and (I-IIa) is Compound 154, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0172] In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 200, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 201, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 202, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 203, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 204, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 205, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 206, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 207, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 208, or a pharmaceutically acceptable

salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 209, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 210, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 211, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 212, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 213, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 214, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 215, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 216, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 217, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 218, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 219, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 220, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IB) is Compound 221, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound

of Formulas (I), (I-I), and (IB) is Compound 222, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 223, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 224, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 225, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 226, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 227, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 228, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 229, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 230, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 231, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 232, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 233, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 234, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound

of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 235, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 236, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 237, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 238, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 239, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 240, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 241, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 242, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 243, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 244, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), (I-IIe) is Compound 245, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), (I-IIb), and (I-IIe) is Compound 246, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IB), (I-II), and (I-IIb) is Compound 247, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0173] In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 300, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 301, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 302, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 303, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IC) is Compound 304, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 305, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 306, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 307, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 308, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 309, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (IC), and (I-II) is Compound 310, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0174] In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 400, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 401, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 402, or a pharmaceutically acceptable salt (e.g., an HCl or TFA

salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 403, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 404, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 405, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 406, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 407, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 408, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 409, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 410, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 411, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 412, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 413, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 414, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 415, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (ID), and (I-II) is Compound 416, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate,

hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 417, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), (ID), and (I-II) is Compound 418, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 419, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (ID) is Compound 420, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof.

[0175] In some embodiments, the compound of Formulas (I), (I-I), and (IE) is Compound 500, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IE) is Compound 501, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IE) is Compound 502, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IE) is Compound 503, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof. In some embodiments, the compound of Formulas (I), (I-I), and (IE) is Compound 504, or a pharmaceutically acceptable salt (e.g., an HCl or TFA salt), solvate, hydrate, tautomer, or stereoisomer thereof.

Pharmaceutical Compositions and Kits

[0176] The present disclosure provides pharmaceutical compositions comprising a compound disclosed herein (e.g., a Compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or a compound listed in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof), and optionally a pharmaceutically acceptable excipient.

[0177] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0178] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-I), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0179] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IA), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IA-a), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IA-b), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0180] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IB), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0181] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IC), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0182] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (ID), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0183] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (IE), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0184] In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-II), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-IIa), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-IIb), or a pharmaceutically

acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-IIc), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-IId), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. In some aspects, a pharmaceutical composition described herein comprises a Compound of Formula (I-IIe), or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient.

[0185] In some aspects, a pharmaceutical composition described herein comprises a compound that is listed in Table 1, or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, and optionally a pharmaceutically acceptable excipient. The compound, or pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, may be provided in an effective amount in the pharmaceutical composition.

[0186] Pharmaceutical compositions of the present disclosure may be prepared by any suitable method known in the art. Such methods can involve a step of bringing the compound (the “active ingredient,” e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or Table 1), into association with one or more pharmaceutically acceptable excipients (e.g., a carrier or binding agent), and may further involve a step of shaping and/or packaging the composition into a single- or multi-dose unit.

[0187] Pharmaceutical compositions may be prepared, packaged, and/or sold in bulk as a single unit dose or a plurality of single unit doses. A single unit dose describes a discrete amount of the pharmaceutical composition comprising a predetermined amount of the active ingredient (e.g., a compound disclosed herein, e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or Table 1). The amount of the active ingredient is typically equal to the dosage of the active ingredient would be administered to a subject, or a convenient fraction of such a dosage.

[0188] Relative amounts of the active ingredient, and the one or more pharmaceutically acceptable excipients, in a pharmaceutical composition of the present disclosure will vary depending on the identity, size, and/or condition of the subject to be treated, and also depending

on the route by which the composition is to be administered. For example, the pharmaceutical composition may comprise between about 0.1 wt% and about 100 wt% of the active ingredient (e.g., a compound of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), or Table 1).

[0189] Compositions of the present disclosure may be administered orally, parenterally (including, without limitation, subcutaneously, intramuscularly, intravenously, and intradermally), by inhalation (e.g., oral inhalation), topically, rectally, nasally, buccally, vaginally, or by an implanted reservoir. In some embodiments, the compositions of the present disclosure are administered orally. In some embodiments, the compositions of the present disclosure are administered intravenously.

[0190] Pharmaceutical compositions of the present disclosure may be orally administered in any acceptable dosage form including, without limitation, capsules, tablets, caplets, powders, lozenges, pastilles, suspensions (e.g., aqueous suspensions), or solutions. Oral dosage forms can include a pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable excipient disclosed herein), e.g., carriers, lubricating agents, diluents, emulsifiers, suspending agents, flavoring agents, coloring agents, disintegrants, or the like. For example, an oral dose form disclosed herein may contain one or more of lactose, corn starch, magnesium stearate, a sweetener, a dye, a polyether (e.g., polyethylene glycol, e.g., PEG-300), a cyclodextrin (e.g., CAPTISOL[®]), or a polysorbate (e.g., a TWEEN[®], e.g., TWEEN-20[®]).

[0191] Pharmaceutical compositions of the present disclosure may be intravenously administered in any acceptable dosage form including, without limitation, aqueous solutions. Intravenous dosage forms can include a pharmaceutically acceptable excipient (e.g., a pharmaceutically acceptable excipient disclosed herein), e.g., carriers, diluents, or the like. For example, an intravenous dose form disclosed herein may contain one or more of a polyether (e.g., polyethylene glycol, e.g., PEG-300), a cyclodextrin (e.g., CAPTISOL[®]), or a polysorbate (e.g., a TWEEN[®], e.g., TWEEN-20[®]).

[0192] A pharmaceutical composition or dosage form disclosed herein (e.g., intravenous dosage form) may be a composition or dosage form that does not contain a solubility-enhancing agent, such as a cyclodextrin (e.g., CAPTISOL[®]). For example, a pharmaceutical composition or dosage form disclosed herein (e.g., intravenous dosage form) may include a compound disclosed herein without cyclodextrin (e.g., CAPTISOL[®]), or with a relatively low amount of the

cyclodextrin, such as a compound:cyclodextrin ratio of less than 1:1, e.g., less than 2:1, less than 3:1, less than 4:1, less than 5:1, less than 6:1, less than 7:1, less than 8:1, less than 9:1, less than 10:1, less than 15:1, less than 20:1, less than 25:1, less than 50:1, less than 99:1, or lower.

[0193] A pharmaceutical composition or dosage form (e.g., intravenous dosage form) disclosed herein may comprise relatively low amounts of a solubility-enhancing agent (e.g., a cyclodextrin, such as CAPTISOL[®]), or no solubility-enhancing agent. For example, a pharmaceutical composition or dosage form (e.g., intravenous dosage form) disclosed herein may comprise no cyclodextrin (e.g., CAPTISOL[®]), or relatively low amounts of cyclodextrin (e.g., CAPTISOL[®]) such as less than 25 wt%, less than 20 wt%, less than 15 wt%, less than 10 wt%, less than 5 wt%, less than 4 wt%, less than 3 wt%, less than 2 wt%, less than 1 wt%, less than 0.5 wt%, of cyclodextrin in the composition.

[0194] Although the descriptions of pharmaceutical compositions provided herein are primarily directed to pharmaceutical compositions which are suitable for administration to humans, it will be understood that such compositions are generally suitable for administration to other animals. It will also be well understood that modifications of pharmaceutical compositions are possible to render the compositions suitable for administration to various animals, and the ordinarily skilled person can design and/or perform such modification with ordinary experimentation.

[0195] Compounds disclosed herein are typically formulated in a dosage unit form, e.g., a single unit dosage form, for ease of administration and uniformity of dosage. However, it will be understood that the total daily usage of the compounds or compositions of the present disclosure will be decided by the attending physician within the scope of sound medical judgment. The specific therapeutically effective dose level for any particular subject or organism will depend upon a variety of factors including, without limitation: the disease or disorder being treated, and the severity of the disease or disorder being treated; the activity of the specific compound or composition being administered; the specific compound or composition being administered; the age, body weight, general health, sex, and/or diet of the subject; the time of administration, route of administration, and rate of excretion or metabolism of the specific compound or composition being administered; the duration of treatment, drugs used in combination or coincidental with the specific compound or composition being administered; and like factors known in the art.

[0196] The amount of a compound or composition required to achieve an effective amount will vary from subject to subject, depending on various factors including, e.g., species, age, and

general condition of the subject; severity of the side-effects or disorder; identity of the particular compound or composition; mode of administration, and the like. The desired dosage may be delivered one or more times a day, e.g., once daily, twice daily, thrice daily, etc., or may be delivered less frequently, e.g., every other day, every third day, every week, every two weeks, every three weeks, monthly, etc. The desired dosage may be delivered on an as needed basis. The desired dosage may also be delivered using multiple administrations, e.g., two, three, four, five, or more administrations.

[0197] An effective amount of a compound for administration will vary depending on the body weight of the subject. For example, an effective amount of a compound for administration one or more times a day to an adult human weighing 70 kg may comprise about 0.0001 mg to about 3 g, e.g., about 0.0001 mg to about 2 g, about 0.0001 mg to about 1 g, about 0.001 mg to about 1 g, about 0.01 mg to about 1 g, about 0.1 mg to about 1 g, about 1 mg to about 1 g, about 1 mg to about 750 mg, about 1 mg to about 500 mg, about 1 mg to about 400 mg, about 1 mg to about 300 mg, about 1 mg to about 250 mg, about 1 mg to about 200 mg, about 1 mg to about 150 mg, about 1 mg to about 100 mg, about 5 mg to about 100 mg, or about 10 mg to about 100 mg, of a compound per unit dosage form.

[0198] It will be understood that dose ranges described herein provide guidance for the administration to an adult, and that the amount to be administered to, e.g., pediatric subjects, can be determined by a medical practitioner or person skilled in the art, and may be lower or the same as that administered to an adult.

[0199] The compounds and compositions described herein may be administered in combination with one or more additional pharmaceutical agents. The compounds and compositions disclosed herein can be administered in combination with additional pharmaceutical agents that improve their bioavailability, improve effectiveness of treatment, reduce or modify metabolism of the compound, or inhibit excretion and/or modify distribution of the compound within the body. It will be understood that the additional pharmaceutical agent employed may achieve a desired effect for the same disorder as the compound or composition, and/or may achieve different effects.

[0200] The compound or composition can be administered concurrently with, prior to, or subsequent to, one or more additional pharmaceutical agents, which can be useful as, e.g., combination therapies. Pharmaceutical agents include therapeutically active agents.

Pharmaceutical agents also include prophylactically active agents. Each additional pharmaceutical agent may be administered at a dose and/or at a time determined for that pharmaceutical agent. The additional pharmaceutical agents may also be administered together with each other and/or with the compound or composition described herein in a single dose or administered separately in different doses. The particular combination to employ in a regimen will take into account compatibility of the inventive compound with the additional pharmaceutical agents and/or the desired therapeutic and/or prophylactic effect to be achieved. In general, it is expected that the additional pharmaceutical agents utilized in combination be utilized at levels that do not exceed the levels and which they are utilized individually. In some aspects, the levels utilized in combination will be lower than those utilized individually.

[0201] Also encompassed by the present disclosure are kits (e.g., pharmaceutical packs). The kits may be useful for preventing and/or treating a disease or disorder disclosed herein, such as a neurological disorder (e.g., epilepsy). The kits may comprise a compound or composition disclosed herein and a container (e.g., a blister pack, vial, bottle, ampule, dispenser package, syringe, or other suitable container). In some embodiments, kits may further include a second container comprising a pharmaceutical excipient, e.g., for dilution or suspension of the compound or composition. In some embodiments, the compound or composition provided in the container, and the second container, are combined to form one unit dosage form, or a multi-unit dosage form.

Pharmacokinetics

[0202] The compounds and pharmaceutical compositions disclosed herein can provide enhanced pharmacokinetic and pharmacodynamic profiles, e.g., relative to ganaxolone. In particular, compounds and pharmaceutical compositions disclosed herein have superior oral bioavailability compared to ganaxolone. Following administration (e.g., oral administration or intravenous administration), the compounds disclosed herein may be converted *in vivo* (e.g., by metabolic processes) to ganaxolone. The compounds disclosed herein may be referred to as ganaxolone prodrugs. Thus, administering a compound disclosed herein may provide a higher amount of serum ganaxolone (e.g., as determined by ganaxolone C_{max} or AUC), compared to administering ganaxolone. Without wishing to be bound by theory, it is believed that the increased bioavailability of the compounds disclosed herein ultimately increase exposure of ganaxolone

and/or improve maintenance of the ganaxolone steady state following administration (e.g., by oral administration), relative to the amounts achieved by administration of ganaxolone itself. This effect can be due in part to the increased solubility, hydrophilicity, and/or rate of absorption of the compounds disclosed herein, compared to ganaxolone, and their ability to be converted to ganaxolone by metabolic processes.

[0203] Similarly, the compounds and pharmaceutical compositions disclosed herein can provide a higher concentration of ganaxolone in the CNS, following administration (e.g., by intravenous or oral administration) to a subject, relative to the concentration achieved when ganaxolone is administered to the subject in an equivalent amount and by the same route of administration.

[0204] The compounds and pharmaceutical compositions disclosed herein can have a bioavailability, e.g., oral bioavailability, with respect to serum concentration of ganaxolone, that is higher as compared to the bioavailability of administering ganaxolone itself (e.g., as determined by ganaxolone $C_{\max}$ or AUC), by at least about 5%, about 10%, about 15%, about 20%, about 30%, about 40%, about 50%, about 60%, about 70, about 80%, about 90%, about 100%, about 110%, about 120%, about 130%, about 140%, about 150%, about 160%, about 170%, about 180%, about 190%, about 200%, about 210%, about 220%, about 230%, about 240%, about 250%, about 260%, about 270%, about 280%, about 290%, about 300%, about 325%, about 350%, about 375%, about 400%, about 425%, about 450%, about 475%, about 500%, about 525%, about 550%, about 575%, about 600%, about 625%, about 650%, about 675%, about 700%, about 725%, about 750%, about 775%, about 800%, about 825%, about 850%, about 875%, about 900%, about 925%, about 950%, about 975%, about 1000% or greater.

[0205] Because the compounds disclosed herein may be converted *in situ* to ganaxolone (e.g., by metabolic processes), the enhanced bioavailability achieved by the compounds disclosed herein can be measured by the $C_{\max}$ levels of ganaxolone in the blood plasma and/or area under the curve (AUC) level of ganaxolone, in addition to measuring the $C_{\max}$ and AUC levels of the prodrug compound itself. In some embodiments, the compounds and pharmaceutical compositions disclosed herein may increase the $C_{\max}$ and/or the AUC of ganaxolone, relative to the $C_{\max}$ and/or AUC achieved following oral administration of a composition comprising ganaxolone.

[0206] The compounds and pharmaceutical compositions described herein may result in a maximum ganaxolone plasma concentration ($C_{\max}$) from about 100 ng/mL to about 1200 ng/mL. For example, the compound may achieve a $C_{\max}$ of about 100 ng/mL, about 110 ng/mL, about 120 ng/mL, about 130 ng/mL, about 140 ng/mL, about 150 ng/mL, about 160 ng/mL, about 170 ng/mL, about 180 ng/mL, about 190 ng/mL, about 200 ng/mL, about 210 ng/mL, about 220 ng/mL, about 230 ng/mL, about 240 ng/mL, about 250 ng/mL, about 260 ng/mL, about 270 ng/mL, about 280 ng/mL, about 290 ng/mL, about 300 ng/mL, about 310 ng/mL, about 320 ng/mL, about 330 ng/mL, about 340 ng/mL, about 350 ng/mL, about 360 ng/mL, about 370 ng/mL, about 380 ng/mL, about 390 ng/mL, about 400 ng/mL, about 410 ng/mL, about 420 ng/mL, about 430 ng/mL, about 440 ng/mL, about 450 ng/mL, about 460 ng/mL, about 470 ng/mL, about 480 ng/mL, about 490 ng/mL, about 500 ng/mL, about 510 ng/mL, about 520 ng/mL, about 530 ng/mL, about 540 ng/mL, about 550 ng/mL, about 560 ng/mL, 570 ng/mL, about 580 ng/mL, about 590 ng/mL, about 600 ng/mL, about 610 ng/mL, about 620 ng/mL, about 630 ng/mL, about 640 ng/mL, about 650 ng/mL, about 660 ng/mL, about 670 ng/mL, about 680 ng/mL, about 690 ng/mL, about 700 ng/mL, about 710 ng/mL, about 720 ng/mL, about 730 ng/mL, about 740 ng/mL, about 750 ng/mL, about 760 ng/mL, about 770 ng/mL, about 780 ng/mL, about 790 ng/mL, 800 ng/mL, about 810 ng/mL, about 820 ng/mL, about 830 ng/mL, about 840 ng/mL, about 850 ng/mL, about 860 ng/mL, about 870 ng/mL, about 880 ng/mL, about 890 ng/mL, about 900 ng/mL, about 910 ng/mL, about 920 ng/mL, about 930 ng/mL, 940 ng/mL, about 950 ng/mL, about 960 ng/mL, about 970 ng/mL, about 980 ng/mL, about 990 ng/mL, about 1000 ng/mL, about 1100 ng/mL, or about 1200 ng/mL, or greater.

[0207] The compounds and pharmaceutical compositions described herein can increase ganaxolone $C_{\max}$ by at least about 1 fold, about 2 fold, about 3 fold, about 4 fold, about 5 fold, about 6 fold, about 7 fold, about 8 fold, about 9 fold, about 10 fold, about 11 fold, about 12 fold, about 13 fold, about 15 fold, about 16 fold, about 17 fold, about 18 fold, about 19 fold, about 20 fold, or greater, relative to other oral compositions comprising ganaxolone.

[0208] The compounds and pharmaceutical compositions disclosed herein can increase the AUC of ganaxolone, relative to AUC achieved following oral administration of another composition comprising ganaxolone. For example, oral administration of a compound or pharmaceutical composition disclosed herein can result in an AUC of ganaxolone of about 100 ng/mL/hr to about 1,200 ng/mL/hr, e.g., about 200 ng/mL/hr to about 1,200 ng/mL/hr, about 300 ng/mL/hr to

about 1,200 ng/mL/hr, about 400 ng/mL/hr to about 1,200 ng/mL/hr, about 500 ng/mL/hr to about 1,200 ng/mL/hr, about 600 ng/mL/hr to about 1,200 ng/mL/hr, about 700 ng/mL/hr to about 1,200 ng/mL/hr, about 800 ng/mL/hr to about 1,200 ng/mL/hr, about 900 ng/mL/hr to about 1,200 ng/mL/hr. The AUC may refer to the AUC calculated to the last measured concentration ($AUC_{0,t}$), such as over a period of 24 hours (AUC_{0-24}).

[0209] The compounds and pharmaceutical compositions disclosed herein can be administered at a dose that results in an average ganaxolone plasma concentration (C_{ave}) of about 100 ng/mL to about 1,200 ng/mL, about 200 ng/mL to about 1,200 ng/mL, about 300 ng/mL to about 1,200 ng/mL, about 400 ng/mL to about 1,200 ng/mL, about 500 ng/mL to about 1,200 ng/mL, about 600 ng/mL to about 1,200 ng/mL, about 700 ng/mL to about 1,200 ng/mL, about 800 ng/mL to about 1,200 ng/mL, or about 900 ng/mL to about 1,200 ng/mL.

[0210] The compounds and pharmaceutical compositions disclosed herein can be administered at a dose that results in plasma ganaxolone concentration of about 100 ng/mL to about 1,200 ng/mL, about 200 ng/mL to about 1,200 ng/mL, about 300 ng/mL to about 1,200 ng/mL, about 400 ng/mL to about 1,200 ng/mL, about 500 ng/mL to about 1,200 ng/mL, about 600 ng/mL to about 1,200 ng/mL, about 700 ng/mL to about 1,200 ng/mL, about 800 ng/mL to about 1,200 ng/mL, or about 900 ng/mL to about 1,200 ng/mL.

Methods of Use

[0211] The present disclosure also relates to methods of treating a disease or disorder. The methods disclosed herein can comprise administering (e.g., orally or intravenously administering) a therapeutically effective amount of a compound or a pharmaceutical composition disclosed herein, to a subject in need thereof.

[0212] The methods can be suitable for treating any type of seizure disorder, epilepsy disorder, genetic epilepsy disorder, epilepsy related disorder, central nervous system disorder, neurological disorder, neurodegenerative disorder, or the like.

[0213] Types of disorders, including epilepsy disorders and/or epilepsy-related disorders, the methods disclosed herein can be suitable for treating include, but are not limited to, focal seizure, essential tremor, a generalized seizure, acute repetitive seizures, pediatric epilepsy, reflex epilepsy, benign rolandic epilepsy, status epilepticus, refractory status epilepticus, super-refractory status epilepticus, SCN8 A epilepsy, catamenial epilepsy, Angelman syndrome,

benign epilepsy with centro-temporal spikes (BECTS), CDKL5 deficiency disorder (CDKL5 disorder), autosomal dominant nocturnal frontal lobe epilepsy (ADFE), absence epilepsy, childhood absence epilepsy (CAE), Doose syndrome, Dravet syndrome, early myoclonic epilepsy (EME), epilepsy with generalized tonic-clonic seizures, epilepsy with myoclonic-absences, infantile spasms (West syndrome), Landau-Kleffner syndrome, Lennox-Gastaut syndrome (LGS), epilepsy with myoclonic absences, frontal lobe epilepsy, juvenile myoclonic epilepsy (JME), Lyfora progressive myoclonus epilepsy, Ohtahara syndrome, Rett syndrome, intractable childhood epilepsy (ICE), Panayiotopoulos syndrome, Rasmussen's syndrome, progressive myoclonic epilepsies, Ring chromosome 20 syndrome, temporal lobe epilepsy, epilepsy of infancy with migrating focal seizures, epilepsy in Fragile X syndrome, Sturge-Weber Syndrome, PCDH19-related epilepsy including PCDH19 pediatric epilepsy, Tuberous Sclerosis Complex, Dup15q Syndrome, Jeavons Syndrome, Febrile Illness-Related Epilepsy Syndrome (FIRES), Autoimmune Encephalitis/Encephalopathy due to Anti-LGI1, Anti-NMDAR, Anti-Gaba-B receptor, or Anti-GAD65 antibodies, FOXG1-related epilepsy, Syngap1-related epilepsy, Aicardi syndrome, sleep-related hypermotor epilepsy, epileptic encephalopathy with Continuous Spike and Wave During Sleep (CSWS), myoclonic epilepsy of infancy, Rasmussen's syndrome, developmental and epileptic encephalopathies (unclassified), focal epilepsy, juvenile absence epilepsy, posttraumatic epilepsy, epilepsy due to cortical dysplasia, and catamenial epilepsy, increased seizure activity, breakthrough seizures, and infantile spasms.

[0214] Epilepsy disorders and/or epilepsy related disorders that are suitable for treatment by the methods disclosed herein include CDKL5 Deficiency Disorder, Tuberous Sclerosis Complex, and PCDH19-related epilepsy. Another disorder that is suitable for treatment by the methods disclosed herein is Lennox-Gastaut syndrome (LGS).

[0215] The methods disclosed herein may also be used for treating other neurological disorders, such as anxiety, agitation, or depression (e.g., post-partum depression).

[0216] Additional medical conditions manifesting with seizures that can be treated with the methods disclosed herein include, but are not limited, to preeclampsia/eclampsia, drug-related seizures (including prescriptions drugs uses as prescribed, e.g., antihistamines, antibiotics, antidepressants, antipsychotics, and also illicit substances, e.g., PCP, cocaine, and amphetamines), drug withdrawal (such as withdrawal from THC, opioids, alcohol, or barbiturates), or antiepileptic drugs (AED) non-compliance.

[0217] Other disorders that may be treated by a method, compound, or composition disclosed herein are described in International Application Nos. PCT/US2006/045626, PCT/US2007/024606, PCT/US2010/045176, PCT/US2016/016977, PCT/US2016/057120, PCT/US2017/056565, PCT/US2018/028151, PCT/US2018/060037, PCT/US2019/064850, PCT/US2020/044843, PCT/US2020/063648, PCT/US2021/060459, and PCT/US2021/061937; U.S. Patent No. 10,391,105; and U.S. Patent Publication No. 2019/0111059, each of which are incorporated herein by reference in their entireties.

[0218] The methods disclosed herein are suitable for treating seizures. For example, the methods disclosed herein are suitable for treating status epilepticus (SE). The methods disclosed herein are suitable for any form of SE. For example, early status epilepticus, established status epilepticus, refractory status epilepticus, super-refractory status epilepticus, non-convulsive status epilepticus (e.g., focal non-convulsive status epilepticus, complex partial non-convulsive status epilepticus, simple partial non-convulsive status epilepticus, subtle non-convulsive status epilepticus), generalized convulsive status epilepticus, complex partial status epilepticus; generalized periodic epileptiform discharges, and periodic lateralized epileptiform discharges. The method can also be used to treat subjects that have failed first-line treatment (e.g., benzodiazepine), second-line treatment (e.g. fosphenytoin, valproic acid or levetiracetam), and/or third-line treatment (thiopental, midazolam, pentobarbital, or propofol).

[0219] Other forms of seizures the methods disclosed herein can be suitable for treating include epileptic seizures, acute repetitive seizures, cluster seizures, continuous seizures, unremitting seizures, prolonged seizures, recurrent seizures, refractory seizures, myoclonic seizures, tonic seizures, tonic-clonic seizures, simple partial seizures, complex partial seizures, secondarily generalized seizures, atypical absence seizures, absence seizures, atonic seizures, benign Rolandic seizures, febrile seizures, emotional seizures, focal seizures, gelastic seizures, generalized onset seizures, infantile spasms, Jacksonian seizures, massive bilateral myoclonus seizures, multifocal seizures, neonatal onset seizures, nocturnal seizures, occipital lobe seizures, post traumatic seizures, subtle seizures, Sylvian seizures, visual reflex seizures, seizures from traumatic brain injury, seizures resulting from exposure to chemical weapons (e.g., organophosphate nerve gas or withdrawal seizures).

[0220] The compounds and pharmaceutical compositions disclosed herein can also be administered as a prophylactic for treating central nervous system disorders and/or neurological

disorders. Exemplary central nervous system disorders and/or neurological disorders that may be suitable for treating using the formulations disclosed herein include autism spectrum disorders, Rett Syndrome, Tourette Syndrome, Obsessive Compulsive Disorder, insomnia, parasomnias, oppositional defiant disorder, conduct disorder, disruptive mood dysregulation disorder, agitation, anxiety, generalized anxiety disorder, social anxiety disorder, panic disorder, anxiety or agitation due to Alzheimer's dementia, schizophrenia, substance withdrawal syndrome (alcohol, benzodiazepine, barbiturate, and cocaine), post-traumatic stress disorder (PTSD), tremors, essential tremor, spasticity due to cerebral palsy, depression (including major depression, major depressive disorder, severe depression, unipolar depression, unipolar disorder, recurrent depression), postnatal or postpartum depression, atypical depression, melancholic depression, Psychotic Major Depression (PMD), catatonic depression, Seasonal Affective Disorder (SAD), dysthymia, double depression, Depressive Personality Disorder (DPD), Recurrent Brief Depression (RBD), minor depressive disorder, bipolar disorder or manic depressive disorder, post-traumatic stress disorders, post-menopausal depression, depression caused by chronic medical conditions, treatment-resistant depression, refractory depression, suicidality, suicidal ideation, mood disorder or suicidal behavior, attention deficit hyperactivity disorder, or disruptions in neurocognition including delirium. The compounds or compositions may also be used as a sedative agent or analgesic agent.

[0221] The disclosure further includes methods of treating seizures arising from neurodegenerative disorders. Such neurodegenerative disorders include Parkinson's disease, Alzheimer's disease, Amyotrophic Lateral Sclerosis, and Huntington's disease. The disclosure includes methods of treating seizure arising from inflammatory disorders, such as multiple sclerosis. The disclosure includes methods of treating seizure disorders arising from lysosomal storage disorders including Neimann-Pick disease type C (NPS, Tay-Sachs, Batten disease, Sandhoff disease, and Gaucher disease.

[0222] Although preferred subjects are human, typically any mammal including domestic animals such as dogs, cats and horses, may also be treated according to the methods disclosed herein.

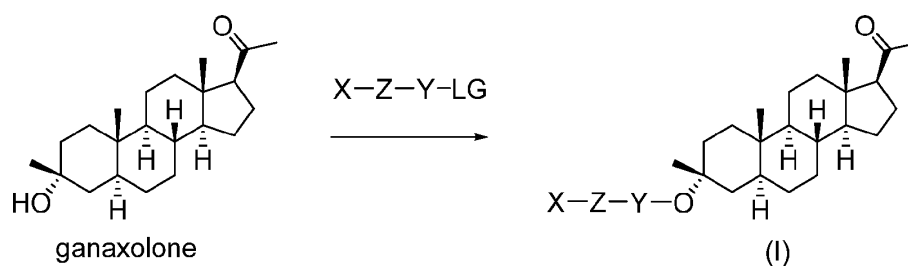
[0223] Modified forms of ganaxolone intended as prodrugs are not predictably converted to ganaxolone. For example, conventional approaches to forming ganaxolone prodrugs have led to compounds that, while having improved aqueous solubility or oral absorption compared to

ganaxolone, are not sufficiently converted to ganaxolone *in vivo* to provide therapeutically effective serum concentrations ganaxolone. Thus, there is a significant level of unpredictability in designing compounds suitable as ganaxolone prodrugs that are sufficiently stable (e.g., relatively bench stable, relatively stable in plasma, and relatively stable in gastric fluid and/or intestinal fluid), that have sufficient oral bioavailability, and can be converted to ganaxolone following administration to provide therapeutic serum concentrations of ganaxolone. Thus, it is both surprising and unexpected that certain compounds disclosed herein are sufficiently stable, have improved solubility and other physicochemical properties linked to bioavailability, and are also efficiently converted to ganaxolone by metabolic processes (see, e.g., Example 121). Even minor modifications to a compound structure was found to significantly reduce or eliminate the ability of the compound to be converted to ganaxolone, or negatively affect its stability, which demonstrates the high degree of unpredictability and difficulty in designing useful ganaxolone prodrugs.

Methods of Synthesis

[0224] The compounds disclosed herein can be prepared according to known processes. Schemes 1-3 below represent general synthetic schemes for preparing compounds of the present disclosure (e.g., compounds of Formulae (I), (I-I), (IA), (IA-a), (IA-b), (IB), (IC), (ID), (IE), (I-II), (I-IIa), (I-IIb), (I-IIc), (I-IId), (I-IIe), and compounds of Table 1). These schemes are illustrative and are not meant to limit the possible techniques one skilled in the art may use to prepare compounds disclosed herein. Different methods will be evident to those skilled in the art. Various modifications to these methods may be envisioned by those skilled in the art to achieve similar results to those described below. Optional protecting groups can be used as described, for example, in Greene et al. *Protective Groups in Organic Synthesis* (4th ed. 2006). It will be appreciated that one or more additional steps of protecting and/or deprotecting, e.g., a nitrogen or oxygen atom, saponification, and/or a step of forming a salt (e.g., by treatment with an acid) may be involved in the syntheses that are not depicted in the generalized schemes for clarity.

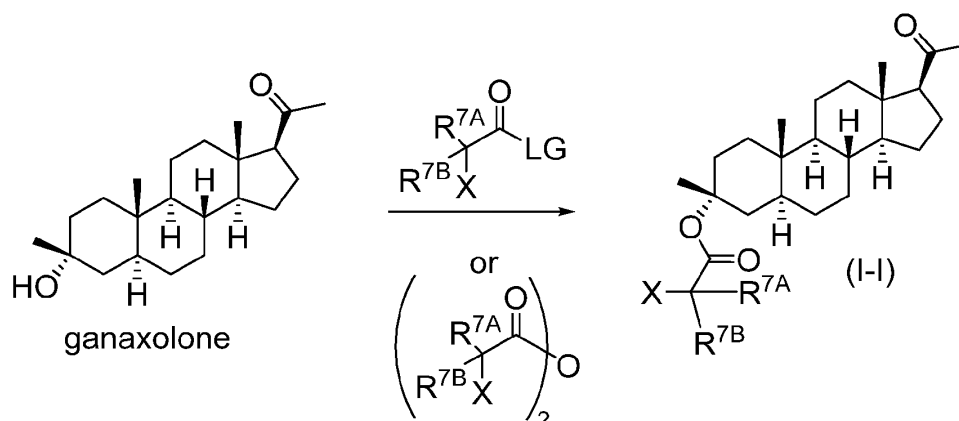
[0225] A compound of Formula (I) can generally be prepared, for example, according to Scheme 1:



Scheme 1. Exemplary synthesis of a compound of Formula (I).

wherein X, Z, and Y are as defined herein, and LG is a suitable leaving group (e.g., halogen, OSO₂Me, OMs, OTs, OTf, or OH). The reaction may be catalyzed by heat and/or a reagent (e.g., acid or base) or catalyst, and can be carried out in any suitable solvent, such as an inert organic solvent.

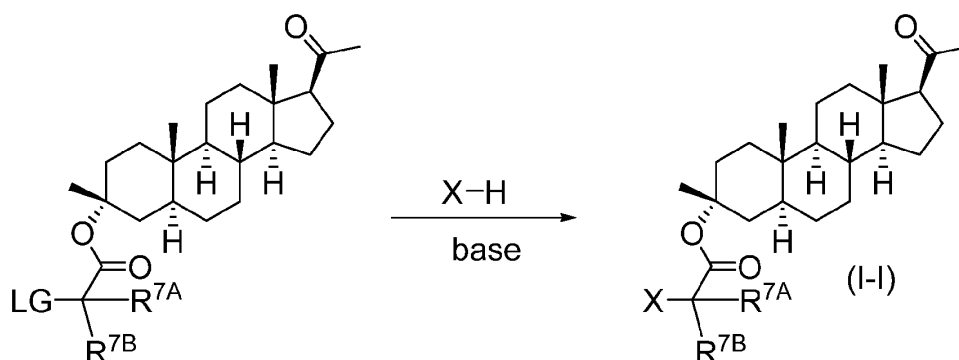
[0226] A compound of Formula (I-I) can generally be prepared, for example, according to Scheme 2:



Scheme 2. Exemplary synthesis of a compound of Formula (I-I).

wherein X, R^{7A} and R^{7B} are as defined herein, and LG is a suitable leaving group (e.g., halogen, OSO₂Me, OMs, OTs, OTf, or OH). The reaction may be catalyzed by heat and/or a reagent (e.g., acid or base) or catalyst, and can be carried out in any suitable solvent, such as an inert organic solvent.

[0227] Alternatively, a compound of Formula (I-I) can generally be prepared, for example, according to Scheme 3:



Scheme 3. Exemplary synthesis of a compound of Formula (I-I).

wherein X , R^{7A} and R^{7B} are as defined herein, and LG is a suitable leaving group (e.g., halogen, OSO_2Me , OMs , OTs , OTf , or OH). The reaction may be catalyzed by heat and/or a reagent (e.g., acid or base) or catalyst, and can be carried out in any suitable solvent, such as an inert organic solvent.

[0228] A base used in the synthesis of a compound disclosed herein, e.g., according to one of Schemes 1-3, may include an inorganic base such as potassium tert-butoxide, sodium hydride, sodium methoxide, sodium ethoxide, sodium hydroxide, potassium hydroxide, or the like, or may include an organic base such as an amine base (e.g., triethylamine (TEA), diisopropylamine, diisopropylethylamine (DIPEA), pyrrolidine, or pyridine).

[0229] An acid used in the synthesis of a compound disclosed herein, e.g., according to one of Schemes 1-3, may include hydrochloric acid, sulfuric acid, nitric acid, tosic acid, trifluoroacetic acid, acetic acid, or the like.

[0230] A solvent used in the synthesis of a compound disclosed herein, e.g., according to one of Schemes 1-3, may include dimethylformamide (DMF), N-methyl-2-pyrrolidone (NMP), tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), dichloromethane (DCM), 1,4-dioxane, acetonitrile, methanol, ethanol, toluene, diethyl ether, methyl tert-butyl ether (MTBE), or the like. Water may also be used as a solvent, either alone or as a mixture with one or more other solvents, e.g., a solvent described herein.

[0231] A reaction to prepare a compound disclosed herein, e.g., according to one of Schemes 1-3, may be carried out at any suitable temperature. For example, a reaction to prepare a compound disclosed herein may be carried out at room temperature, below room temperature, or above room temperature. A reaction to prepare a compound disclosed herein may be carried out

at 0 °C or less, e.g., -5 °C, -10 °C, -25 °C, -50 °C, -78 °C, -80 °C, -100 °C, or less. A reaction to prepare a compound disclosed herein may be carried out at 25 °C or more, e.g., 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 60 °C, 70 °C, 80 °C, 90 °C, 100 °C, 110 °C, 120 °C, or more.

[0232] A reaction described herein, e.g., according to one of Schemes 1-3, can be subsequently followed by further separation and purification steps, such as chromatography (*e.g.*, flash column chromatography, high-performance liquid chromatography (HPLC), ultra-performance liquid chromatography (UPLC), etc.), crystallization, trituration, filtration, lyophilization, and the like.

Equivalents

[0233] It will be readily apparent to those skilled in the art that other suitable modifications and adaptations of the compounds, compositions, kits, and methods of the present disclosure are obvious and may be made using suitable equivalents without departing from the scope of the disclosure or the embodiments. Having now described certain compounds, compositions, kits, and methods in detail, the same will be more clearly understood by reference to the following examples, which are introduced for illustration only and not intended to be limiting.

EXAMPLES

Materials and Methods

[0234] Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification.

Preparative and Analytical Methods

[0235] LC/MS data (ESI+) were determined with a Waters Alliance 2695 HPLC/MS (Waters Symmetry C18, 4.6 × 75 mm, 3.5 μm) or (Phenomenex C18, 4.6 × 75 mm, 3.0 μm) with a 2996 diode array detector from 210–400 nm; the solvent system is 5–95% acetonitrile (MeCN) in water (with 0.1% trifluoroacetic acid (TFA)) over nine minutes using a linear gradient, and retention times are in minutes. Mass spectrometry was performed on a Waters ZQ using electrospray in positive mode.

[0236] LC/MS data (ESI-) were determined with a Shimadzu Prominence HPLC/MS (Phenomenex Luna C18, 3.0 × 50 mm, 3 μm) with a 2996 diode array detector from 210–400 nm; the solvent system is 5–95% MeCN in water (with 0.1% formic acid) over five minutes using a linear gradient, and retention times are in minutes. Mass spectrometry was performed on a Applied Biosystems MDS Sciex API 2000 using electrospray in negative mode. Alternatively

LC/MS data (ESI-) were determined with a Waters Alliance 2695 HPLC/MS (Phenomenex C18, 4.6×75 mm, $3.0 \mu\text{m}$) with a 2996 diode array detector from 210–400 nm; the solvent system is 5–95% MeCN in water (with 0.1% formic acid) over nine minutes using a linear gradient, and retention times are in minutes. Mass spectrometry was performed on a Waters ZQ using electrospray in positive mode.

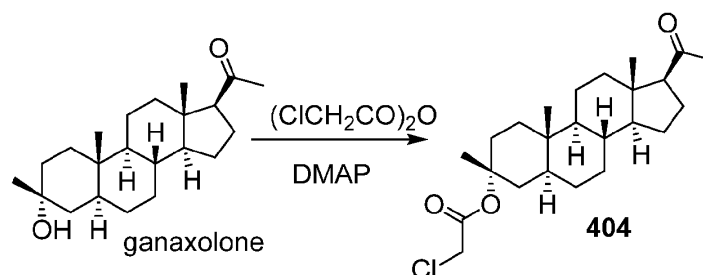
[0237] HRMS data were determined by The University of Notre Dame Mass Spectrometry & Proteomics Facility on a Bruker micrOTOF II.

[0238] Preparative reversed phase HPLC was performed on a Waters Sunfire column (19×50 mm, C18, $5 \mu\text{m}$) with a 10 min mobile phase gradient of 10% acetonitrile/water to 90% acetonitrile/water, with 0.1% TFA as buffer, using 214 and 254 nm as detection wavelengths. Injection and fraction collection were performed with a Gilson 215 liquid handling apparatus using Trilution LC software.

[0239] NMR was recorded with a Varian Oxford 300 MHz, in CDCl_3 , unless otherwise noted. Chemical shifts (δ) are expressed in ppm downfield from tetramethylsilane (TMS).

[0240] Purities are generally $\geq 95\%$ by NMR or LCMS except otherwise noted.

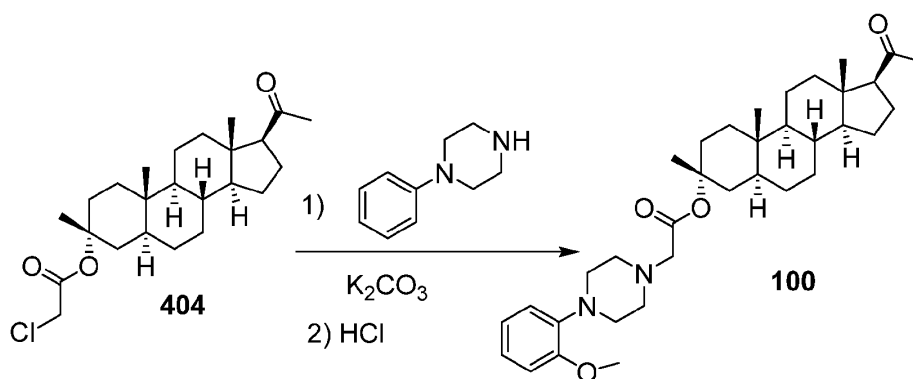
Example 1. Synthesis of Compound 404.



[0241] To a 250 mL 3-neck flask equipped with an overhead stirrer, drying tube and addition funnel was charged ganaxolone (1.01 g, 3.04 mmol) and 30 mL of 1,2-dichloroethane to produce a thick slurry. To this was charged DMAP (0.74 g, 6.04 mmol), which clarified the reaction mixture. To this was charged Et_3N (2.55 mL, 13.28 mmol), producing a clear solution which was stirred at ambient temperature for 15 min. A solution of chloroacetic anhydride (5.18 g, 30.3 mmol) dissolved in 35 mL of 1,2-DCE was added via an addition funnel over the course of 15 min. Upon the addition, the reaction instantly became a neon yellow solution, then a slurry and finally a dark brown solution. The reaction was allowed to stir for 1h and then was quenched with 100 mL of 1M HCl. This mixture was allowed to stirred for 5 minutes. The phases were

separated and the lower organic was dried with Na₂SO₄ for ~30 minutes, concentrated and dried on high vacuum pump to a dark semi solid material. The solid was dissolved in 10 mL of DCM and then concentrated onto silica gel. The resulting brown solid was dried under high vacuum for 30 minutes. A 20-gram silica cartridge was then prepped for use, a gradient of 0-5% EtOAc/hexanes was run over 10 volumes, followed by a hold at 5% for 15 volumes. After the hold, the EtOAc was ramped to 100%, then held for 5 volumes. Concentration of the product containing fractions provided compound **404** as a solid (1.1439 g). HRMS (ESI⁺): calculated for C₂₄H₃₈ClO₃ m/z [M+H]⁺: 409.2504, observed 409.2517; ¹H NMR 300MHz DMSO, d₆ δ: 3.98-4.05 (s, 2H), 2.47-2.58 (m, 1H), 2.09-2.30 (m, 4H), 1.89-2.06 (m, 2H), 1.47-1.77 (m, 10H), 1.90-1.46 (m, 10H), 0.69-1.03 (m, 5H), 0.57-0.67 (m, 3H).

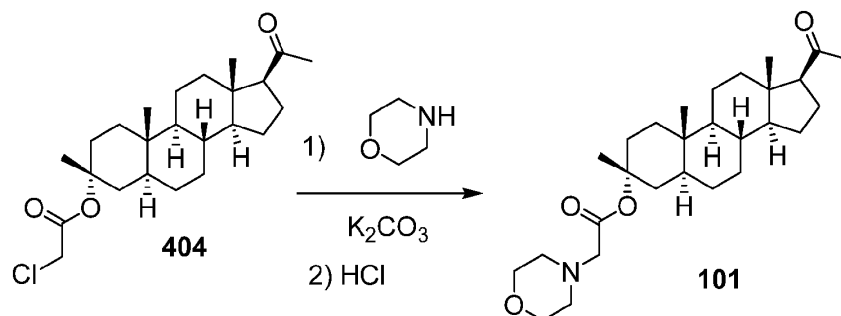
Example 2. Synthesis of Compound 100



[0242] To a solution of 1-(2-methoxyphenyl)-piperazine (12.9 mg, 0.07 mmol) and K₂CO₃ (10 mg, 0.07 mmol) in MeCN (0.55 mL) was added Compound **404** (25 mg, 0.06 mmol), and the contents were stirred and heated to 50 °C overnight. Once the reaction was deemed complete by TLC, 0.5 M HCl (15 mL) was added, followed by ethyl acetate (15 mL). The organic layer was separated, washed with water (15 mL) and brine (15 mL), and dried with Na₂SO₄. The organic layer was decanted, and solvent was removed *in vacuo*. The crude product was purified by column chromatography using an ISCOTM chromatography system. The resulting free base was treated with 2.0 M HCl/diethyl ether (2 mL), and solvent was removed *in vacuo* to provide compound **100** as a solid (44.7 mg). LCMS (ESI⁺): RT = 5.55 min, (M+H)⁺ = 565.55; HRMS (ESI⁺): calculated for C₃₅H₅₃N₂O₄ m/z [M+H]⁺: 565.4000, observed 565.4003; ¹H NMR 300 MHz CD₃OD δ: 6.87 - 7.13 (m, 4 H), 4.21 (s, 2 H), 3.85 (s, 3 H), 3.44-3.67 (m, 4 H), 3.14-3.39 (m, 4 H, coincident with solvent), 2.54-2.63 (br. s, 1 H), 2.10 - 2.30 (m, 2 H), 2.09 (s, 3 H), 1.84

- 2.07 (m, 2 H), 1.57 - 1.77 (m, 5 H), 1.55 (s, 3 H), 1.09 - 1.52 (m, 11 H), 0.85 - 1.06 (m, 1 H), 0.83 (s, 3 H), 0.74 (m, 1 H), 0.59 (s, 3 H).

Example 3. Synthesis of Compound 101

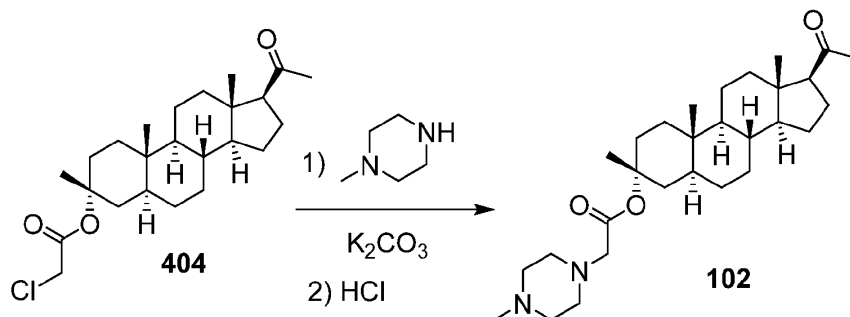


[0243] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with morpholine, Compound **101** was obtained as an HCl salt.

LCMS (ESI) m/z ($M+1$)⁺ 460.36; HRMS (ESI⁺) calculated for C₂₈H₄₆NO₄ m/z [$M+H$]⁺:

460.3421, observed 460.3416; ¹H NMR δ : 4.03-4.22 (br. s, 4 H), 3.77 (s, 2 H), 3.38 - 3.52 (br. s, 4 H), 2.48-2.57 (br. s, 1 H), 2.15 - 2.29 (m, 2 H), 2.11 (s, 3 H), 1.80 - 2.06 (m, 2 H), 1.54 - 1.75 (m, 5 H), 1.53 (s, 3 H), 1.12 - 1.49 (m, 11 H), 0.82 - 1.11 (m, 1 H), 0.77 (s, 3 H), 0.69-0.75 (m, 1 H), 0.60 (s, 3 H).

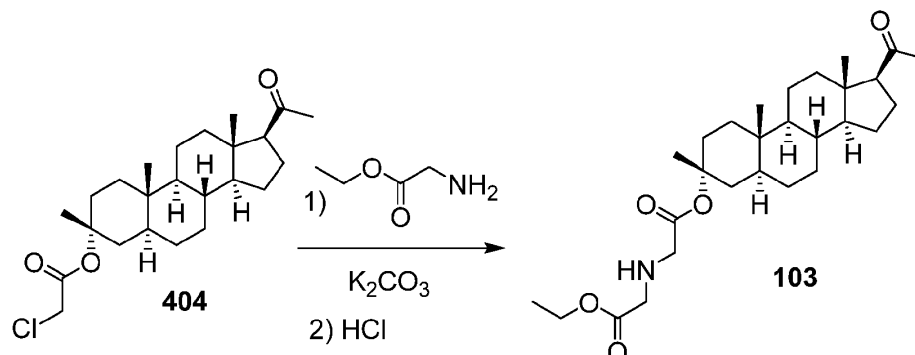
Example 4. Synthesis of Compound 102



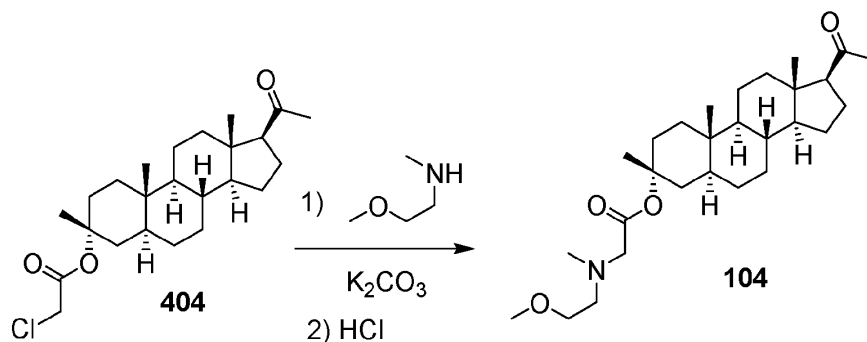
[0244] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with methylpiperazine, Compound **102** was obtained as an HCl salt.

LCMS (ESI) m/z ($M+1$)⁺ 473.39; HRMS (ESI⁺) calculated for C₂₉H₄₉N₂O₃ m/z [$M+H$]⁺:

473.3738, observed 473.3732; ¹H NMR (CD₃OD) δ : 3.83 (s, 2 H), 3.12-3.62 (m, 8 H, coincident with solvent), 2.94 (s, 3 H), 2.54-2.62 (br. s, 1 H), 2.10-2.28 (m, 2 H), 2.08 (s, 3 H), 1.82 - 2.05 (m, 2 H), 1.52 - 1.75 (m, 5 H), 1.50 (s, 3 H), 1.08 - 1.48 (m, 11 H), 0.83 - 1.06 (m, 1 H), 0.81 (s, 3 H), 0.68-0.79 (m, 1 H), 0.58 (s, 3 H).

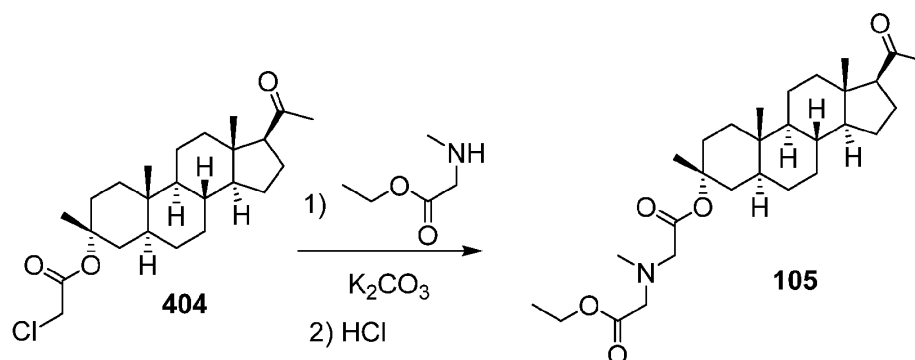
Example 5. Synthesis of Compound 103

[0245] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with glycine ethyl ester, Compound **103** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁺ 476.45; HRMS (ESI⁺) calculated for C₂₈H₄₆NO₅ m/z [$M+H$]⁺: 476.3370, observed 476.3362; ¹H NMR CD₃OD δ : 4.30 (q, $J=7.4$ Hz, 2 H), 4.00 (s, 2 H), 3.98 (s, 2 H), 2.59 (t, $J=8.4$ Hz, 1 H), 2.10 - 2.25 (m, 2 H), 2.09 (s, 3 H), 1.85 - 2.06 (m, 2 H), 1.54 - 1.76 (m, 5 H), 1.52 (s, 3 H), 1.08 - 1.50 (m, 14 H), 0.84 - 1.02 (m, 1 H), 0.82 (s, 3 H), 0.64-0.80 (m, 1 H), 0.59 (s, 3 H).

Example 6. Synthesis of Compound 104

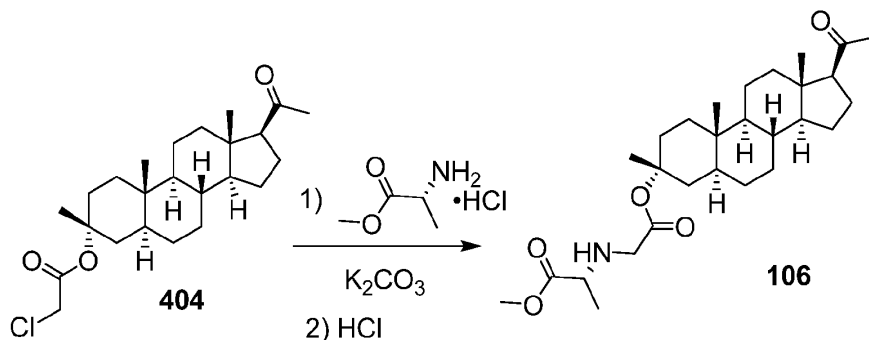
[0246] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with N-(2-methoxyethyl)methylamine, Compound **104** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁺ 462.36; HRMS (ESI⁺) calculated for C₂₈H₄₈NO₄ m/z [$M+H$]⁺: 462.3578, observed 462.3566; ¹H NMR CD₃OD δ : 4.09-4.23 (br. s., 2 H), 3.75 (t, $J=5.0$ Hz, 2 H), 3.43 - 3.54 (br. s, 2 H), 3.41 (s, 3 H), 2.99 (s, 3 H), 2.60 (t, $J=9.08$ Hz, 1 H), 2.12 - 2.29 (m, 2 H), 2.10 (s, 3 H), 1.85 - 2.08 (m, 2 H), 1.55 - 1.79 (m, 5 H), 1.54 (s, 3 H), 1.11 - 1.53 (m, 11 H), 0.86 - 1.05 (m, 1 H), 0.84 (s, 3 H), 0.65 - 0.82 (m, 1 H), 0.61 (s, 3 H).

Example 7. Synthesis of Compound 105



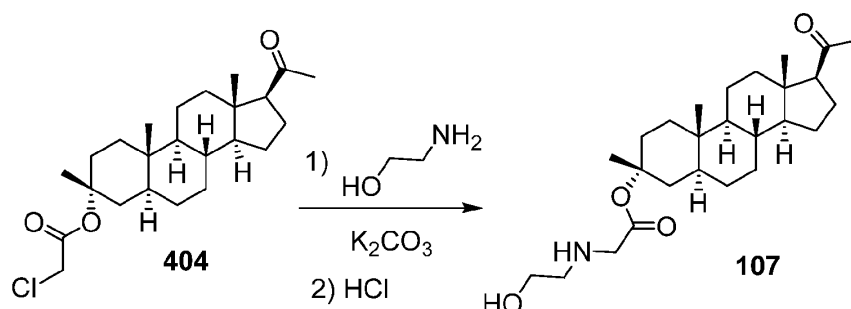
[0247] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with sarcosine ethyl ester, Compound **105** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁻ 490.41; ¹H NMR CD₃OD δ : 4.33 (q, $J=7.0$ Hz, 2 H), 4.20 (s, 4 H), 3.05 (s, 3 H), 2.60 (t, $J=8.6$ Hz, 1 H), 2.12 - 2.29 (m, 2 H), 2.10 (s, 3 H), 1.87 - 2.08 (m, 2 H), 1.56 - 1.82 (m, 5 H), 1.55 (s, 3 H), 1.13 - 1.54 (m, 14 H), 0.86 - 1.07 (m, 1 H), 0.84 (s, 3 H), 0.69 - 0.83 (m, 1 H), 0.60 (s, 3 H).

Example 8. Synthesis of Compound 106



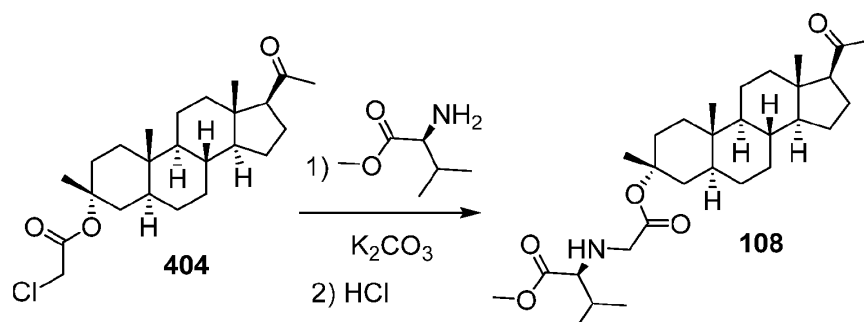
[0248] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with D-alanine methyl ester hydrochloride, Compound **106** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁺ 476.31; HRMS (ESI⁺) calculated for C₂₈H₄₆NO₅ m/z [$M+H$]⁺: 476.3370, observed 476.3376; ¹H NMR CD₃OD δ : 4.15 (q, $J=7.0$ Hz, 1 H), 3.98 (d, $J=2.3$ Hz, 2 H), 3.86 (s, 3 H), 2.60 (t, $J=8.8$ Hz, 1 H), 2.12 - 2.28 (m, 2 H), 2.10 (s, 3 H), 1.87 - 2.08 (m, 2 H), 1.55 - 1.78 (m, 8 H), 1.54 (s, 3 H), 1.12 - 1.53 (m, 11 H), 0.87 - 1.06 (m, 1 H), 0.84 (s, 3 H), 0.74 - 0.82 (m, 1 H), 0.60 (s, 3 H).

Example 9. Synthesis of Compound 107



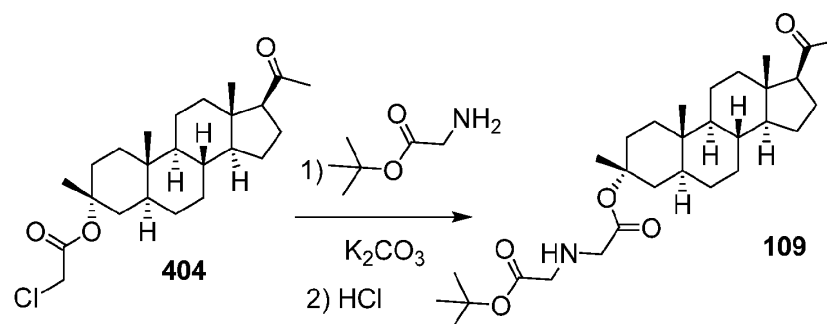
[0249] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with aminoethanol, Compound **107** was obtained as an HCl salt. LCMS (ESI) m/z $(M+1)^+$ 434.16; HRMS (ESI+) calculated for $C_{26}H_{44}NO_4$ m/z $[M+H]^+$: 434.3265, observed 434.3258; ^1H NMR CD_3OD δ : 3.95 (s, 2 H), 3.81 (t, $J=5.2$ Hz, 2 H), 3.18 (t, $J=5.0$ Hz, 2 H), 2.60 (t, $J=8.8$ Hz, 1 H), 2.12 - 2.28 (m, 2 H), 2.10 (s, 3 H), 1.88 - 2.08 (m, 2 H), 1.55 - 1.77 (m, 5 H), 1.53 (s, 3 H), 1.11 - 1.52 (m, 11 H), 0.88 - 1.06 (m, 1 H), 0.84 (s, 3 H), 0.74 - 0.82 (m, 1 H), 0.60 (s, 3 H).

Example 10. Synthesis of Compound 108



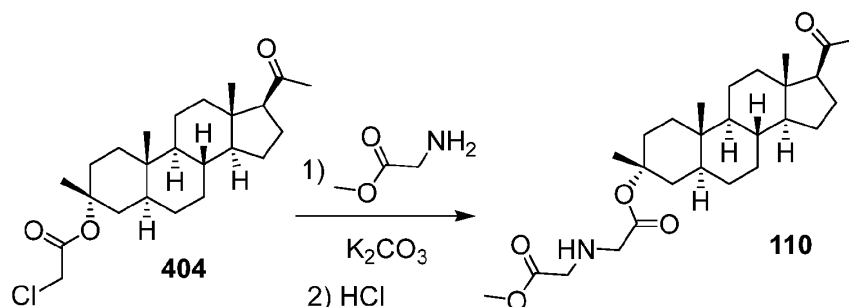
[0250] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with L-valine methyl ester, Compound **108** was obtained as an HCl salt. LCMS (ESI) m/z $(M+1)^+$ 504.30; HRMS (ESI+) calculated for $C_{30}H_{50}NO_5$ m/z $[M+H]^+$: 504.3684, observed 504.3695; ^1H NMR CD_3OD δ : 4.03 (d, $J=3.5$ Hz, 1 H), 3.98 (s, 2 H), 3.88 (s, 3 H), 2.61 (t, $J=8.8$ Hz, 1 H), 2.31 - 2.46 (m, 1 H), 2.13 - 2.30 (m, 2 H), 2.11 (s, 3 H), 1.86 - 2.09 (m, 2 H), 1.55 - 1.79 (m, 5 H), 1.54 (s, 3 H), 1.17 - 1.53 (m, 11 H), 1.14 (d, $J=7.0$ Hz, 3 H), 1.07 (d, $J=7.0$ Hz, 3 H), 0.87 - 1.02 (m, 1 H), 0.84 (s, 3 H), 0.65 - 0.83 (m, 1 H), 0.60 (s, 3 H).

Example 11. Synthesis of Compound 109



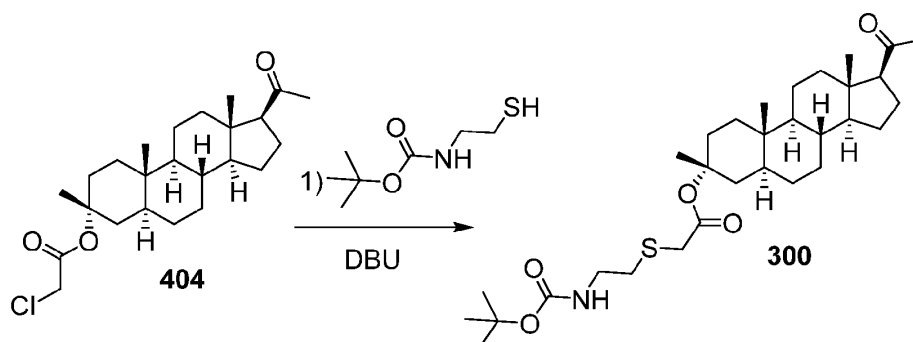
[0251] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with glycine tert-butyl ester, Compound **109** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁻ 504.23; HRMS (ESI⁺) calculated for $\text{C}_{30}\text{H}_{50}\text{NO}_5$ m/z [$M+H$]⁺: 504.3684, observed 504.3673; ^1H NMR δ : 3.39 - 3.50 (m, 4 H), 2.75-2.90 (br. s, 1 H), 2.51 (t, $J=9.1$ Hz, 1 H), 2.11 - 2.26 (m, 2 H), 2.10 (s, 3 H), 1.82 - 2.09 (m, 2 H), 1.51 - 1.73 (m, 5 H), 1.49 (s, 3 H), 1.48 (s, 9 H), 1.04 - 1.46 (m, 11 H), 0.82 - 1.02 (m, 1 H), 0.76 (s, 3 H), 0.64 - 0.75 (m, 1 H), 0.59 (s, 3 H).

Example 12. Synthesis of Compound 110



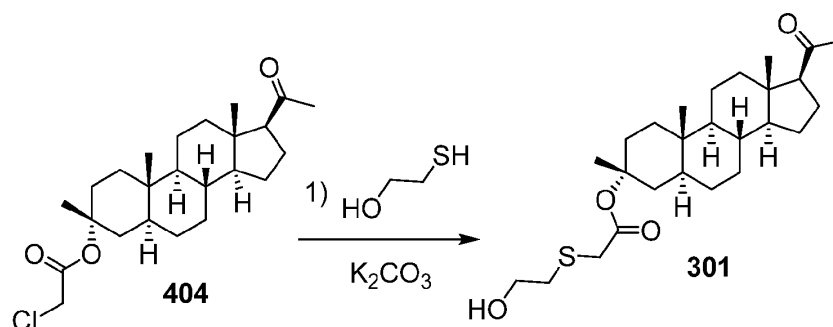
[0252] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with glycine methyl ester, Compound **110** was obtained as an HCl salt. LCMS (ESI) m/z ($M+1$)⁻ 462.29; HRMS (ESI⁺) calculated for $\text{C}_{27}\text{H}_{44}\text{NO}_5$ m/z [$M+H$]⁺: 462.3214, observed 462.3207; ^1H NMR δ : 4.03 (s, 2 H), 4.00 (s, 2 H), 3.86 (s, 3 H), 2.61 (t, $J=8.8$ Hz, 1 H), 2.13 - 2.28 (m, 2 H), 2.11 (s, 3 H), 1.88 - 2.08 (m, 2 H), 1.56 - 1.80 (m, 5 H), 1.54 (s, 3 H), 1.14 - 1.54 (m, 11 H), 0.87 - 1.07 (m, 1 H), 0.84 (m, 3 H), 0.72 - 0.82 (m, 1 H), 0.60 (s, 3 H).

Example 13. Synthesis of Compound 300



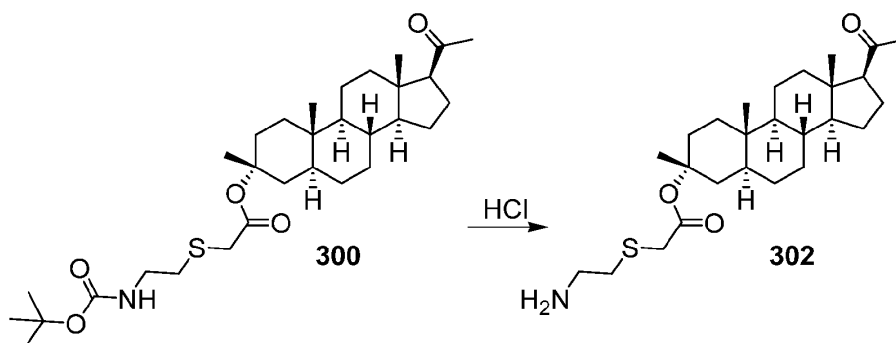
[0253] To a solution of BOC-cysteamine (23.8 mg, 0.13 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (20.5 mg, 0.13 mmol), and NaI (9.2 mg, 0.06 mmol) in MeCN (2 mL) was added compound **404** (50 mg, 0.12 mmol). The contents were stirred at ambient temperature overnight. Once the reaction was deemed complete by TLC, a 1:1 mixture (7 mL) of saturated aqueous NH_4Cl and water was added, followed by dichloromethane (DCM) (9 mL). The organic layer was separated, washed with 1:1 NH_4Cl :water (9 mL), dried over Na_2SO_4 , and filtered through a phase separator column. The aqueous phase from the extraction was washed with DCM (9 mL), which was then separated, dried over Na_2SO_4 , and filtered through the aforementioned phase separator column. The organic layers were combined, and solvent was removed *in vacuo*. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide compound **300** as an oil (61.6 mg). LCMS (ESI⁺): RT = 7.91 min, (M+H)⁺ = 550.45; HRMS (ESI⁺): calculated for $\text{C}_{31}\text{H}_{51}\text{NNaO}_5\text{S}$ m/z [M+H]⁺: 572.3380, observed 572.3371; ^1H NMR 300 MHz δ : 4.92-5.05 (br. s, 1 H), 3.28 - 3.50 (m, 2 H), 3.18 (s, 2 H), 2.77 (t, J=6.1, 2 H), 2.53 (t, J=8.8, 1 H), 2.13 - 2.25 (m, 2 H), 2.11 (s, 3 H), 1.88 - 2.03 (m, 2 H), 1.49 - 1.74 (m, 5 H), 1.48 (s, 3 H), 1.45 (s, 9 H), 1.08 - 1.43 (m, 11 H), 0.83 - 1.01 (m, 1 H), 0.77 (s, 3 H), 0.68 - 0.75 (m, 1 H), 0.60 (s, 3 H).

Example 14. Synthesis of Compound 301



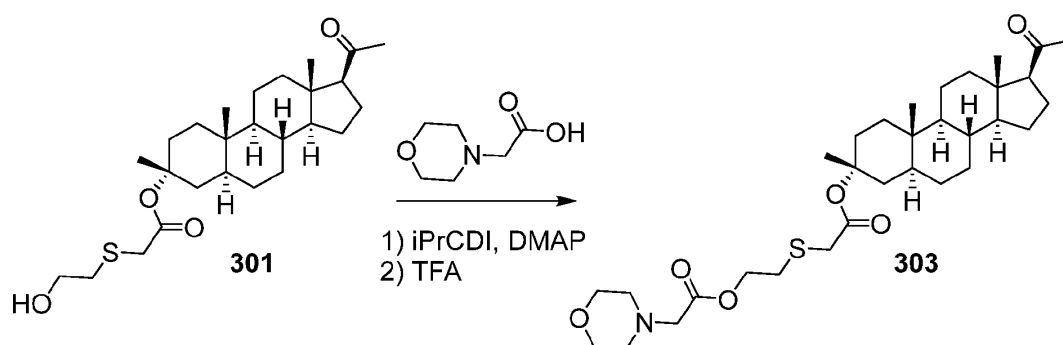
[0254] To a solution of 2-mercaptoethanol (57.3 mg, 0.73 mmol) and K_2CO_3 (101 mg, 0.73 mmol) in MeCN (2 mL) was added compound **404** (200 mg, 0.49 mmol). The contents were stirred and heated to 50 °C overnight. Once the reaction was deemed complete by TLC, a 1:1 mixture (7 mL) of saturated aqueous NH_4Cl and water was added, followed by DCM (9 mL). The organic layer was separated, washed with 1:1 NH_4Cl :water (9 mL), dried over Na_2SO_4 , and filtered through a phase separator column. The aqueous phase from the extraction was washed with DCM (9 mL), which was then separated, dried over Na_2SO_4 , and filtered through the aforementioned phase separator column. The organic layers were combined, and solvent was removed *in vacuo*. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide compound **301** as a solid (177 mg). LCMS (ESI⁺): RT = 6.86 min, $(M+H)^+ = 451.25$; HRMS (ESI⁺): calculated for $C_{26}H_{42}NaO_4S$ m/z $[M+H]^+$: 473.2696, observed 473.2692; ^1H NMR 300 MHz δ : 3.78 (t, $J=5.5$ Hz, 2 H), 3.22 (s, 2 H), 2.84 (t, $J=5.5$ Hz, 2 H), 2.52 (t, $J=8.8$ Hz, 1 H), 2.13-2.24 (m, 2 H), 2.11 (s, 3 H), 1.90-2.07 (m, 2 H), 1.51 - 1.73 (m, 6 H), 1.48 (s, 3 H), 1.09 - 1.47 (m, 11 H), 0.83 - 1.00 (m, 1 H), 0.77 (s, 3 H), 0.66 - 0.76 (m, 1 H), 0.60 (s, 3 H).

Example 15. Synthesis of Compound 302



[0255] A solution of compound **300** (43.2 mg, 0.08 mmol) in 4 N HCl/dioxane (1 mL) was vigorously stirred at ambient temperature for 10 min. The mixture was diluted with DCM (9 mL), followed by water (8 mL). The organic layer was separated, washed with brine (9 mL), dried over Na₂SO₄, and filtered through a phase separator column. The aqueous layer was washed with DCM (9 mL), which was then separated, dried over Na₂SO₄, and filtered through the aforementioned phase separator column. The organic layers were combined, and solvent was removed *in vacuo*, followed by lyophilization to remove residual dioxane. Compound **302** was isolated as a solid (HCl salt; 30.7 mg). LCMS (ESI+): RT = 5.64 min, (M+H)⁺ = 450.25; HRMS (ESI+): calculated for C₂₆H₄₄NO₃S m/z [M+H]⁺: 450.3036, observed 450.3042; ¹H NMR 300 MHz CD₃OD δ: 3.33 (s, 2 H), 3.15 (t, J=6.7 Hz, 2 H), 2.91 (t, J=6.7 Hz, 2 H), 2.61 (t, J=9.1 Hz, 1 H), 2.13 - 2.24 (m, 2 H), 2.11 (s, 3 H), 1.87 - 2.08 (m, 2 H), 1.49 - 1.83 (m, 5 H), 1.48 (s, 3 H), 1.13 - 1.48 (m, 11 H), 0.86 - 1.06 (m, 1 H), 0.83 (s, 3 H), 0.63-0.82 (m, 1 H), 0.60 (s, 3 H).

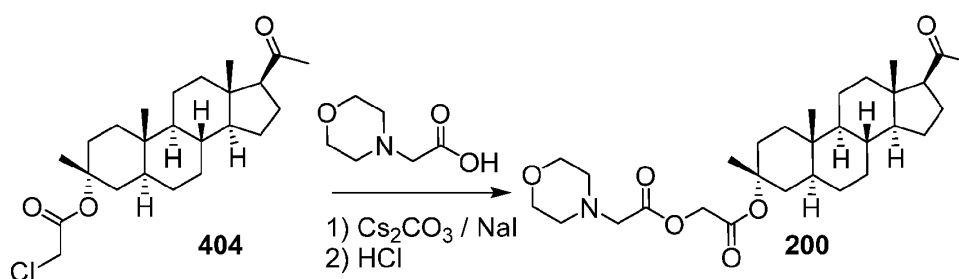
Example 16. Preparation of Compound 303



[0256] To a solution of morpholin-4-yl-acetic acid (184 mg, 1.3 mmol), N,N'-diisopropylcarbodiimide (479 mg, 3.8 mmol), and 4-(dimethylamino)pyridine (464 mg, 3.8 mmol) in DCM (4 mL) was added compound **301** (190 mg, 0.42 mmol). The contents were stirred at ambient temperature overnight. Once the reaction was deemed complete by TLC, a 1:1 mixture (18 mL) of saturated aqueous NH₄Cl and water was added, followed by DCM (14 mL). The organic layer was separated, washed with 1:1 NH₄Cl:water (18 mL), dried over Na₂SO₄, and filtered through a phase separator column. The aqueous phase from the extraction was washed with DCM (18 mL), which was then separated, dried over Na₂SO₄, and filtered through the aforementioned phase separator column. The organic layers were combined, and solvent was removed *in vacuo*. The crude product was purified by column chromatography using an ISCOTM

chromatography system, followed by further purification using a Gilson™ Semi Prep HPLC system to provide compound **303** as a solid (TFA salt; 166 mg). LCMS (ESI+): RT = 5.51 min, (M+H)⁺ = 578.34; HRMS (ESI+): calculated for C₃₂H₅₂NO₆S m/z [M+H]⁺: 578.3510, observed 578.3504; ¹H NMR 300 MHz CD₃OD δ: 4.48 (t, J=6.5 Hz, 2 H), 4.24 (s, 2 H), 3.88-4.00 (br. s, 4 H), 3.35-3.50 (br. s, 4 H), 3.27 (s, 2 H), 2.96 (t, J=4.7, 2 H), 2.61 (t, J=9.1 Hz, 1 H), 2.12 - 2.22 (m, 2 H), 2.11 (s, 3 H), 1.88 - 2.07 (m, 2 H), 1.48 - 1.77 (m, 5 H), 1.47 (s, 3 H), 1.15 - 1.45 (m, 11 H), 0.86 - 1.05 (m, 1 H), 0.83 (s, 3 H), 0.72 - 0.81 (m, 1 H), 0.60 (s, 3 H).

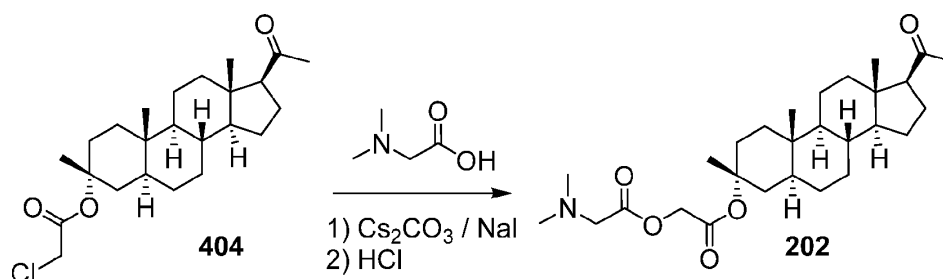
Example 17: Synthesis of Compound 200



[0257] Anhydrous DMF (3 mL) was added to compound **404** (75.6 mg, 0.18 mmol), 4-morpholineacetic acid (125 mg, 0.95 mmol) and sodium iodide (46.7 mg, 0.31 mmol) to produce a clear orange solution. The solution was stirred ambient temperature for 15 minutes. After 15 mins, Cs₂CO₃ (292 mg, 0.90 mmol) was added and the resulting mixture was heated to 70 °C and allowed to stir overnight. The reaction mixture was cooled and diluted with 25 mL of EtOAc, and then quenched with 15 mL of water. The layers were separated and the EtOAc layer was washed with 2x15 mL of saturated NaHCO₃ solution, dried with Na₂SO₄ for 30 minutes, filtered and concentrated to provide a clear orange oil. The crude mixture was purified by column chromatography. The oil was dissolved in DCM and stripped on to silica gel. The silica gel was dried under high vacuum for 15 minutes, then loaded onto a 4-gram cartridge and eluted with EtOAc in hexanes running isocratic at 25% EtOAc, then ramping to 50%, followed by ramping to 100% EtOAc. The compound **200** (free base; 81.1 mg) was obtained as an oil. HRMS (ESI+): calculated for C₃₀H₄₈NO₆ m/z [M+H]⁺: 518.3476, observed 518.3484; ¹H NMR 300MHz δ: 4.50-4.68 (m, 2H), 3.71-3.83 (m, 4H), 3.29-3.38 (m, 2H), 2.58-2.73 (m, 4H), 2.45-2.57 (m, 1H), 2.06-2.30 (m, 6H), 1.94-2.05 (m, 1H), 1.86 (dd, J=11.14 Hz, 2.34 Hz, 1H), 1.05-1.76 (m, 19H), 0.71-1.03 (m, 4H), 0.57-0.65 (m, 3H).

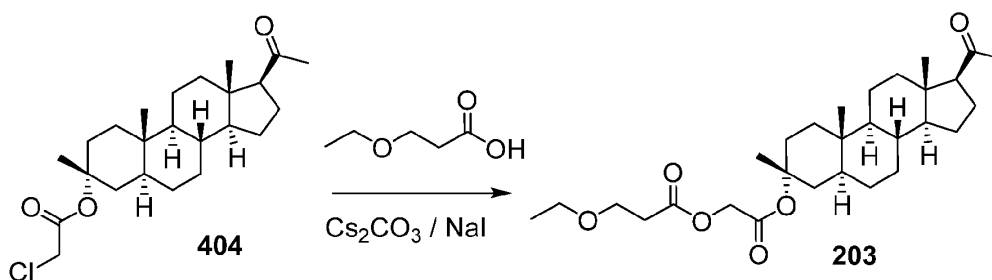
[0258] Compound **200** (free base; 42.4 mg, 0.08 mmol) was dissolved in 2 mL of Et₂O to produce a clear solution and stirred for 5 minutes. 2M HCl in Et₂O (50 μ L, 0.1 mmol) was added and a white precipitate formed. The reaction was allowed to stir for 10 minutes. The precipitate was isolated by filtration and washed with 5 mL of Et₂O. The solid was then placed under high vacuum to dry overnight to afford compound **200** HCl salt. HRMS (ESI⁺): calculated for C₃₀H₄₈NO₆ m/z [M+H]⁺: 518.3476, observed 518.3484; ¹H NMR 300MHz δ : 4.58-4.81 (m, 2H), 4.02-4.36 (m, 3H), 3.94 (br. s., 2H), 3.40-3.61 (m, 4H), 2.53 (t, J = 8.76 Hz, 1H), 2.08-2.28 (m, 5H), 1.95-2.07 (m, 1H), 1.86 (d, J = 8.79 Hz, 1H), 1.08-1.78 (m, 19 H), 0.74-1.04 (m, 4H), 0.59-0.73 (m, 4H).

Example 18: Synthesis of Compound 202



[0259] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with dimethyl glycine, Compound **202** was obtained as an HCl salt. HRMS (ESI⁺) calculated for C₂₈H₄₆NO₅ m/z [M+H]⁺: 476.3370, observed 476.3372; ¹H NMR δ : Free base) δ : 4.45-4.75 (m, 2H), 3.29 (s, 2H), 2.28-2.72 (m, 4H), 1.76-2.28 (m, 5H), 1.02-1.75 (m, 23H), 0.67-1.02 (M, 6H), 0.58 (s, 3H).

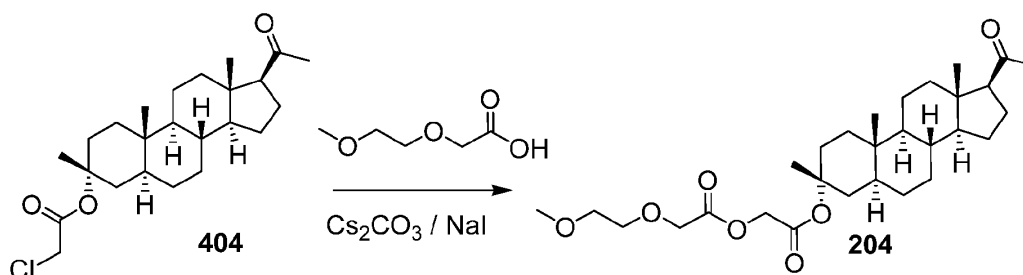
Example 19: Synthesis of Compound 203



[0260] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with 3-ethoxypropionic acid, Compound **203** was obtained. HRMS (ESI⁺) calculated for C₂₉H₄₆NaNO₆ m/z [M+H]⁺:

513.3187, observed 513.3198; ^1H NMR δ : 4.46-4.64 (m, 2H), 3.66-3.81 (m, 2H), 3.43-3.59 (m, 2H), 2.63-2.77 (m, 2H), 2.45-2.57 (m, 1H), 2.05-2.29 (m, 5H), 1.93-2.04 (m, 1H), 1.81-1.92 (m, 1H), 1.05-1.73 (m, 22H), 0.71-1.00 (m, 5H), 0.51-0.66 (s, 3H).

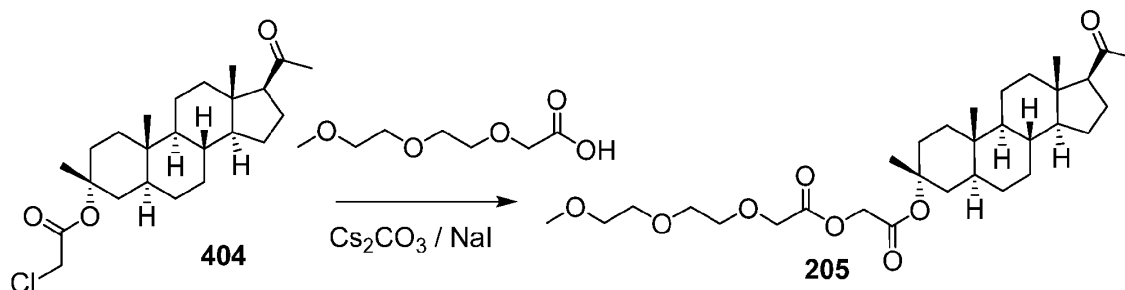
Example 20: Synthesis of Compound 204



[0261] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with 2-(2-methoxyethoxy)acetic acid, Compound **204** was obtained. HRMS (ESI+) calculated for $\text{C}_{29}\text{H}_{46}\text{NaNO}_7$ m/z $[\text{M}+\text{H}]^+$:

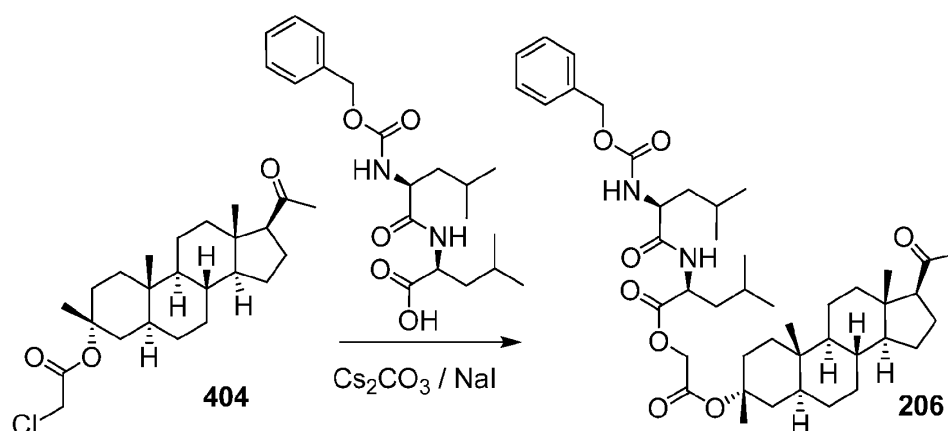
529.3136, observed 529.3137; ^1H NMR δ : 4.54-4.72 (m, 2H), 4.27 (s, 2H), 3.71-3.83 (m, 2H), 3.56-3.69 (m, 2H), 3.33-3.47 (m, 3H), 2.44-2.59 (m, 1H), 2.07-2.28 (m, 5H), 1.82-2.05 (m, 2H), 1.07-1.76 (m, 19H), 0.70-1.01 (m, 5H), 0.58 (s, 3H).

Example 21: Synthesis of Compound 205



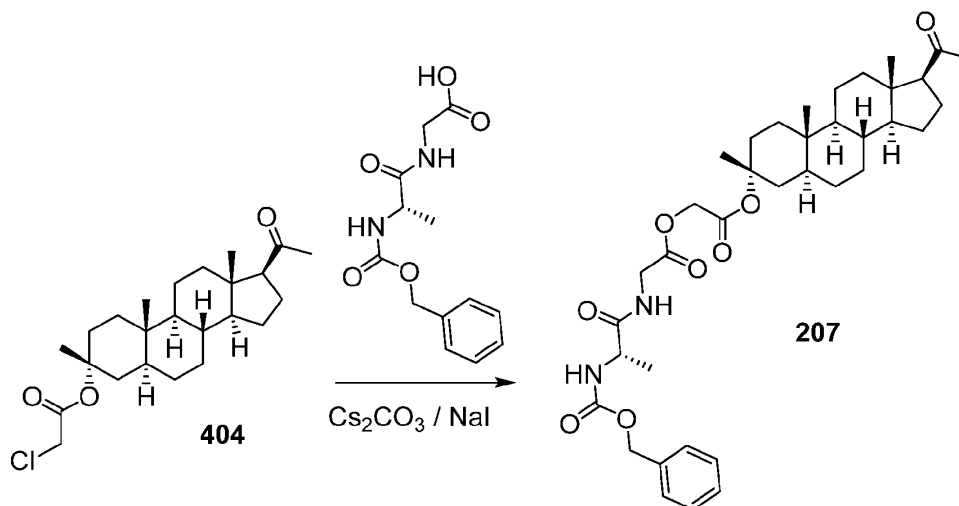
[0262] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with 2-[2-(2-methoxyethoxy)ethoxy]acetic acid, Compound **205** was obtained. HRMS (ESI+) calculated for $\text{C}_{31}\text{H}_{50}\text{NaO}_8$ m/z $[\text{M}+\text{H}]^+$: 573.3398, observed 573.3399; ^1H NMR δ : 4.51-4.69 (m, 2H), 4.25 (s, 2H), 3.50-3.86 (m, 8H), 3.36 (s, 3H), 2.46-2.55 (m, 1H), 2.06-2.27 (m, 6H), 1.97 (d, $J=11.72$ Hz, 1H), 1.86 (d, $J=11.14$ Hz, 2H), 1.09-1.73 (m, 18H), 0.71-1.01 (m, 4H), 0.57 (s, 3H).

Example 22: Synthesis of Compound 206



[0263] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with N-[(phenylmethoxy)carbonyl]-L-leucyl-L-leucine, Compound **206** was obtained. HRMS (ESI+) calculated for $C_{44}H_{67}N_2O_8$ m/z $[M+H]^+$: 751.489194, observed 751.489134; ^1H NMR δ : 7.22-7.42 (m, 5H), 6.52 (d, $J = 7.62$ Hz, 1H), 5.35 (d, $J = 8.21$ Hz, 1H), 5.08 (s, 2H), 4.55-4.73 (m, 2H), 4.20-4.24 (m, 1H), 2.41-2.56 (m, 1H), 1.83-2.27 (m, 8H), 1.08-1.78 (m, 24H), 0.83-1.00 (m, 13H), 0.67-0.80 (m, 4H), 0.57 (s, 3H).

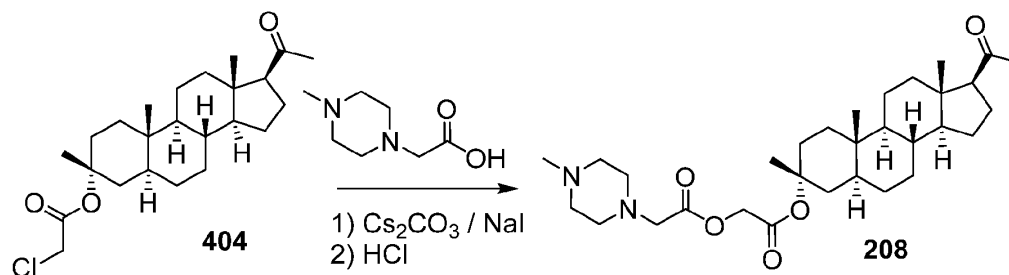
Example 23: Synthesis of Compound 207



[0264] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with CBz-L-Ala-Gly-OH, Compound **207** was obtained. HRMS (ESI+) calculated for $C_{37}H_{53}N_2O_8$ m/z $[M+H]^+$: 653.379643, observed

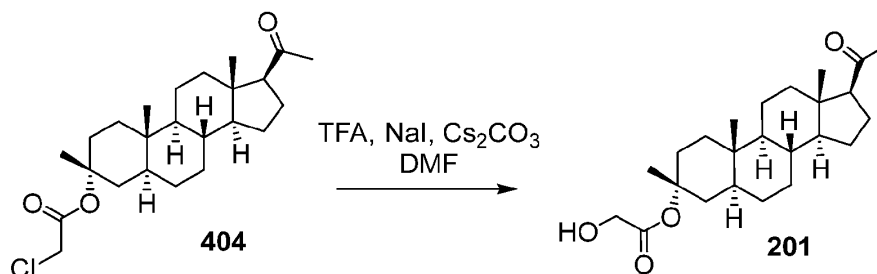
653.378352; ^1H NMR δ : 7.28-7.45 (m, 5H), 6.74 (br. s, 1H), 5.44 (d, J = 6.45 Hz, 1H), 5.03-5.23 (m, 2H), 4.51-4.68 (m, 2H), 4.24-4.41 (m, 1H), 4.10-4.24 (m, 2H), 2.46-2.59 (m, 1H), 2.07-2.30 (m, 5H), 1.85-2.04 (m, 2H), 1.07-1.77 (m, 20H), 0.83-1.02 (m, 1H), 0.68-1.04 (m, 7H), 0.59 (s, 3H).

Example 24: Synthesis of Compound 208



[0265] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with 4-methyl-1-piperazineacetic acid, Compound **208** was obtained as a bis-HCl salt. HRMS (ESI $^+$) calculated for $\text{C}_{31}\text{H}_{51}\text{N}_2\text{O}_5$ m/z $[\text{M}+\text{H}]^+$: 531.379249, observed 531.378222; ^1H NMR (MeOD) δ : 4.88-5.00 (m, 4H), 4.73-4.85 (m, 2H), 4.29-4.43 (m, 2H), 3.02 (s, 3H), 2.63 (t, J = 8.79 Hz, 1H), 1.98-2.27 (m, 7H), 1.86-1.95 (m, 1H), 1.13-1.78 (m, 23H), 0.92-1.08 (m, 2H), 0.73-0.86 (m, 4H), 0.60 (s, 3H).

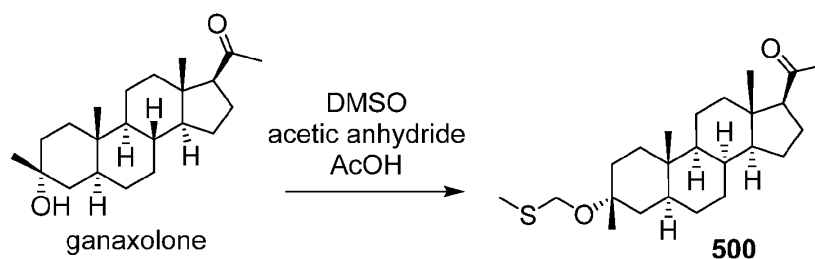
Example 25: Synthesis of Compound 201



[0266] To a suspension of compound **404** (72.1 mg, 0.18 mmol), trifluoroacetic acid (100 mg, 0.88 mmol) and sodium iodide (30 mg, 0.20 mmol) was added in 3 mL of anhydrous DMF to produce a clear orange solution. This solution was allowed to stir at ambient temperature for 15 minutes. After 15 mins, Cs_2CO_3 (278 mg, 0.85 mmol) was added and the resulting mixture was heated to 70 $^\circ\text{C}$. After stirring for 18h, the reaction was cooled, diluted with 25 mL of EtOAc, and then quenched with 15 mL of water. After separation of the layers, the EtOAc layer was washed with 2x15 mL of saturated NaHCO_3 solution, dried with Na_2SO_4 , filtered and

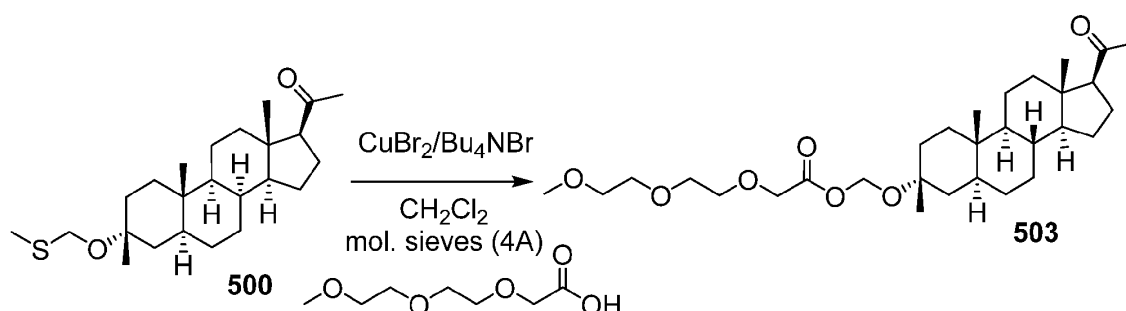
concentrated to provide a clear orange oil. The crude mixture was purified by column chromatography. The oil was dissolved in DCM and stripped on to silica gel. The silica gel was dried under high vacuum for 30 minutes, then loaded onto a 4-gram cartridge and eluted with EtOAc in hexanes running 0-10% EtOAc over 10 volumes, hold at 10% for 10 volumes, then ramping to 50%, followed by a final ramp to 100% EtOAc. Compound **201** (73.3 mg) was obtained as a crystalline solid. HRMS (ESI⁺): calculated for C₂₄H₃₈NaNO₄ m/z [M+H]⁺: 413.2662, observed 413.2662; ¹H NMR 300MHz CDCl₃ δ: 4.04-4.11 (m, 2H), 2.52 (t, J=9.08 Hz, 1H), 2.38-2.45 (m, 1H), 2.08-2.27 (m, 5H), 1.89-2.05 (m, 2H), 1.05-1.73 (m, 20H), 0.87-1.01 (m, 1H), 0.67-0.80 (m, 4H), 0.59 (s, 3H).

Example 26: Synthesis of Compound 500



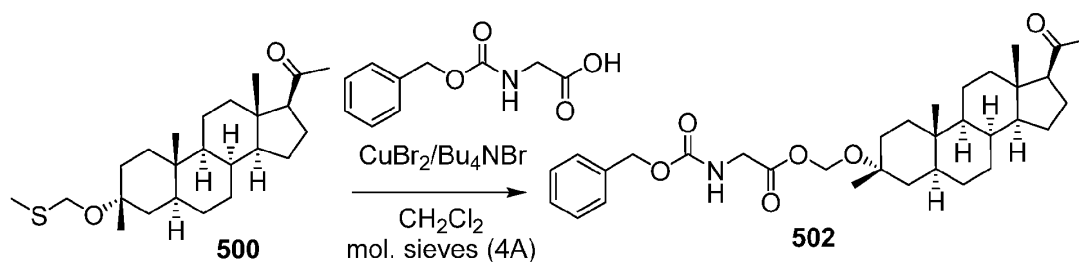
[0267] Ganaxolone (2.53 g, 7.61 mmol) was added to a solution of 75 mL of DMSO and acetic anhydride (26 mL, 275.05 mmol) to produce a thin slurry. To this slurry was added acetic acid (0.5 mL, 8.73 mmol) and the reaction was stirred at room temperature overnight resulting in a clear solution. The reaction was diluted with 300 mL of EtOAc, followed by 75 mL of H₂O. The mixture was agitated and allowed to settle. The lower aqueous layer was dropped and the process was repeated a total of 4 times. The washed organic was dried with sodium sulfate, filtered and concentrated to provide a clear faint yellow oil, which was dried under vacuum. The crude reaction mixture was purified via column chromatography. The oil was loaded onto an 80-gram cartridge eluting with 0.5% to 3% EtOAc/hexanes. The desired fractions were combined and concentrated. Compound **500** was obtained as a solid after drying under vacuum (2.31 g). HRMS (ESI⁺): calculated for C₂₄H₄₁O₂S m/z [M+H]⁺: 393.2822, observed 393.2830; ¹H NMR 300MHz CDCl₃ δ: 4.36-4.50 (m, 2H), 2.46-2.57 (m, 1H), 2.06-2.23 (m, 7H), 1.94-2.06 (m, 2H), 1.10-1.79 (m, 22H), 0.83-1.01 (m, 1H), 0.70-0.81 (m, 4H), 0.59 (s, 3H).

Example 27: Synthesis of Compound 503



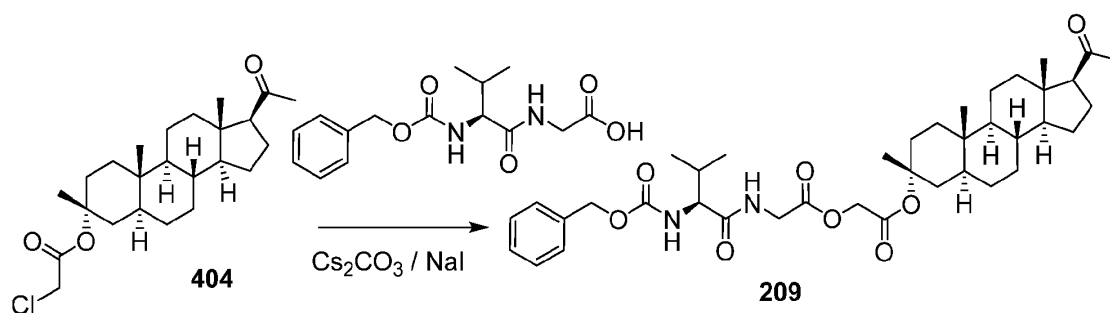
[0268] 4A molecular sieves (0.25 g) were added to a solution of compound **500** (107 mg, 0.27 mmol), 2-[2-(2-methoxyethoxy)ethoxy]acetic acid (60.4 mg, 0.34 mmol) and 3 mL of dichloromethane to produce a thick white slurry. The reaction was cooled to 0 °C in an ice bath and Bu₄NBr (0.1 mg, 0.31 mmol) was added followed by CuBr₂ (68.5 mg, 0.31 mmol). Upon addition of the CuBr₂, the reaction turned a deep purple color. The reaction was warmed to ambient temperature. After stirring for 18h, the reaction was diluted with 25 mL of EtOAc, then filter to remove the molecular sieves. The sieves were washed with 15 ml of EtOAc. The combined organic phase was then washed with 2x15 ml of saturated NaHCO₃ solution, followed by 15 mL of sat. NaCl solution. The washed organic phase was dried with Na₂SO₄, filtered and concentrated to provide a clear orange oil. The crude mixture was purified by column chromatography. The oil was dissolved in CH₂Cl₂ and stripped on to silica gel. The silica gel was dried under high vacuum for 30 minutes, then loaded onto a 4-gram cartridge and eluted with EtOAc in hexanes: 15% EtOAc, hold for 10 volumes then ramp to 100 over 5 volumes then hold for 10 volumes. Compound **503** (57.3 mg) was obtained as an oil. HRMS (ESI⁺): calculated for C₃₀H₅₀NaO₇ m/z [M+H]⁺: 545.3449, observed 545.3448; ¹H NMR 300MHz CDCl₃ δ: 5.33-5.44 (m, 2H), 4.10 (s, 2H), 3.59-3.77 (m, 6H), 3.49-3.57 (m, 2H), 3.34 (s, 3H), 2.44-2.55 (m, 1H), 2.05-2.18 (m, 4H), 1.91-2.01 (m, 1H), 1.09-1.77 (m, 21H), 0.97-1.08 (m, 1H), 0.70-0.96 (m, 4H), 0.55 (s, 3H).

Example 28: Synthesis of Compound 502



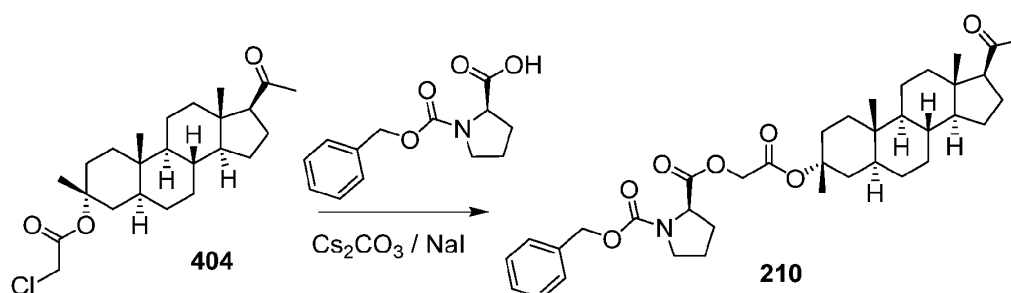
[0269] In a similar manner to the procedure outlined in Example 27, substituting 2-[2-(2-methoxyethoxy)ethoxy]acetic acid with N-Cbz-glycine, Compound **502** was obtained. HRMS (ESI⁺) calculated for C₃₃H₄₇NNaO₆ m/z [M+H]⁺: 576.3296, observed 576.3287; ¹H NMR δ : 7.27-7.45 (m, 5H), 5.37-5.50 (M, 2H), 5.24-5.32 (m, 1H), 5.10-5.18 (m, 2H), 3.95-4.02 (m, 2H), 2.46-2.57 (m, 1H), 2.07-2.20 (m, 4H), 1.92-2.05 (m, 1H), 1.10-1.82 (m, 21H), 0.74-1.04 (m, 5H), 0.55-0.69 (m, 3H).

Example 29: Synthesis of Compound 209



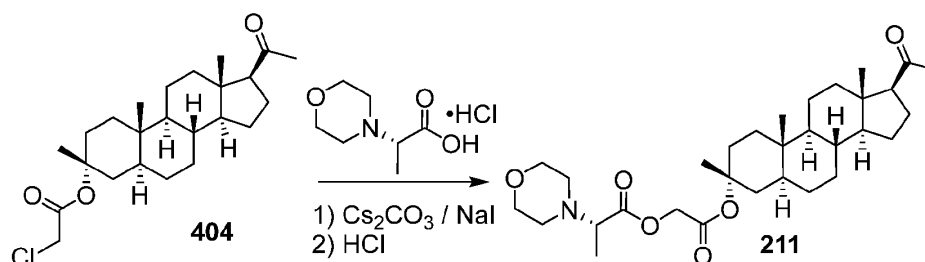
[0270] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with Cbz-L-valyl-glycine, Compound **209** was obtained. HRMS (ESI⁺) calculated for C₃₉H₅₇N₂O₈ m/z [M+H]⁺: 681.410943, observed 681.411352; ¹H NMR δ : 7.30-7.41 (m, 5H), 6.81 (d, *J* = 4.69 Hz, 1H), 5.53 (d, *J* = 9.38 Hz, 1H), 5.06-5.14 (m, 2H), 4.55-4.63 (m, 2H), 4.05-4.20 (m, 3H), 2.46-2.58 (m, 1H), 2.07-2.27 (m, 5H), 1.93-2.04 (m, 2H), 1.82-1.92 (m, 1H), 1.43-1.75 (m, 10H), 1.08-1.43 (m, 1H), 0.89-1.07 (m, 6H), 0.71-0.84 (m, 3H), 0.57 (s, 3H).

Example 30: Synthesis of Compound 210



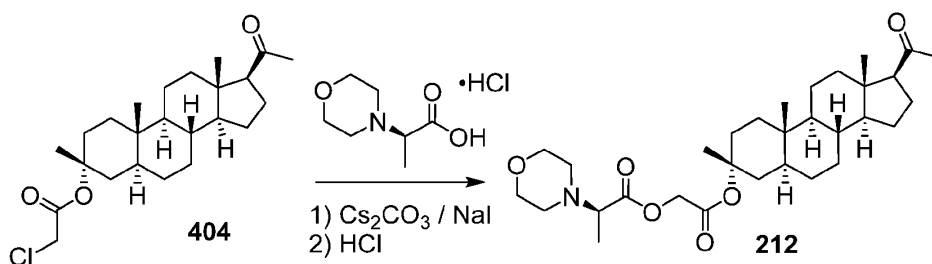
[0271] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with Cbz-D-proline, Compound **210** was obtained. HRMS (ESI+) calculated for $C_{37}H_{52}NO_7$ m/z $[M+H]^+$: 644.355774, observed 644.355320; ^1H NMR δ : 7.26-7.44 (m, 5H), 5.06-5.22 (m, 2H), 4.33-4.55 (m, 2H), 3.59-3.71 (m, 1H), 3.43-3.58 (m, 1H), 2.53 (t, $J = 8.79$ Hz, 1H), 2.16-2.30 (m, 3H), 2.11 (s, 3H), 1.80-2.04 (m, 4H), 1.10-1.74 (m, 21H), 0.83-1.02 (m, 2H), 0.76 (s 3H), 0.60 (s, 3H).

Example 31: Synthesis of Compound 211



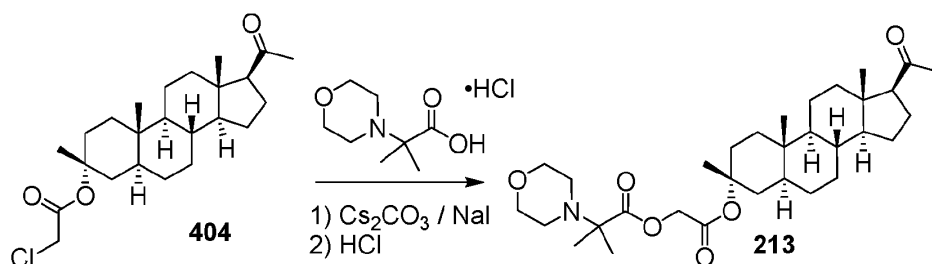
[0272] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with (S)-2-morpholin-4-yl-propionic acid hydrochloride, Compound **211** was obtained as a hydrochloride salt. HRMS (ESI+) calculated for $C_{31}H_{50}NO_6$ m/z $[M+H]^+$: 532.363265, observed 532.362510; ^1H NMR δ : 4.08-4.30 (m, 2H), 3.74-4.07 (m, 2H), 3.39-3.74 (m, 4H), 2.80-3.28 (m, 5H), 1.95-2.13 (m, 1H), 1.47-1.83 (m, 7H), 0.59-1.47 (m, 21H), 0.43 (br s, 1H), 0.19-0.36 (m, 4H), 0.04-0.19 (m, 3H).

Example 32: Synthesis of Compound 212



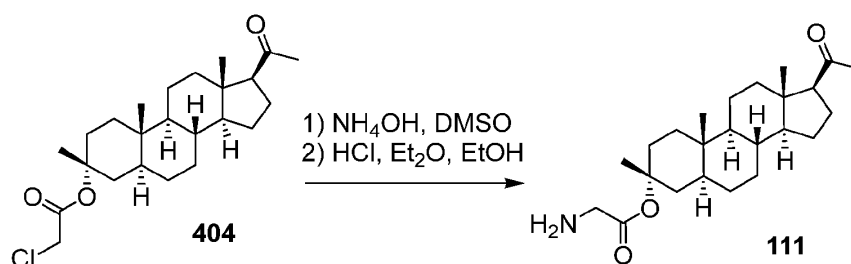
[0273] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with (R)-2-morpholin-4-yl-propionic acid hydrochloride, Compound **212** was obtained as a hydrochloride salt. HRMS (ESI⁺) calculated for C₃₁H₅₀NO₆ m/z [M+H]⁺: 532.363265, observed 532.363688; ¹H NMR δ: 4.57-4.76 (m, 2H), 4.24-4.52 (m, 2H), 3.92-4.17 (m, 3H), 3.29-3.70 (m, 4H), 2.52 (t, *J* = 8.79 Hz, 1H), 2.08-2.29 (m, 5H), 2.01 (d, *J* = 11.14 Hz, 1H), 1.85 (d, *J* = 4.69 Hz, 3H), 1.53-1.76 (m, 9H), 1.49 (s, 3H), 1.04-1.47 (m, 11H), 0.87-1.03 (m, 1H), 0.69-0.82 (m, 3H), 0.60 (s, 3H).

Example 33: Synthesis of Compound 213



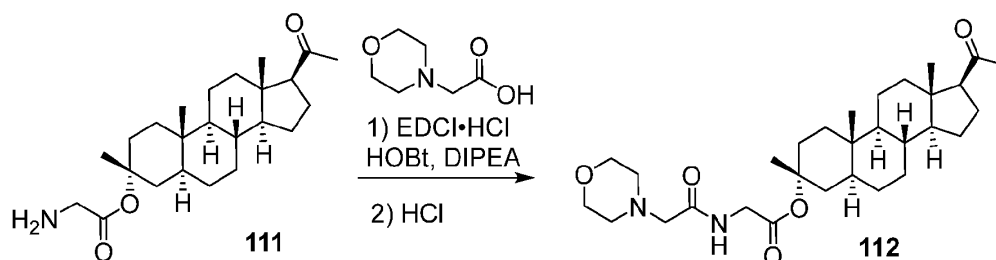
[0274] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with α,α-dimethyl-4-morpholineacetic acid hydrochloride, Compound **213** was obtained as a hydrochloride salt. HRMS (ESI⁺) calculated for C₃₂H₅₂NO₆ m/z [M+H]⁺: 546.378915, observed 546.378119; ¹H NMR δ: 4.59-4.75 (m, 2H), 4.42-4.58 (m, 2H), 3.98 (d, *J* = 12.31 Hz, 2H), 3.54 (br. s 4H), 2.51 (t, *J* = 9.08 Hz, 1H), 2.07-2.28 (m, 6H), 1.80-2.06 (m, 9H), 1.04-1.75 (m, 24H), 0.85-1.01 (m, 1H), 0.68-0.81 (m, 4H), 0.60 (s, 3H).

Example 34: Synthesis of Compound 111



[0275] Compound **404** (114 mg 0.28 mmol) was dissolved in 5 mL of DMSO to produce a clear nearly colorless solution after 10 minutes. To this solution was added ammonium hydroxide 28-30 wt% (0.25 mL, 2.07 mmol) causing an immediate color change to a red-orange. The reaction was allowed to stir at ambient temperature. After stirring for 18h, the reaction was worked up as follows: dilute with 25 mL of EtOAc, then quench with 15 mL of water. Transfer to a separatory funnel and drop the lower aqueous. Extract with 2x15 mL of H_2O , dropping the lower aqueous each time. The washed organic layers were then dried with Na_2SO_4 for 30 minutes, filtered and concentrated to provide a clear orange oil upon drying. The sample was dissolved in 2 mL of absolute EtOH to produce a clear light brown solution. To this was charged 2N HCl in Et₂O (0.2 mL, 0.4 mmol), the solution darkened, but no solids were observed. After stirring for 30 minutes, the reaction was placed on the rotary evaporator and the solvent removed. This resulted in the formation of a foam that was allowed to dry under high vacuum, to provide Compound **111** (91.2 mg) as a hydrochloride salt. HRMS (ESI⁺): calculated for $\text{C}_{24}\text{H}_{41}\text{ClNO}_3$ m/z $[\text{M}+\text{H}]^+$: 390.300271, observed 390.300526; ^1H NMR (MeOD) δ : 3.98 (d, $J = 2.34$ Hz, 1H), 3.25-3.42 (m, 2H overlaps with solvent), 2.61 (t, $J = 8.50$ Hz, 1H), 1.89-2.28 (m, 6H), 1.15-1.79 (m, 24H), 0.75-1.06 (m, 4H), 0.60 (s, 3H).

Example 35: Synthesis of Compound 112

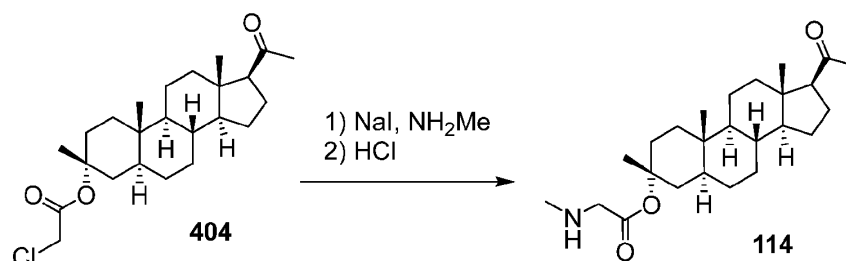


[0276] DCM (4 mL) was added to compound **111** (from Example 34, 31.6 mg, 0.07 mmol) and 4-morpholinylacetic acid (13.2 mg, 0.09 mmol). The mixture was cooled to 0 °C in an ice water

bath and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (19 mg, 0.10 mmol), and hydroxybenzotriazole (14.5 mg, 0.11 mmol) were added to produce a slurry that clarified upon the addition of diisopropylethylamine (40 μ L, 0.23 mmol). The resulting orange solution was allowed to warm to ambient temperature overnight. The reaction was diluted with 10 mL of DCM and quenched with 10 mL of H₂O. The mixture was transferred to a separatory funnel and the phases were separated. The organic was then washed with 10 mL of saturated NaHCO₃, then 10 mL of NaCl. The washed organic was dried with Na₂SO₄, filtered and concentrated to provide the crude product. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide compound **112** (free base) as a solid (17.1 mg). HRMS (ESI⁺): calculated for C₃₀H₄₉N₂O₅ m/z [M+H]⁺: 517.3636, observed 517.3635; ¹H NMR δ : 7.57 (br. s., 1H), 3.93-4.16 (m, 3H), 3.66-3.83 (m, 5H), 3.06 (s, 2H), 2.45-2.65 (m, 6H), 1.93-2.30 (m, 9H), 1.85 (d, *J* = 12.89 Hz, 1H), 1.04-1.75 (m, 27H), 0.84-1.02 (m, 2H), 0.68-0.81 (m, 5H), 0.59 (s, 3H).

[0277] The resulting free base was treated with 2.0 M HCl/diethyl ether (2 mL), and solvent was removed *in vacuo* to provide Compound **112** as a solid hydrochloride salt (19.8 mg). HRMS (ESI⁺): calculated for C₃₀H₄₉N₂O₅ m/z [M+H]⁺: 517.3636, observed 517.3635; ¹H NMR δ : 9.07 (br. s., 1H), 4.11 (br. s., 4H), 3.96 (br. s., 4H), 3.74 (br. s., 2H), 3.28 (br. s., 2H), 2.60-2.49 (m, 1H), 2.30-2.07 (m, 6H), 2.06-1.95 (mm 2H), 1.83(d, *J* = 13.5 hz, 2H), 1.76-7.56 (m, 5H), 1.54-1.08 (m, 21H), 1.00 (br. s., 1H), 0.85-0.71 (m, 5H), 0.60 (s, 3H).

Example 36: Synthesis of Compound 114

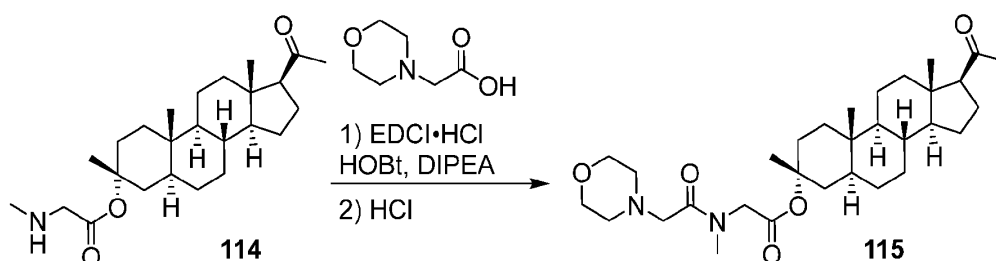


[0278] Compound **404** (125 mg, 0.31 mmol) and sodium iodide (46.7 mg, 0.31 mmol) were dissolved in 3 mL of anhydrous DMF to produce a clear orange solution. This solution was allowed to stir at ambient temperature for 15 minutes and then a 2M solution of methylamine in tetrahydrofuran (THF) (150 μ L, 0.30 mmol) was added followed by Cs₂CO₃ (127.4 mg, 0.39 mmol) and the resulting mixture was heated to 70 °C. After stirring for 2h, the reaction was

cooled, diluted with 25 mL of EtOAc, and then quenched with 15 mL of water. After separation of the layers the EtOAc layer was washed with 2x15 ml of saturated NaHCO₃ solution. The washed organic phase was dried with Na₂SO₄, filtered and concentrated to provide a clear orange oil. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide compound **114** (free base; 36.1 mg) as a solid. HRMS (ESI+): calculated for C₂₅H₄₂NO₃ m/z [M+H]⁺: 404.3159, observed 404.3159; ¹H NMR δ: 3.36-3.54 (m, 2H), 2.42-2.59 (m, 4H), 1.81-2.30 (m, 8H), 10.03-1.73 (m, 23H), 0.82-1.02 (m, 2H), 0.65-0.82 (m, 5H), 0.49-0.63 (m, 3H).

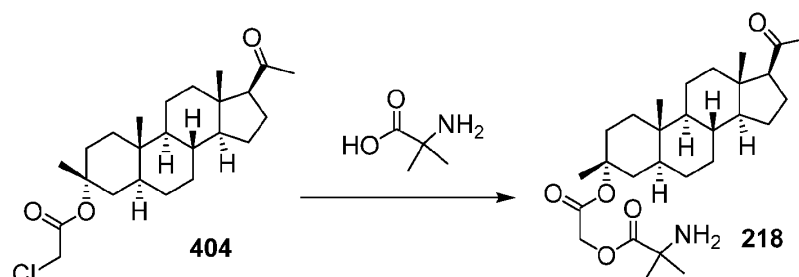
[0279] Diethyl ether (Et₂O; 2 mL) was added to the free base **114** (33.6 mg, 0.08 mmol) to produce a clear solution. The solution was allowed to stir for 5 minutes. 2M HCl in Et₂O (50 ul 0.100 mmol) was added to the reaction flask and a precipitate formed. The reaction was stirred for an additional 10 minutes. The precipitate was isolated by filtration and washed with 5 mL of Et₂O and dried under vacuum to obtain Compound **114** as a hydrochloride salt (31.4 mg). HRMS (ESI+): calculated for C₂₅H₄₂NO₃ m/z [M+H]⁺: 404.3159, observed 404.3159; ¹H NMR δ: 3.78 (br. s., 2H), 2.84 (br. s., 3H), 2.53 (t, *J* = 8.50 Hz, 1H), 2.08-2.35 (m, 5H), 2.00 (d, *J* = 11.14 Hz, 1H), 1.89 (d, *J* = 8.21 Hz, 1H), 1.07-1.78 (m, 23H), 0.97 (d, *J* = 8.21 Hz, 1H), 0.72-0.85 (m, 4H), 0.60 (s, 3H).

Example 37: Synthesis of Compound 115



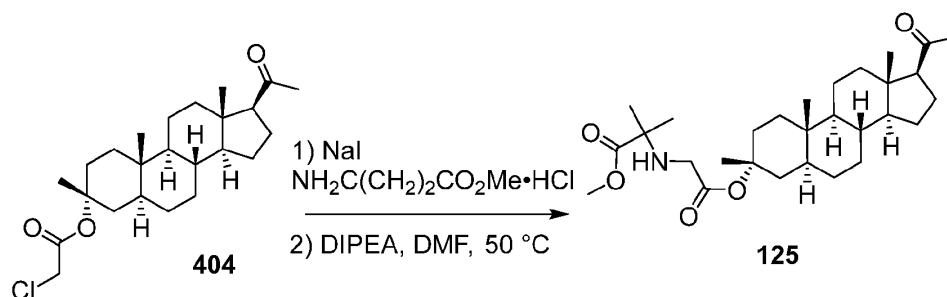
[0280] In a similar manner to the procedure outlined in Example 35, substituting Compound **404** with Compound **114**, compound **115** was obtained as a hydrochloride salt (18.7 mg). HRMS (ESI+): calculated for C₃₁H₅₁N₂O₅ m/z [M+H]⁺: 531.3792, observed 531.3782; ¹H NMR δ: 4.25 (s, 1H), 4.17-3.95 (m, 2H), 3.66-3.86 (m, 7H), 3.25 (s, 2H), 3.22-3.12 (m, 4H), 2.98 (s, 2H), 2.58-2.52 (m, 8H), 2.40-2.09 (m, 11H), 2.07-1.80 (m, 4H), 1.79-1.08 (m, 33H), 1.03-0.75 (m, 7H), 0.74-0.57 (m, 4H).

Example 38: Synthesis of Compound 218



[0281] In a similar manner to the procedure outlined in Example 17, substituting 4-morpholineacetic acid with 2-aminoisobutyric acid, Compound **218** (101.6 mg) was obtained as a solid. HRMS (ESI⁺): calculated for C₂₈H₄₆NO₅ m/z [M+H]⁺: 476.3370, observed 476.3370; ¹H NMR δ: 4.63-4.45 (m, 2H), 2.56-2.43 (m, 1H), 2.30-2.03 (m, 6H), 2.01-1.92 (m, 1H), 1.89-1.73 (m, 4H), 1.72-1.05 (m, 29H), 1.00-0.82 (m, 1H), 0.81-0.66 (m, 4H), 0.62-0.51 (m, 3H).

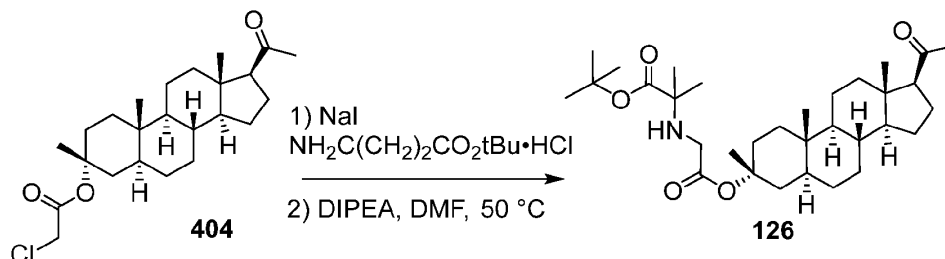
Example 39: Preparation of Compound 125



[0282] Anhydrous DMF (3 mL) was added compound **404** (150 mg, 0.37 mmol) and sodium iodide (96 mg, 0.64 mmol) to produce a clear orange solution. This solution was allowed to stir at ambient temperature for 15 minutes and methyl-2-aminoisobutyrate·HCl (302 mg, 1.96 mmol) was added followed by diisopropylethylamine (850 μL, 0.49 mmol) and the resulting mixture was heated to 50 °C. After 22h, the reaction was cooled. The reaction was diluted with 25 mL of EtOAc, then quenched with 15 mL of water. After separation of layers the EtOAc layer was washed with 2x15 mL of 1N HCl, and then 15 mL of brine. The washed organic was dried with Na₂SO₄ for 30 minutes, filtered and concentrated to provide a clear light brown oil. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **125** (85.1 mg) as an oil. HRMS (ESI⁺): calculated for C₂₉H₄₈NO₅ m/z [M+H]⁺: 490.3527, observed 490.3527; ¹H NMR δ: 3.71 (s, 3H), 3.30 (s, 2H), 2.52 (t, J = 8.8

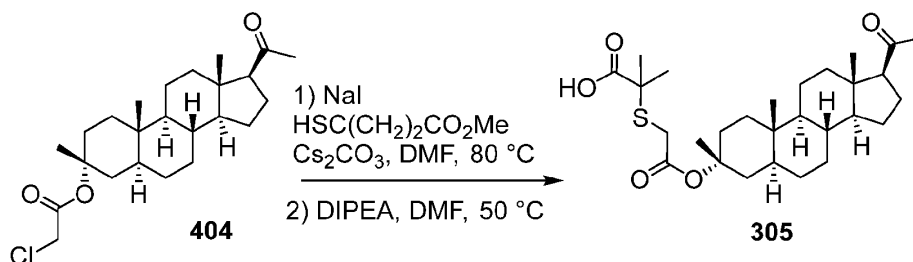
Hz, 1H), 2.30-2.08 (m, 6H), 2.05-1.87 (m, 2H), 1.74-1.38 (m, 20H), 1.38-1.33 (m, 8H), 0.92 (dq, $J = 5.3, 11.9$ Hz, 1H), 0.81-0.68 (m, 4H), 0.60 (s, 3H).

Example 40: Synthesis of Compound 126



[0283] In a similar manner to the procedure outlined in Example 39, substituting methyl-2-aminoisobutyrate·HCl with tert-butyl 2-amino-2-methylpropanoate·HCl (302 mg, 1.96 mmol), compound 126 (188 mg) was obtained as a solid. HRMS (ESI⁺): calculated for $\text{C}_{32}\text{H}_{54}\text{NO}_5$ m/z $[\text{M}+\text{H}]^+$: 532.3997, observed 532.3999; ^1H NMR δ : 8.03 (s, 1H), 3.79-3.56 (m, 2H), 2.96 (s, 3H), 2.89 (s, 3H), 2.52 (t, $J = 8.8$ Hz, 1H), 2.31-2.08 (m, 6H), 2.04-1.88 (m, 2H), 1.78-1.11 (m, 27H), 1.06-0.89 (m, 1H), 0.85-0.73 (m, 4H), 0.60 (s, 3H).

Example 41: Synthesis of Compound 305

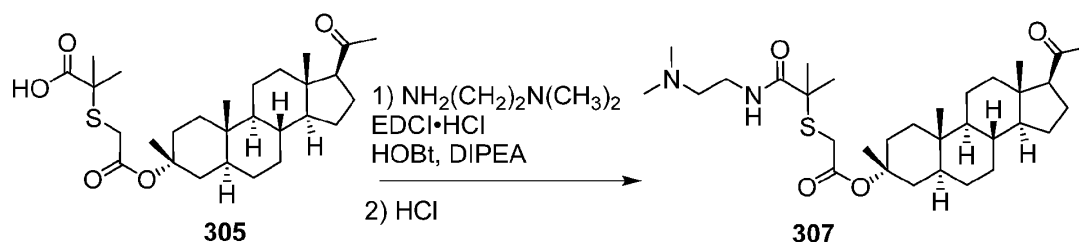


[0284] In a similar manner to the procedure outlined in Example 39, substituting methyl-2-aminoisobutyrate·HCl with 2-mercapto-2-methylpropanoic acid methyl ester, a methyl ester compound (39.1 mg) was obtained as an oil that was used directly in the next step without further purification. HRMS (ESI⁺): calculated for $\text{C}_{29}\text{H}_{47}\text{O}_5\text{S}$ m/z $[\text{M}+\text{H}]^+$: 507.313872, observed 507.313659; ^1H NMR δ : 3.77-3.69 (m, 3H), 3.37 (s, 2H), 2.58-2.47 (m, 1H), 2.23-2.08 (m, 6H), 2.04-1.88 (m, 2H), 1.74-1.43 (m, 21H), 1.42-1.32 (m, 4H), 1.31-1.11 (m, 8H), 0.92 (dq, $J = 5.3, 11.9$ Hz, 1H), 0.82-0.71 (m, 4H), 0.59 (s, 3H).

[0285] Aqueous NaOH (1.0 M, 1 mL) was added to the ester at room temperature (62 mg, 0.13 mmol) in methanol (5 mL). After 18hr the reaction was diluted with 25 mL of EtOAc, and then

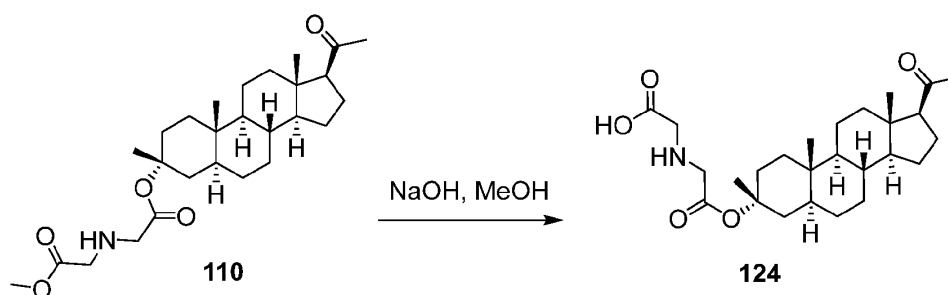
quenched with 15 mL of H₂O. The layers were separated and the aqueous layer was acidified with 2.0 mL of 2N HCl to a pH of 1. The aqueous layer was extracted 2x15 mL of DCM. The DCM phase was dried using Na₂SO₄, filtered and concentrated to provide Compound **305** as an oil (10 mg). ¹H NMR δ: 3.42 (s, 2H), 2.51 (t, J = 9.08 Hz, 1H), 2.26-2.06 (m, 6H), 2.06-1.85 (m, 3H), 1.72-1.58 (m, 4H), 1.54 (s, 6H), 1.51-1.45 (m, 5H), 1.42-1.31 (m, 5H), 1.30-1.08 (m, 10H), 1.00-0.81 (m, 2H), 0.80-0.70 (m, 4H), 0.58 (s, 3H).

Example 42: Synthesis of Compound 307



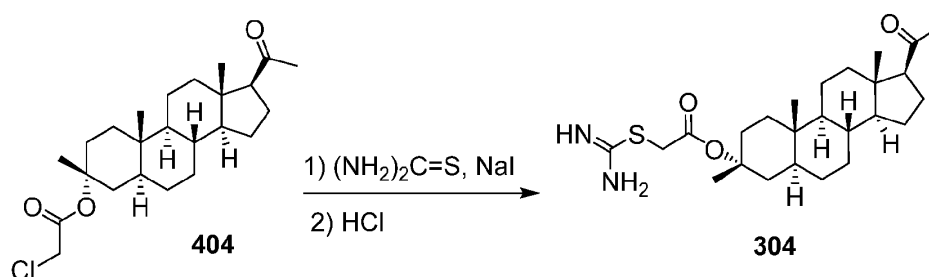
[0286] N,N-Dimethyl-1,2-ethylenediamine (38.9 mg, 0.44 mmol) and Compound **305** (45 mg, 0.091 mmol) were dissolved in 4 mL of DCM. The mixture was cooled to ~0 °C in an ice bath and EDCI·HCl (22 mg, 0.11 mmol), HOBt (16 mg, 0.12 mmol) and DIPEA (40 µL, 0.23 mmol) were added. The resulting pale-yellow solution was allowed to slowly warm to ambient temperature overnight. After 21h the reaction was diluted with 25 mL of EtOAc, then quenched with 15 mL of H₂O. The mixture was transferred to a separatory funnel and the lower aqueous was discarded. The organic was washed with 15 mL of saturated NaHCO₃ solution, then 15 mL of saturated brine. The organic layer was then dried with Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **307** as an oil (free base; 34.3 mg). The free base was treated with 2.0 M HCl/diethyl ether (2 mL), and solvent was removed *in vacuo* to provide Compound **307** as a solid hydrochloride salt (38.3 mg). HRMS (ESI⁺): calculated for C₃₂H₅₅N₂O₄S m/z [M+H]⁺: 563.3863, observed 563.3877; ¹H NMR δ: 8.10 (br. s., 1H), 3.76-3.53 (m, 3H), 3.38 (s, 2H), 3.21 (t, J = 5.0 Hz, 2H), 2.88 (s, 6H), 2.53 (t J = 9.1 Hz, 1H), 2.25-2.06 (m, 6H), 1.99 (d, J = 12.3 Hz, 1H), 1.87 (d, J = 14.1 Hz, 1H), 1.73-1.09 (m, 24H), 1.02-0.70 (m, 5H), 0.59 (s, 3H).

Example 43: Synthesis of Compound 124



[0287] Compound **110** (from Example 12; 62 mg, 0.13 mmol) was dissolved in 5 mL of MeOH. 1 mL of 1M aqueous NaOH was added and the resulting solution was allowed to stir at ambient temperature. After 21h the reaction was diluted with 25 mL of EtOAc, then quenched with 15 mL of H₂O. The mixture was transferred to a separatory funnel and the upper organic was discarded. The aqueous layer was then dried acidified with 2.0 mL of 2N HCl to a pH of 1. The aqueous layer was extracted 2x15 mL of DCM. The organic was dried using Na₂SO₄, filtered and concentrated to provide Compound **124** as an oil (58.9 mg). HRMS (ESI⁺): calculated for C₂₆H₄₂NO₅ m/z [M+H]⁺: 448.3027, observed 448.3051; ¹H NMR δ: 4.01-3.88 (m, 2H), 3.68 (s, 2H), 2.62 (t, J = 8.8 Hz, 1H), 2.30-1.86 (m, 7H), 1.78-1.10 (m, 19H), 1.07-0.69 (m, 7H), 0.60 (s, 3H).

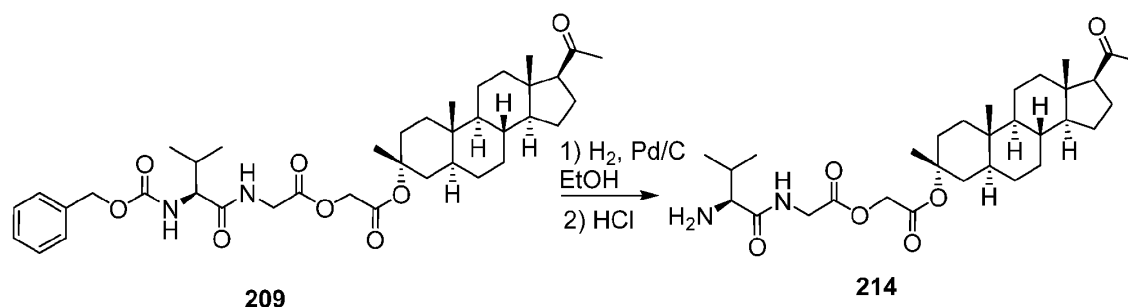
Example 44: Synthesis of Compound 304



[0288] Compound **404** (74 mg, 0.18 mmol) and sodium iodide (49 mg, 0.33 mmol) were suspended in 5 mL of 1,4 dioxane, thiourea (14.5 mg, 0.19 mmol) was added and the mixture was then heated to 85 °C. After stirring for 18h, the reaction was cooled, diluted with 25 mL of EtOAc, then quenched with 15 mL of water. The EtOAc layer was washed with 1x15 mL of H₂O, then 15 mL of brine and dried with Na₂SO₄ to then in vacuo provide a yellow solid. The solid was then taken up in 10 mL of 1,4 dioxane to provide a clear yellow solution. To this was added 4N HCl in 1,4 dioxane (50 µL, 0.200 mmol). The solution was allowed to stir for 15

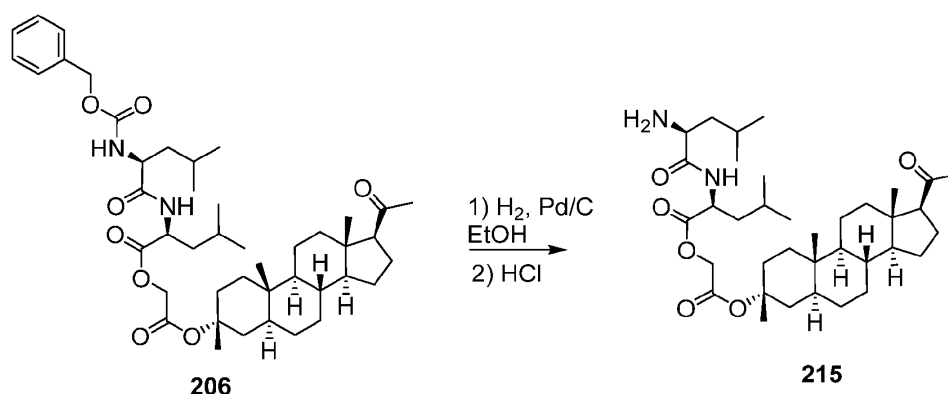
minutes, then was frozen in dry ice. The yellow solid was placed on the lyophilizer and freeze dried to provide compound **304** as a solid hydrochloride salt (77.8 mg). HRMS (ESI+): calculated for $C_{25}H_{41}ClN_2O_3S$ m/z $[M+H]^+$: 449.2832, observed 449.2827; ^1H NMR δ : 9.63-8.79 (bs. s., 3H), 4.03-3.84 (s, 1H), 3.77-3.58 (m, 3H), 2.51 (q, $J = 8.8$ Hz, 1H), 2.26-2.02 (m, 6H), 1.51-1.06 (m, 17H), 1.51-1.06 (m, 17H), 1.04-0.78 (m, 2H), 0.76-0.69 (m, 3H), 0.56 (s, 3H).

Example 45: Synthesis of Compound 214



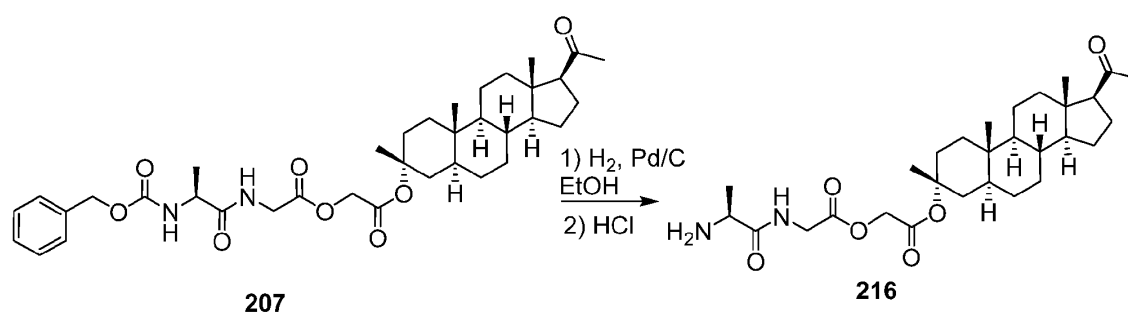
[0289] Compound **209** (from Example 29; 97 mg, 0.14 mmol) was dissolved in 10 mL of anhydrous EtOH. The solution was degassed under vacuum, then back filled with nitrogen. This was completed 3 times. To the solution was charged 5% wet Pd/C (98.1 mg, 0.05 mmol). The dark suspension was degassed under vacuum, then back filled with hydrogen. This was completed 3 times and the reaction was allowed to stir overnight under a H_2 balloon. After stirring for 18h the reaction was diluted with 25 mL of EtOAc and filtered through a Celite plug. The plug was rinsed with additional EtOAc, then concentrated to provide a hazy residue. To the flask containing the residue was dissolved in 2 mL of Et₂O. 2M HCl in Et₂O (100 μ L 0.2 mmol) was added to the reaction flask. Upon addition of the HCl, the resulting precipitate was isolated by filtration and washed with 5 mL of Et₂O. The solid was then placed under high vacuum to dry overnight to provide compound **214** (57.3 mg) as a hydrochloride salt. HRMS (ESI+): calculated for $C_{31}H_{51}ClN_2O_6$ m/z $[M+H]^+$: 547.3742, observed 547.3731; ^1H NMR δ : 4.71-4.53 (m, 2H), 4.31-3.92 (m, 3H), 3.25 (br. s., 1H), 2.59-2.48 (m, 1H), 2.28-2.08 (m, 5H), 2.07-1.77 (m, 5H), 1.75-1.35 (m, 14H), 1.33-1.03 (m, 16H), 1.03-0.87 (m, 3H), 0.82-0.69 (m, 4H), 0.61 (s, 3H).

Example 46: Synthesis of Compound 215



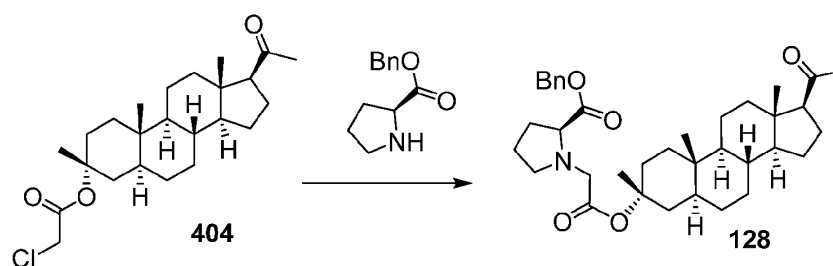
[0290] In a similar manner to the procedure outlined in Example 45, substituting Compound **209** with Compound **206** (from Example 22), Compound **215** was obtained. HRMS (ESI+) calculated for $C_{36}H_{61}ClN_2O_6$ m/z $[M+H]^+$: 617.4524, observed 617.4526; ^1H NMR δ : 4.85-4.73 (m, 1H), 4.73-4.59 (m, 2H), 4.58-4.39 (m, 1H), 2.84-2.60 (m, 1H), 2.50 (t, $J = 8.5$ Hz, 1H), 2.30-2.06 (m, 5H), 2.04-1.78 (m, 4H), 1.75-1.53 (m, 7H), 1.52-1.06 (m, 19H), 1.03-0.83 (m, 13H), 0.74 (s, 4H), 0.58 (s, 3H).

Example 47: Synthesis of Compound 216



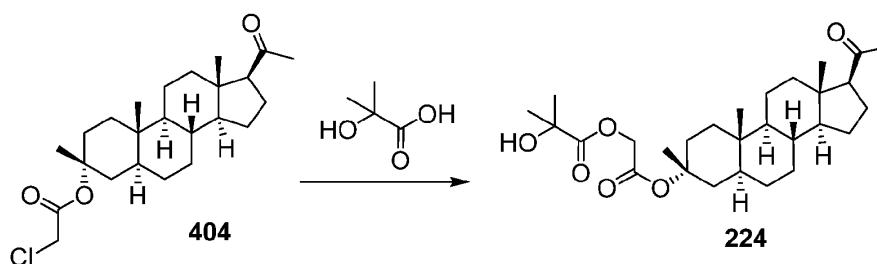
[0291] In a similar manner to the procedure outlined in Example 45, substituting Compound **209** with Compound **207** (from Example 23), Compound **216** was obtained. HRMS (ESI+) calculated for $C_{29}H_{47}CN_2O_6$ m/z $[M+H]^+$: 519.3429, observed 519.3418; ^1H NMR (MeOD) δ : 4.59-4.69 (m, 2H), 4.10-4.69 (m, 2H), 4.02 (s, 1H), 3.90-3.95 (m, 1H), 3.05 (q, $J = 7.03$ Hz, 1H), 2.57-2.68 (m, 1H), 1.85-2.27 (m, 7H), 1.12-1.76 (m, 29H), 0.73-1.06 (m, 6H), 0.60 (s, 3H δ).

Example 48: Synthesis of Compound 128



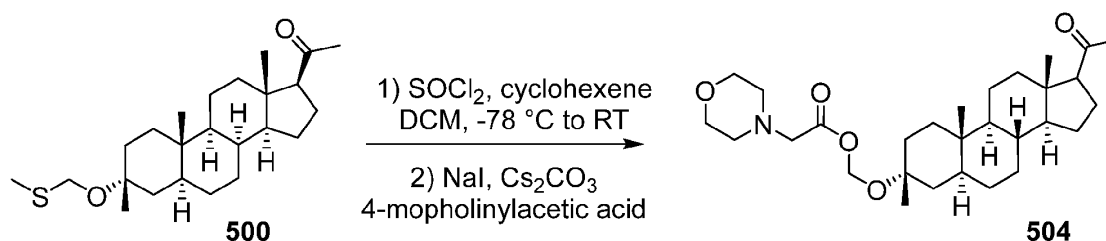
[0292] In a similar manner to the procedure outlined in Example 2, substituting 1-(2-methoxyphenyl)-piperazine with L-proline benzyl ester hydrochloride (297 mg, 1.23 mmol) Compound **128** (79.6 mg) was obtained as a solid. HRMS (ESI⁺): calculated for C₃₆H₅₂NO₅ m/z [M+H]⁺: 578.3840, observed 578.3844; ¹H NMR δ : 7.45-7.19 (m, 5H), 5.28-5.07 (m, 2H), 3.77 (dd, J = 4.4, 9.1 Hz, 1H), 3.59-3.44 (m, 2H), 3.23-3.08 (m, 1H), 2.92 (q, J = 7.6 Hz, 1H), 2.51 (t, J = 8.5 Hz, 1H), 2.31-1.81 (m, 13H), 1.76-1.06 (m, 16H), 1.03-0.67 (m, 6H), 0.60 (s, 3H).

Example 49: Synthesis of Compound 224



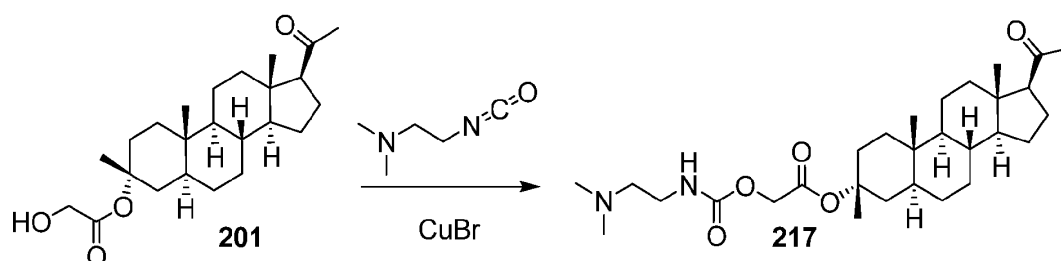
[0293] In a similar manner to the procedure outlined in Example 17 (not including the step for forming an HCl salt), substituting 4-morpholineacetic acid with 2-hydroxyisobutyric acid (166 mg, 1.60 mmol), Compound **224** (91.3 mg) was obtained as a foam. HRMS (ESI⁺): calculated for C₂₈H₄₄NaO₆ m/z [M+H]⁺: 499.3030, observed 499.3027; ¹H NMR δ : 4.63 (s, 2H), 3.00 (s, 1H), 2.60-2.46 (m, 1H), 2.35-1.97 (m, 8H), 1.85 (d, J = 11.7 Hz, 1H), 1.75-1.07 (m, 21H), 1.04-0.86 (m, 2H), 0.83-0.68 (m, 5H), 0.61 (s, 3H).

Example 50: Synthesis of Compound 504



[0294] A solution of Compound **500** (from Example 26; 122 mg, 0.31 mmol), cyclohexene (0.5 ml, 4.94 mmol) in DCM was cooled to -78 °C in a dry ice acetone bath. After stirring for 5 minutes, thionyl chloride (22 µL, 0.30 mmol) was added in a single portion and the contents were allowed to slowly warm to ambient temperature overnight. After stirring for 18 h the reaction mixture was concentrated to a residue. The residue was then dissolved in 5 mL of DMF and NaI (62.1 mg, 0.41 mmol) and 4-morpholinylacetic acid (182 mg, 1.25 mmol) were added. The resulting mixture was stirred for 5 minutes, then cesium carbonate (430 mg, 1.32 mmol) was added resulting in a bright yellow slurry. The slurry was heated to 70 °C. After stirring for 18 h the reaction was diluted with 25 mL of EtOAc and 15 mL of H₂O to produce a clear biphasic solution. After separation, EtOAc layer was washed with 2x15 mL of saturated NaHCO₃, then 15 mL of saturated NaCl solution. The organic phase was dried using Na₂SO₄, filtered and concentrated to produce an orange residue which was then dried under high vacuum. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **504** as a solid (47.1 mg). HRMS (ESI⁺): calculated for C₂₉H₄₈NO₅ m/z [M+H]⁺: 490.3527, observed 490.3527; ¹H NMR δ: 5.44-5.30 (m, 2H), 3.80-3.65 (m, 4H), 3.16-3.12 (s, 2H), 2.59-2.52 (m, 5H), 2.15-1.91 (m, 9H), 1.73-1.49 (m, 8H), 1.46-1.02 (m, 22H), 0.95-0.78 (m, 1H), 0.58-0.53 (m, 4H), 0.54 (s, 3H).

Example 51: Synthesis of Compound 217

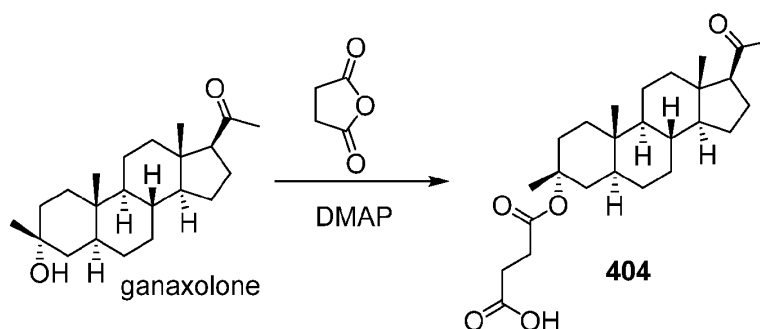


[0295] Compound **201** (From Example 25; 75.7 mg, 0.19 mmol) and CuBr (40 mg, 0.18 mmol) were dissolved in 5 mL of DCM to produce a deep green solution. To this solution was added N-(2-isocyanatoethyl)-N,N-dimethylamine (23.4 mg, 0.21 mmol). The reaction was stirred at ambient temperature for 20h, then diluted with 25 mL of EtOAc, washed with 3x15 ml with H₂O, followed by 15 mL of brine. The washed aqueous was then dried with Na₂SO₄, filtered and concentrated to provide the crude product as a clear oil. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **217**

(free base; 18.7 mg). ^1H NMR δ : 5.71 (br. s., 1H), 4.65-4.41 (m, 2H), 3.46-3.30 (m, 3H), 2.67-2.48 (m, 4H), 2.46-2.31 (m, 7H), 2.31-2.07 (m, 6H), 2.05-1.83 (m, 2H), 1.78-1.07 (m, 23H), 1.04-0.75 (m, 5H), 0.59 (s, 3H).

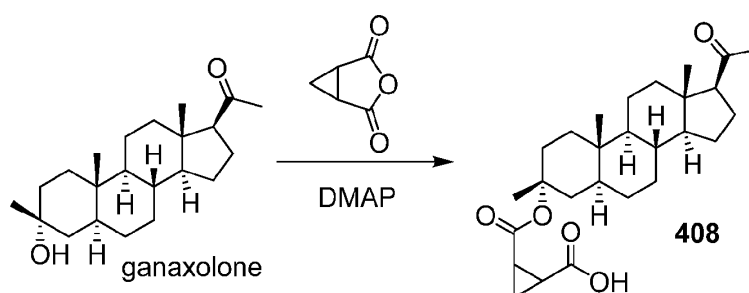
[0296] This free base was treated with 2.0 M HCl/diethyl ether (200uL), and solvent was removed *in vacuo* to provide Compound **217** as a solid hydrochloride salt (21.9 mg). HRMS (ESI⁺): calculated for $\text{C}_{29}\text{H}_{49}\text{N}_2\text{O}_5$ m/z $[\text{M}+\text{H}]^+$: 505.3636, observed 505.3624; ^1H NMR δ : 7.01-6.84 (m, 1H), 4.65-4.39 (m, 2H), 3.69 (br. s., 2H), 3.25 (br. s., 2H), 2.90 (br. s, 6H), 2.52 (t, J = 8.5 Hz, 1H), 2.79-1.78 (m, 8H), 1.75-1.54 (m, 5H), 1.53-1.07 (m, 22H), 1.03-0.67 (m, 7H), 0.59 (s, 3H).

Example 52. Synthesis of Compound 407



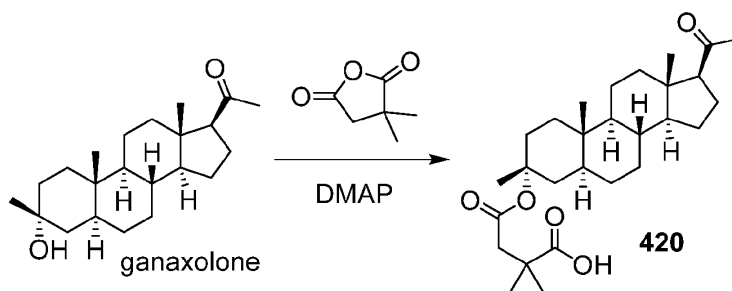
[0297] To a solution of ganaxolone (665 mg, 2.0 mmol) in pyridine (4.65 mL) was added succinic anhydride (1.2 g, 12 mmol) and DMAP (244 mg, 2.0 mmol). The reaction vessel was sealed and heated to reflux, which dissolved the reagents. After 42 h, the reaction mixture was cooled to ambient temperature and poured into cold water (95 mL). The pH was adjusted to 3 with 1N HCl and the organic layer was extracted with ethyl acetate (75 mL, 2x). The combined organic layers were washed with brine and dried over sodium sulfate. After filtration, the organic extracts were concentrated and purified via silica gel chromatography using 0-100% ethyl acetate/hexanes to provide Compound **404** as a solid 225 mg. HRMS (ESI⁺): calculated for $\text{C}_{26}\text{H}_{40}\text{NaO}_5$ m/z $[\text{M}+\text{Na}]^+$: 455.2768, observed 455.2762; ^1H NMR δ = 2.96 - 2.78 (m, 2H), 2.70 - 2.53 (m, 10H), 2.44 - 2.40 (m, 1H), 2.40 - 2.36 (m, 1H), 2.25 - 2.15 (m, 2H), 2.11 (s, 4H), 1.99 (br d, J =11.7 Hz, 1H), 1.94 - 1.84 (m, 2H), 1.72 - 1.60 (m, 4H), 1.59 - 1.49 (m, 2H), 1.48 - 1.42 (m, 5H), 1.41 - 1.33 (m, 4H), 1.26 (t, J =7.0 Hz, 5H), 1.22 - 1.09 (m, 6H), 0.89 (s, 1H), 0.80 - 0.72 (m, 4H), 0.59 (s, 3H).

Example 53: Synthesis of Compound 408



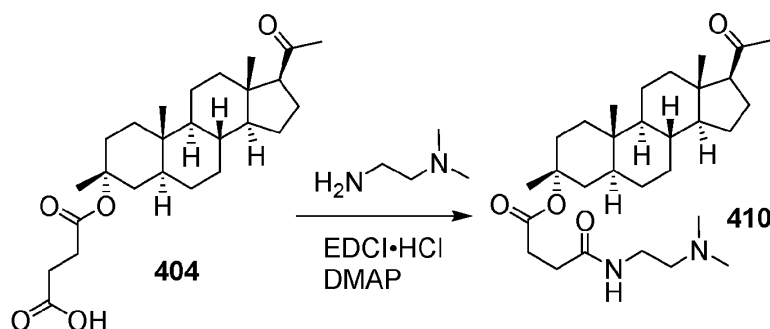
[0298] In a similar manner to the procedure outlined in Example 52, substituting succinic anhydride with 3-oxabicyclo[3.1.0]hexane-2,4-dione, Compound **408** was obtained. LCMS (ESI) m/z 467.41 ($M+Na$)⁺; HRMS (ESI⁺) calculated for $C_{27}H_{41}O_5$ m/z [$M+H$]⁺: 445.2949, observed 445.2950; ¹H NMR $CDCl_3$ δ : 2.79 (dd, $J=2.6, 8.5$ Hz, 1H), 2.59 - 2.45 (m, 1H), 2.22 (br d, $J=2.9$ Hz, 1H), 2.17 (br s, 1H), 2.30 - 2.15 (m, 1H), 2.11 (s, 5H), 2.09 (s, 1H), 2.08 (s, 1H), 2.04 - 1.95 (m, 2H), 1.89 (ddd, $J=2.6, 6.6, 11.9$ Hz, 2H), 1.74 - 1.52 (m, 8H), 1.47 (s, 4H), 1.43 - 1.29 (m, 7H), 1.26 (t, $J=7.0$ Hz, 6H), 0.90 (s, 1H), 0.83 - 0.72 (m, 5H), 0.60 (s, 3H).

Example 54: Synthesis of Compound 420



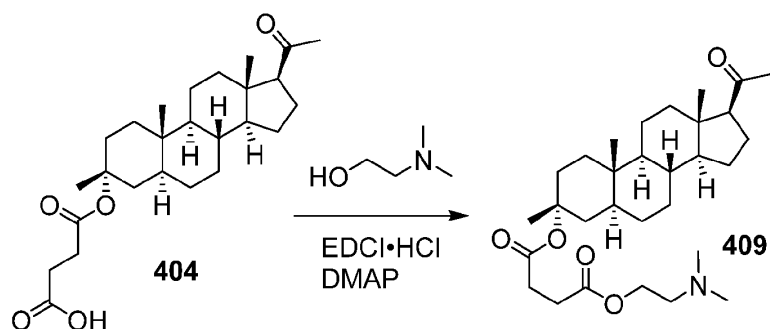
[0299] In a similar manner to the procedure outlined in Example 52, substituting succinic anhydride with 2,2-dimethylsuccinic anhydride, Compound **420** was obtained. LCMS (ESI) m/z 483.24 ($M+Na$)⁺; ¹H NMR δ : 2.62 (s, 1H), 2.60 (d, $J=2.9$ Hz, 2H), 2.52 (br t, $J=8.8$ Hz, 2H), 2.27 - 2.13 (m, 3H), 2.11 (s, 6H), 2.05 - 1.96 (m, 3H), 1.90 (br d, $J=12.9$ Hz, 2H), 1.77 - 1.54 (m, 8H), 1.45 (d, $J=1.2$ Hz, 7H), 1.39 (br d, $J=2.9$ Hz, 4H), 1.31 (s, 14H), 1.28 - 1.16 (m, 13H), 1.02 - 0.80 (m, 4H), 0.77 (s, 2H), 0.76 (s, 4H), 0.74 - 0.65 (m, 3H), 0.60 (s, 5H).

Example 55. Synthesis of Compound 410



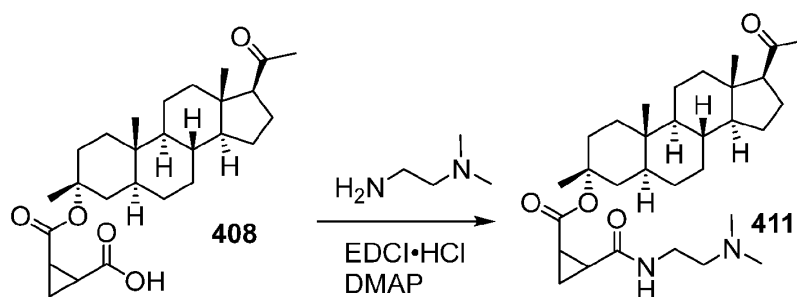
[0300] To a solution of Compound **404** (from Example 52; 96 mg, 0.22 mmol) in dichloromethane (1.1 mL), was added sequentially EDCI·HCl (85 mg, 0.44 mmol), 2-dimethylaminoethylamine (0.048 mL, 0.44 mmol), and DMAP (27 mg, 0.22 mmol). The reaction mixture was stirred overnight at ambient temperature. The reaction was diluted with ethyl acetate and 1 N HCl (aq) was added. Brine was added to break up the resulting emulsion and the phases were separated. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic layers were dried over sodium sulfate and filtered. The combined extracts were concentrated and purified via silica gel chromatography using 0-10% methanol/dichloromethane buffered with ammonium hydroxide to give impure material which was purified via reversed-phase preparative HPLC 5-95% acetonitrile/water buffered with trifluoroacetic acid. Lyophilization of the fractions containing product provided Compound **410** as the trifluoroacetic acid salt (53 mg). HRMS (ESI⁺): calculated for C₃₀H₅₁N₂O₄ m/z [M+H]⁺: 503.3843, observed 503.3856; ¹H NMR (DMSO-d₆) δ = 3.42 - 3.29 (m, 3H), 3.10 (q, *J*=5.9 Hz, 3H), 2.78 (d, *J*=4.1 Hz, 7H), 2.53 (s, 1H), 2.45 (d, *J*=5.9 Hz, 2H), 2.39 - 2.28 (m, 2H), 2.16 - 1.89 (m, 7H), 1.79 - 1.67 (m, 1H), 1.66 - 1.46 (m, 5H), 1.43 - 1.19 (m, 11H), 1.12 (br s, 5H), 0.73 (s, 4H), 0.49 (s, 3H).

Example 56: Synthesis of Compound 409



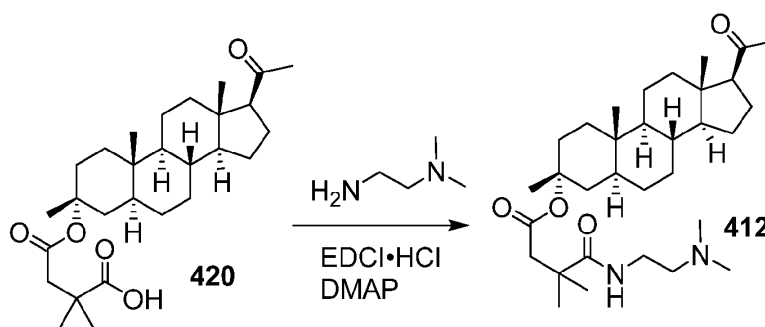
[0301] In a similar manner to the procedure outlined in Example 55, substituting dimethylaminoethylamine with 2-dimethylaminoethanol, Compound **409** was obtained as a hydrochloride salt. LCMS (ESI) m/z 504.31 ($M+H$)⁺; HRMS (ESI⁺) calculated for $C_{30}H_{50}NO_5$ m/z $[M+H]^+$: 504.3684, observed 504.3690; ^1H NMR DMSO- d_6) δ = 4.38 - 4.27 (m, 3H), 3.36 (br d, $J=4.7$ Hz, 2H), 2.81 (d, $J=4.7$ Hz, 5H), 2.54 (td, $J=2.6, 4.8$ Hz, 4H), 2.09 (br s, 1H), 1.95 (br d, $J=11.7$ Hz, 1H), 1.80 - 1.70 (m, 1H), 1.68 - 1.47 (m, 3H), 1.40 (br s, 1H), 1.38 (s, 3H), 1.33 - 1.20 (m, 3H), 1.12 (br s, 4H), 0.99 - 0.78 (m, 1H), 0.74 (s, 2H), 0.71 - 0.62 (m, 1H), 0.50 (s, 2H).

Example 57: Synthesis of Compound 411



In a similar manner to the procedure outlined in Example 55, substituting Compound **404** with Compound **408** (from Example 53), Compound **411** was obtained as a trifluoroacetate salt. LCMS (ESI) m/z 515.75 ($M+H$)⁺; HRMS (ESI⁺) calculated for $C_{31}H_{51}N_2O_4$ m/z $[M+H]^+$: 515.3843, observed 515.3857; ^1H NMR (DMSO- d_6) δ = 8.23 - 8.13 (m, 2H), 6.87 (d, $J=7.0$ Hz, 2H), 3.11 (s, 6H), 2.80 - 2.66 (m, 2H), 2.31 - 2.22 (m, 1H), 2.09 - 2.02 (m, 4H), 2.01 - 1.87 (m, 4H), 1.82 - 1.68 (m, 1H), 1.64 - 1.47 (m, 4H), 1.34 - 1.30 (m, 5H), 1.21 (s, 2H), 1.17 - 1.06 (m, 5H), 0.75 - 0.68 (m, 4H), 0.49 (s, 3H).

Example 58: Synthesis of Compound 412

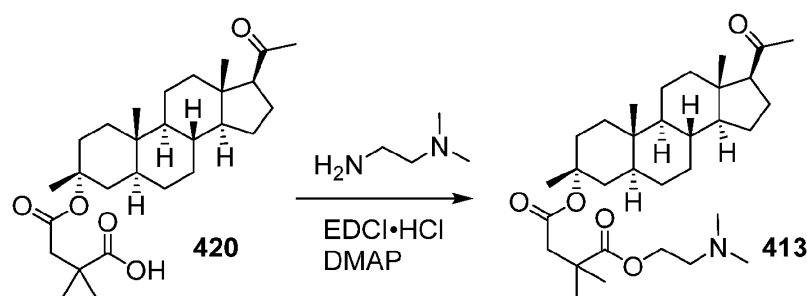


In a similar manner to the procedure outlined in Example 55, substituting Compound **404** with Compound **420** (from Example 54), Compound **412** was obtained as a trifluoroacetate salt.

LCMS (ESI) m/z 531.41 ($M+H$)⁺; HRMS (ESI⁺) calculated for $C_{32}H_{55}N_2O_4$ m/z [$M+H$]⁺:

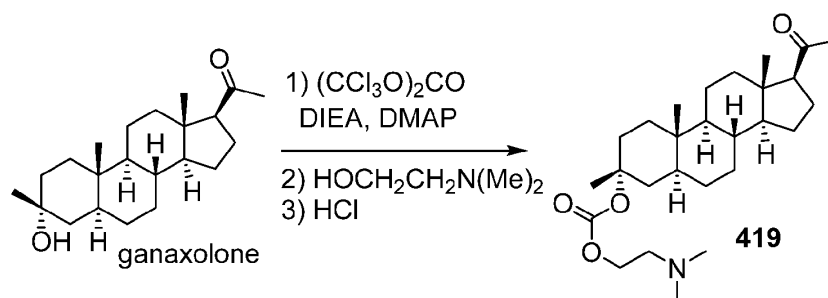
531.4156, observed 531.4150; ¹H NMR (DMSO-*d*₆) δ = 7.79 (t, J =5.6 Hz, 1H), 3.36 (q, J =5.9 Hz, 3H), 3.10 (q, J =5.9 Hz, 2H), 2.80 (d, J =4.7 Hz, 6H), 2.59 - 2.50 (m, 1H), 2.02 (br s, 2H), 1.73 (br d, J =11.7 Hz, 1H), 1.67 - 1.47 (m, 4H), 1.36 (s, 7H), 1.29 - 1.20 (m, 3H), 1.14 (s, 7H), 0.97 - 0.80 (m, 1H), 0.73 (s, 3H), 0.70 - 0.63 (m, 1H), 0.49 (s, 3H).

Example 59: Synthesis of Compound 413



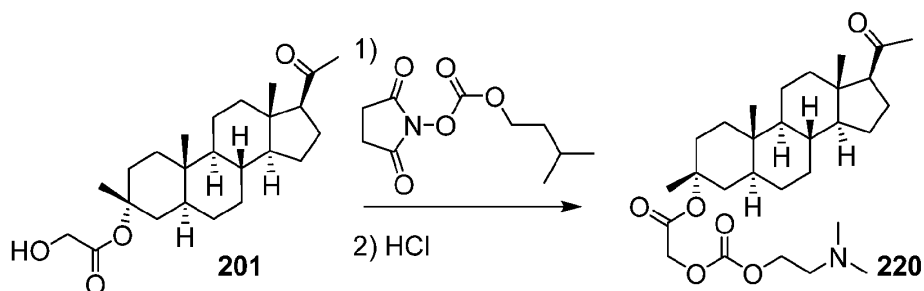
In a similar manner to the procedure outlined in Example 55, substituting Compound **404** with Compound **420** (from Example 54), and substituting dimethylaminoethanol with 2-dimethylaminoethanol, Compound **413** was obtained as a trifluoroacetate salt. LCMS (ESI) m/z 532.39 ($M+H$)⁺; HRMS (ESI⁺) calculated for $C_{32}H_{54}NO_5$ m/z [$M+H$]⁺: 532.3997, observed 532.3986; ¹H NMR (DMSO-*d*₆) δ = 4.36 - 4.22 (m, 3H), 3.37 (br s, 3H), 3.15 - 2.86 (m, 6H), 2.81 (br d, J =4.7 Hz, 7H), 2.76 - 2.69 (m, 1H), 2.65 - 2.56 (m, 4H), 2.04 (s, 6H), 1.99 - 1.91 (m, 2H), 1.77 - 1.68 (m, 1H), 1.55 (br d, J =10.5 Hz, 6H), 1.37 (s, 8H), 1.31 - 1.23 (m, 4H), 1.18 (br s, 8H), 1.12 (br s, 4H), 0.73 (s, 3H), 0.49 (s, 3H).

Example 60. Synthesis of Compound 419



[0302] To a solution of ganaxolone (83 mg, 0.25 mmol) and DMAP (37 mg, 0.3 mmol) in dichloromethane (2 mL) under a nitrogen atmosphere at 0 °C was added N,N-diisopropylethylamine (0.174 mL, 1 mmol) followed by dropwise addition a solution of triphosgene (49 mg, 0.165 mmol) in dichloromethane (1.1 mL). The reaction stirred for 3.5 h at this temperature before being cooled to 0 °C and 2-dimethylaminoethylamine (0.13 mL, 1.25 mmol) was added. The reaction was allowed to warm to ambient temperature as it stirred overnight. The reaction was then diluted with water and extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over sodium sulfate. The extracts were filtered, concentrated, and purified via silica gel chromatography using 0-10% methanol/dichloromethane to provide Compound **419** which was converted to the hydrochloride salt with HCl (15 mg). HRMS (ESI⁺): calculated for C₂₇H₄₆NO₄ m/z [M+H]⁺: 448.3421, observed 448.3421; ¹H NMR δ = 4.17 (t, *J*=5.9 Hz, 2H), 2.62 (t, *J*=5.9 Hz, 2H), 2.56 - 2.45 (m, 1H), 2.31 (s, 5H), 2.10 (s, 3H), 2.03 - 1.94 (m, 1H), 1.88 (td, *J*=2.6, 14.1 Hz, 1H), 1.73 - 1.53 (m, 4H), 1.46 (s, 3H), 1.44 - 1.33 (m, 3H), 1.27 - 1.11 (m, 7H), 1.08 (s, 1H), 1.01 - 0.80 (m, 2H), 0.76 (s, 4H), 0.59 (s, 3H).

Example 61. Synthesis of Compound 220

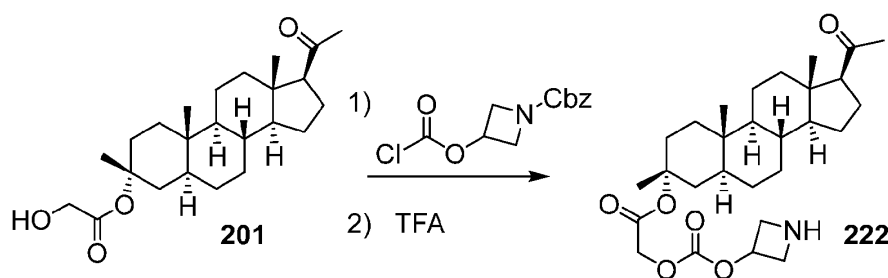


[0303] To a solution of di(N-succinimidyl) carbonate (384 mg, 1.5 mmol) in dichloromethane (14 mL) under nitrogen was added, dropwise, 2-dimethylaminoethanol (0.17 mL, 1.65 mmol). The reaction was stirred overnight at ambient temperature to give a 0.11 M solution of N',N'-dimethylaminoethyl O-succinimidyl carbonate which was used directly in the next step without any purification. LCMS: m/z = 252.54 (M+Na)⁺.

[0304] To a mixture of Compound **201** (from Example 25; 76 mg, 0.2 mmol) and DMAP (48 mg, 0.39 mmol) under nitrogen was added a 0.11 M solution of solution of N',N'-dimethylaminoethyl O-succinimidyl carbonate in dichloromethane (5.6 mL) followed by N,N-diisopropylethylamine (0.07 mL, 0.39 mmol). The reaction was stirred overnight under nitrogen

at ambient temperature. The mixture was diluted with water and the organic phase was extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over sodium sulfate. The extracts were filtered, concentrated, and purified via silica gel chromatography with 0-10% methanol/dichloromethane to provide Compound **220** which was converted to the hydrochloride salt using HCl (36 mg). HRMS (ESI⁺): calculated for C₂₉H₄₈NO₆ m/z [M+H]⁺: 506.3476, observed 506.3486; ¹H NMR δ = 4.55 (d, *J*=3.5 Hz, 2H), 4.29 (t, *J*=5.9 Hz, 2H), 2.63 (t, *J*=5.9 Hz, 2H), 2.56 - 2.47 (m, 1H), 2.33 - 2.28 (m, 6H), 2.27 - 2.15 (m, 1H), 2.11 (s, 3H), 2.03 - 1.95 (m, 1H), 1.91 (dd, *J*=2.6, 11.4 Hz, 1H), 1.51 - 1.46 (m, 4H), 1.45 - 1.11 (m, 13H), 0.97 (t, *J*=7.3 Hz, 1H), 0.94 - 0.85 (m, 1H), 0.82 - 0.73 (m, 4H), 0.59 (s, 3H).

Example 62. Synthesis of Compound 222



[0305] To a solution of Compound **201** (from Example 25, 78 mg, 0.2 mmol) in pyridine under nitrogen cooled to -20 °C was added dropwise a solution of tert-butyl 3-

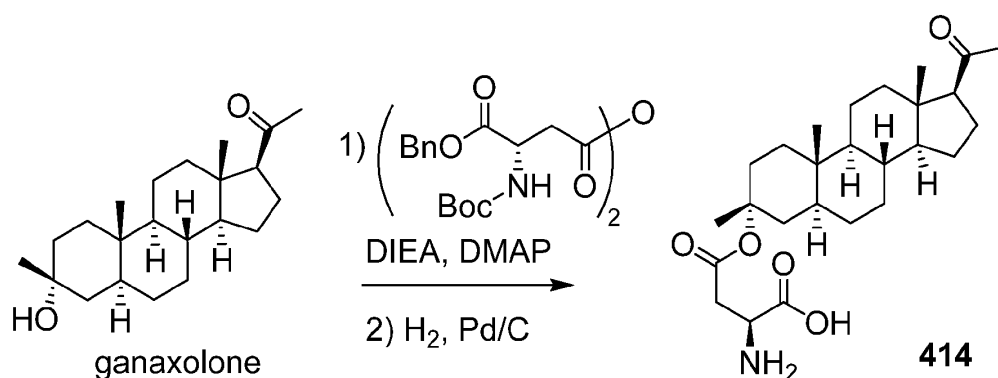
[(chlorocarbonyl)oxy]azetidine-1-carboxylate (235 mg, 1.0 mmol) in dichloromethane (1 mL).

The reaction was slowly warmed to ambient temperature over 4 hours as it stirred. The reaction was cooled to 0 °C and quenched with 1 N HCl (aq) and extracted with ethyl acetate (2x). The combined organic layers were washed with brine and dried over sodium sulfate. The extracts were filtered, concentrated, and purified via silica gel chromatography using 0-25% ethyl acetate/hexanes to give an intermediate Cbz-containing compound that was used immediately in the next step (109 mg). LCMS: m/z 612.37 (M+Na)⁺.

[0306] To the Cbz containing compound (25 mg, 0.045 mmol) in dichloromethane (0.95 mL) was added trifluoroacetic acid (0.047 mL). The reaction was stirred (2 h) before being concentrated and purified via reversed-phase preparative HPLC. Lyophilization of the fractions containing product provided Compound **111** as a trifluoroacetate salt, 14 mg. HRMS (ESI⁺): calculated for C₂₈H₄₄NO₆ m/z [M+H]⁺: 490.3163, observed 490.3165; ¹H NMR (DMSO-d₆) δ =

5.36 - 5.09 (m, 1H), 4.68 (s, 2H), 4.31 (br dd, $J=5.9, 12.3$ Hz, 2H), 4.12 - 3.93 (m, 2H), 2.71 (quin, $J=1.8$ Hz, 1H), 2.57 - 2.53 (m, 2H), 2.42 (t, $J=1.8$ Hz, 1H), 2.25 (quin, $J=1.9$ Hz, 1H), 2.13 - 2.06 (m, 1H), 2.05 - 2.01 (m, 4H), 2.00 - 1.91 (m, 2H), 1.87 - 1.71 (m, 1H), 1.56 (br d, $J=5.9$ Hz, 4H), 1.53 (s, 2H), 1.41 (s, 3H), 1.31 (br d, $J=8.2$ Hz, 4H), 1.22 (s, 1H), 1.11 (br d, $J=2.9$ Hz, 5H), 0.76 (s, 1H), 0.74 (s, 2H), 0.49 (s, 3H).

Example 63. Synthesis of Compound 414



[0307] To a solution of N-(tert-butoxycarbonyl)aspartic acid 1-benzyl ester (1.94 g, 6 mmol) in dichloromethane (6 mL) was added a 1M solution of N,N'-dicyclohexylcarbodiimide (3 mL, 3 mmol). The reaction was stirred at ambient temperature overnight before being filtered and concentrated. The resulting oily residue, N-(tert-butoxycarbonyl) 1-benzyl ester 4-aspartic anhydride, was used in the next step without further purification.

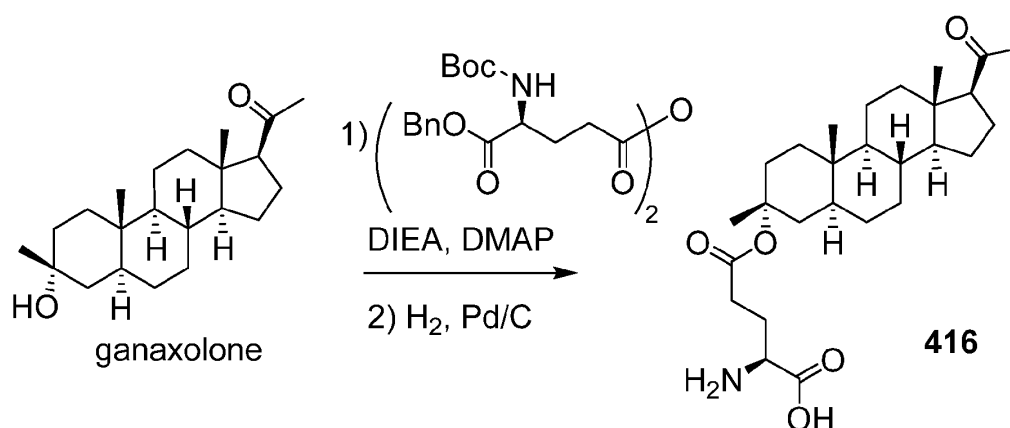
[0308] To a solution of ganaxolone (100 mg, 0.3 mmol) and DMAP (73 mg, 0.6 mmol) in dichloromethane (3 mL) under nitrogen was added N,N-diisopropylethylamine (0.23 mL, 1.3 mmol) followed by a solution of the N-(tert-butoxycarbonyl) 1-benzyl ester 4-aspartic anhydride (3 mmol) in dichloromethane (3.5 mL). The reaction was stirred overnight under nitrogen at ambient temperature. The reaction was quenched with the addition of saturated aqueous sodium bicarbonate and diluted with dichloromethane and the layers were separated. The organic layer was washed with 1 N HCl (aq) and dried over sodium sulfate. The extract was filtered, concentrated, and purified via silica gel chromatography using 0-25% ethyl acetate to provide an intermediate containing Boc and benzyl ester protecting groups (194 mg) as a solid that was used directly in the next step without further purification. LCMS: $m/z = 660.48$ ($M+\text{Na}^+$).

[0309] To a solution of the protected intermediate (190 mg, 0.3 mmol) in methanol (6.0 mL) was added palladium on carbon (35 mg, 10% by mass). The reaction mixture was purged and back-

filled with hydrogen (3x) and stirred vigorously overnight. Consumption of starting material was apparent by LC/MS and the reaction mixture was filtered and the filtrate concentrated to give a Boc-protected intermediate that was used directly in the next step.

[0310] The Boc-protected intermediate (64 mg, 0.117 mmol) was dissolved in 2 N HCl/diethyl ether (0.58 mL, 1.17 mmol) at ambient temperature. Complete consumption of starting material was apparent by LC/MS after approximately 1 h and the reaction mixture was concentrated. Purification via reversed-phase preparative HPLC using 5-95% acetonitrile buffered with trifluoroacetic acid, and lyophilization, provided Compound **414** as a trifluoroacetate salt, 20 mg. HRMS (ESI⁺): calculated for C₂₆H₄₂NO₅ m/z [M+H]⁺: 448.3057, observed 448.3050; ¹H NMR (DMSO-d₆) δ = 2.99 - 2.65 (m, 2H), 2.59 - 2.51 (m, 1H), 2.16 - 2.06 (m, 1H), 2.03 (s, 3H), 1.97 (t, *J*=11.7 Hz, 2H), 1.76 (br d, *J*=11.1 Hz, 1H), 1.67 - 1.47 (m, 5H), 1.40 (s, 4H), 1.37 - 1.24 (m, 5H), 1.12 (br s, 6H), 0.98 - 0.82 (m, 1H), 0.73 (s, 3H), 0.71 - 0.63 (m, 1H), 0.49 (s, 3H); MS: m/z = 448.23 (M+ H⁺).

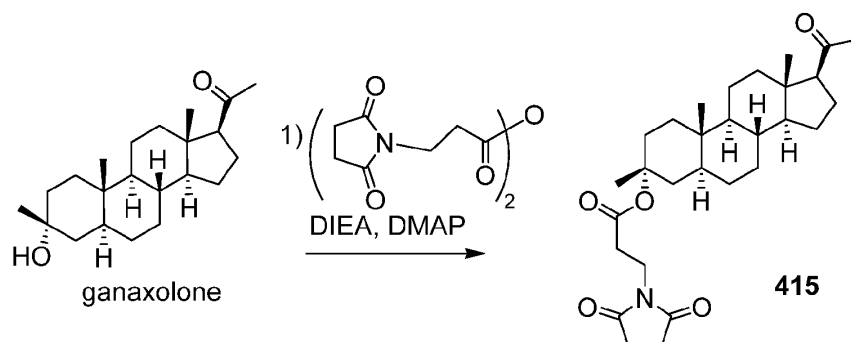
Example 64: Synthesis of Compound 416



[0311] In a similar manner to the procedure outlined in Example 63, substituting N-(tert-butoxycarbonyl)aspartic acid 1-benzyl ester with N-(tert-butoxycarbonyl)-L-glutamic acid 1-benzyl ester, Compound **416** was obtained as a trifluoroacetic acid salt. LCMS (ESI) m/z 484.21 (M+Na)⁺; HRMS (ESI⁺) calculated for C₂₇H₄₄NO₅ m/z [M+H]⁺: 448.3057, observed 448.3050; ¹H NMR (DMSO-d₆) δ = 3.80 - 3.65 (m, 2H), 3.58 (d, *J*=11.1 Hz, 1H), 2.85 - 2.75 (m, 1H), 2.75 - 2.68 (m, 1H), 2.58 - 2.52 (m, 2H), 2.46 - 2.33 (m, 1H), 2.33 - 2.23 (m, 1H), 2.15 - 2.06 (m, 2H), 2.05 (s, 1H), 2.04 (s, 3H), 2.00 - 1.87 (m, 4H), 1.80 - 1.67 (m, 2H), 1.66 - 1.48 (m, 5H), 1.39 (s,

5H), 1.37 - 1.21 (m, 7H), 1.12 (br s, 7H), 0.96 - 0.86 (m, 1H), 0.86 - 0.82 (m, 1H), 0.74 (s, 4H), 0.70 - 0.62 (m, 1H), 0.49 (s, 3H).

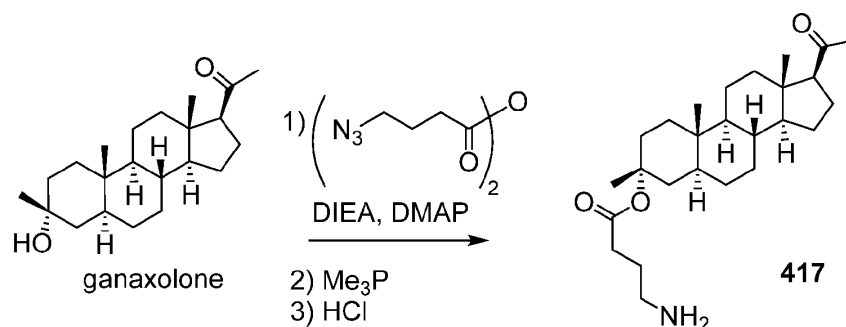
Example 65. Synthesis of Compound 415



[0312] To a solution of 2,5-dioxo-1-pyrrolidinepropanoic acid (465 mg, 2.7 mmol) in dichloromethane (5.4 mL) was added a 1M solution of N,N'-dicyclohexylcarbodiimide (1.35 mL, 1.35 mmol). The reaction was stirred at ambient temperature 3 h before being filtered and the filtrate concentrated. The resulting oily residue, 2,5-dioxo-1-pyrrolidinepropanoic anhydride, was used as-is in the next step.

[0313] To a solution of ganaxolone (50 mg, 0.15 mmol) and DMAP (37 mg, 0.3 mmol) in dichloromethane (1.5 mL) under nitrogen was added N,N-diisopropylethylamine (0.12 mL, 0.66 mmol) followed by a solution of 2,5-dioxo-1-pyrrolidinepropanoic anhydride (1.35 mmol) in dichloromethane (1.75 mL). The reaction was stirred overnight under nitrogen at ambient temperature. The reaction was quenched with the addition of 1 N HCl (aq) and diluted with dichloromethane. The layers were separated and the organic layer was washed with brine and dried over sodium sulfate. The extract was filtered, concentrated, and purified via silica gel chromatography using 0-75% ethyl acetate/hexanes to provide Compound **415** as a solid (54 mg). HRMS (ESI⁺): calculated for C₂₉H₄₃NNaO₅ m/z [M+Na]⁺: 508.3033, observed 508.3035; ¹H NMR δ = 3.84 - 3.75 (m, 2H), 2.72 (s, 4H), 2.66 - 2.47 (m, 4H), 2.25 - 2.13 (m, 1H), 2.11 (s, 3H), 2.04 - 1.94 (m, 1H), 1.93 - 1.82 (m, 1H), 1.75 - 1.65 (m, 3H), 1.65 - 1.62 (m, 2H), 1.57 - 1.56 (m, 1H), 1.57 (s, 20H), 1.53 - 1.49 (m, 1H), 1.45 (s, 4H), 1.43 - 1.32 (m, 4H), 1.30 - 1.14 (m, 9H), 1.13 - 1.04 (m, 2H), 0.76 (s, 4H), 0.60 (s, 3H).

Example 66. Synthesis of Compound 417

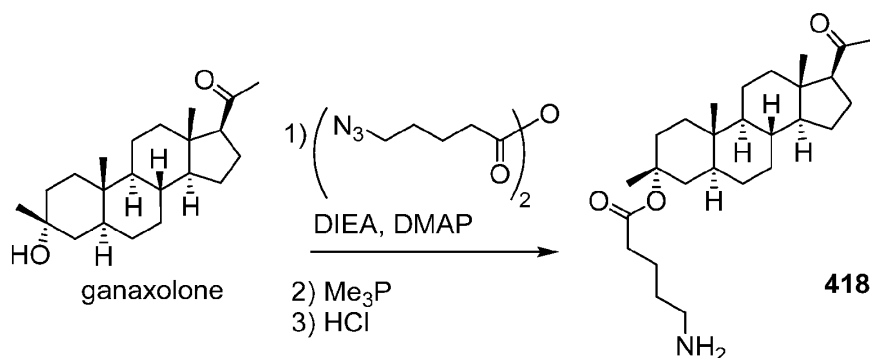


[0314] To a solution of 4-azidobutanoic acid (387 mg, 3.0 mmol) in dichloromethane (3.0 mL) was added a 1M solution of N,N'-dicyclohexylcarbodiimide (1.5 mL, 1.5 mmol). The reaction was stirred at ambient temperature for 1 h before being filtered and concentrated. The resulting oily residue, 4-azidobutanoic anhydride, was used as-is in the next step.

[0315] To a solution of ganaxolone (50 mg, 0.15 mmol) and DMAP (37 mg, 0.3 mmol) in dichloromethane (1.5 mL) under nitrogen was added N,N-diisopropylethylamine (0.12 mL, 0.66 mmol) followed by a solution of 4-azidobutanoic anhydride (1.5 mmol) in dichloromethane (1.75 mL). The reaction was stirred overnight under nitrogen at ambient temperature. The reaction was quenched with the addition of 1 N HCl (aq) and diluted with dichloromethane. The layers were separated and the organic layer was washed with brine and dried over sodium sulfate. The extract was filtered, concentrated, and purified via silica gel chromatography using 0-25% ethyl acetate to provide 43 mg of an azide-containing intermediate as a solid that was used directly in the next step.

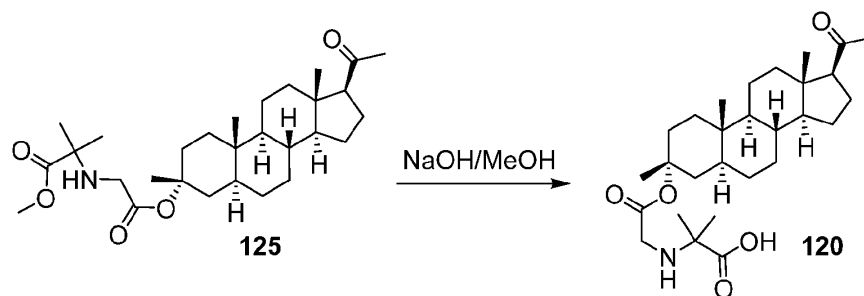
[0316] To a solution of the azide-containing intermediate (24 mg, 0.054 mmol) in tetrahydrofuran (0.22 mL) was added dropwise a 1M solution of trimethylphosphine (0.07 mL, 0.07 mmol) in tetrahydrofuran. The reaction mixture was stirred 3.5 h at ambient temperature. Water (1.5 mL) was added and the mixture was stirred 10 min and then diluted with dichloromethane (3 mL). The layers were separated and the organic phase was extracted with dichloromethane (3 mL, 2x). The combined organic layers were dried over sodium sulfate. The extract was filtered, concentrated, and purified via silica gel chromatography using 0-15% methanol/dichloromethane. Concentration of the fractions containing product provided Compound **417** which was converted to the hydrochloride salt (36 mg) using HCl.

Example 67: Synthesis of Compound 418



[0317] In a similar manner to the procedure outlined in Example 66, substituting 4-azidobutanoic acid with 5-azidopentanoic acid, Compound **418** was obtained as a hydrochloride salt. LCMS (ESI) m/z 432.33 ($M+H$)⁺; HRMS (ESI+) calculated for $C_{27}H_{46}NO_3$ m/z [$M+H$]⁺: 432.3472, observed 432.3471; ¹H NMR δ : 3.43 - 3.14 (m, 1H), 2.64 - 2.46 (m, 1H), 2.42 - 2.25 (m, 8H), 2.24 - 2.13 (m, 3H), 2.11 (s, 3H), 1.86 (br d, $J=11.7$ Hz, 10H), 1.79 - 1.55 (m, 14H), 1.43 (s, 3H), 1.29 - 1.03 (m, 16H), 0.76 (s, 4H), 0.59 (s, 3H).

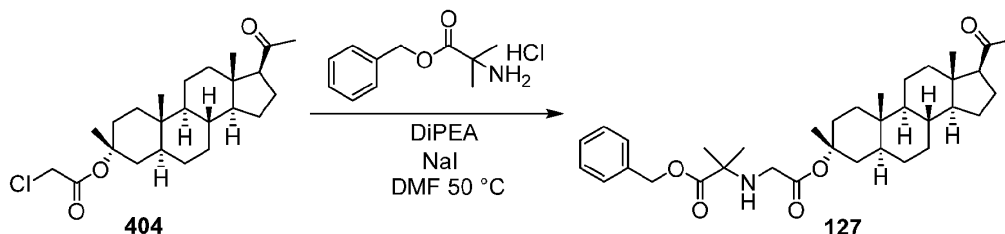
Example 68: Synthesis of Compound 120 (using Compound 125 as precursor)



[0318] Aqueous NaOH (1M, 250 μ L) was added to a solution of Compound 125 (from Example 39, 119.5 mg, 0.244 mmol) and 2.5 mL of MeOH and the resulting solution was allowed to stir at ambient temperature for 2.5 hours. The reaction mixture was then concentrated with a rotary evaporator to remove the bulk of the MeOH, and diluted with 25 mL of EtOAc, then quenched with 5 mL of 1N NaOH. The mixture was transferred to a separatory funnel and the upper organic layer was discarded. The aqueous layer was then acidified with 3.0 mL of 2N HCl to a pH of 1. The aqueous layer was extracted 2x15 mL of DCM. The organic was dried using Na_2SO_4 , filtered and concentrated to provide a foam (30.1 mg) containing a 9:1 ratio of Compound **120** to Compound **125**, as determined by LCMS. HRMS (ESI+): calculated for $C_{28}H_{46}NO_5$ m/z [$M+H$]⁺: 476.337050, observed 476.336738; ¹H NMR δ : 3.84 (br s, 2H) 2.52 (br s, 1H), 2.27-

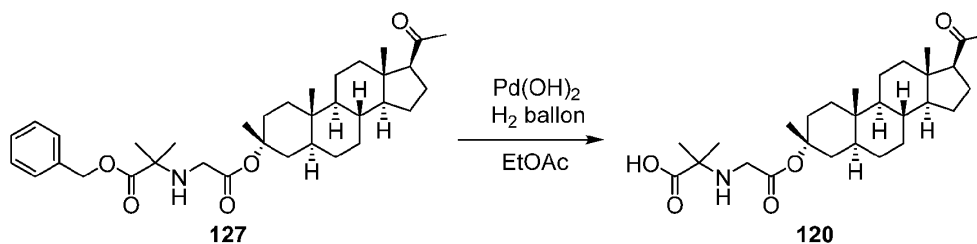
2.11 (m, 9H), 2.01-1.98 (m, 2H), 1.93-1.82 (m, 1H), 1.79-1.10 (m, 21H), 1.06-0.92 (m, 1H), 0.88-0.72 (m, 6H), 0.60 (2s, 3H).

Example 69. Synthesis of Compound 127



[0319] Compound **404** (from Example 1; 496 mg, 1.21 mmol), and sodium iodide (256 mg, 1.71 mmol) were dissolved in anhydrous DMF (8 mL) to produce a clear orange solution. After stirring for 15 minutes, benzyl-2-amino-2-methylpropanoate·HCl (1.35 g, 6.10 mmol) was added followed by DiPEA (2.5 mL, 14.35 mmol) and the resulting mixture was heated to 50 °C. After stirring for 22 hours, the reaction mixture was cooled then diluted with 40 mL of EtOAc, then quenched with 35 mL of water. The EtOAc phase was extracted with 2x25 mL of H₂O, then 25 mL of brine. The washed organic phase was dried with Na₂SO₄, filtered and concentrated to provide an oil that was purified by column chromatography using an ISCOTM chromatography system, to provide Compound **127** (375 mg) as an oil. HRMS (ESI⁺): calculated for C₂₈H₄₄NaO₆ m/z [M+H]⁺: 499.3030, observed 499.3027; ¹H NMR δ : 7.44-7.28 (m, 5H), 5.20-5.11 (m, 2H), 3.35-3.23 (m, 2H), 2.55-2.50 (t, *J* = 8.8 Hz, 1H), 2.22-2.08 (m, 5H), 2.06-1.87 (m, 3H), 1.74-1.07 (m, 26H), 1.02-0.83 (m, 1H), 0.83-0.66 (m, 4H), 0.60 (m, 3H).

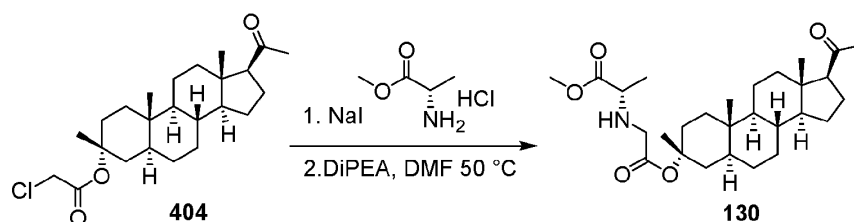
Example 70. Synthesis of Compound 120 (using Compound 127 as a precursor)



[0320] Compound **127** (from Example 69; 257 mg, 0.45 mmol) was dissolved in EtOAc (10 mL) and 20 wt% Pd(OH)₂ (27.6 mg, 0.0393 mmol) to produce a black slurry. The reaction was evacuated, then back filled with H₂. This was repeated 3 times, then the reaction was allowed to

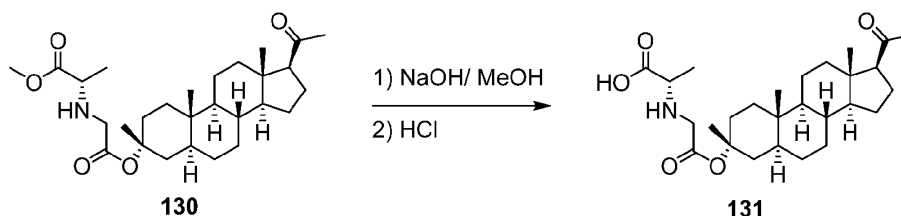
stir under a H₂ atmosphere until complete. The reaction mixture was filtered through a plug of CELITE[®] and rinsed with MeOH (3x15 mL). The solution was concentrated and dried to provide Compound **120** as a solid (190.7 mg). HRMS (ESI⁺): calculated for C₂₈H₄₆NO₅ m/z [M+H]⁺: 476.337050, observed 476.336738; ¹H NMR δ : 3.85-3.69 (m, 2H), 2.52 (t, J = 8.5 Hz, 1H), 2.27-2.07 (m, 6H), 2.05-1.95 (m, 1H), 1.91-1.81 (m, 1H), 1.75-1.05 (m, 28H), 1.04-0.85 (m, 1H), 0.84-0.71 (m, 4H), 0.60 (s, 3H).

Example 71. Synthesis of Compound 130



[0321] Compound **130** was prepared following a similar procedure as outlined in Example 69, using L-alanine methyl ester •HCl (279 mg, 2.0 mmol) instead of benzyl-2-amino-2-methylpropanoate•HCl. Compound **130** was obtained as a solid (98.7 mg). ¹H NMR δ : 3.75 (s, 3H), 3.39-3.32 (m, 3H), 2.59-2.46 (m, 1H), 2.28-1.79 (m, 11H), 1.67-1.06 (m, 18H), 1.01-0.86 (m, 2H), 0.77-0.72 (m, 4H), 0.61 (s, 3H).

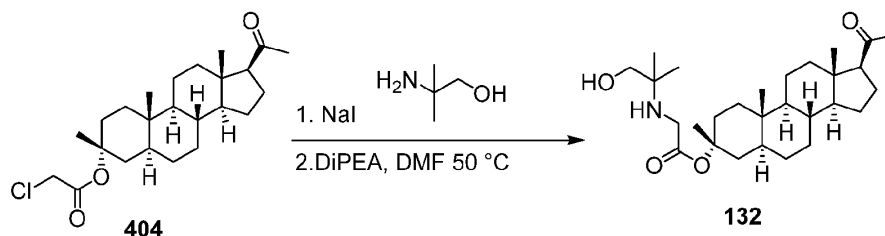
Example 72. Synthesis of Compound 131



[0322] 1N NaOH (1 mL) was added dropwise to a solution of Compound 130 (from Example 71; 99 mg, 0.21 mmol) in MeOH (5 mL). The reaction was concentrated to remove a significant portion of the MeOH. The mixture was transferred to a separatory funnel and diluted with 5 mL of 1N NaOH. The mixture was then extracted DCM (2x5 mL). The extractions formed emulsions that took time to split. The organic layers were combined, dried using Na₂SO₄, filtered and then concentrated. Compound **131** was obtained as an oil (20 mg). HRMS (ESI⁺): calculated for C₂₆H₄₄N₃O₄ m/z [M+H]⁺: 462.332633, observed 462.331726; ¹H NMR δ : 3.99-

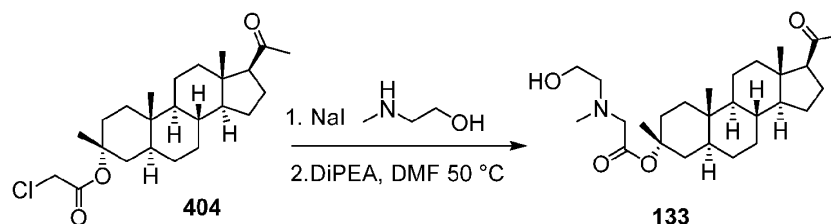
3.80 (m, 3H), 2.51 (t, $J = 8.8$ Hz, 1H), 2.29-2.06 (m, 6H), 2.04-1.94 (m, 2H), 1.87 (d, $J = 11.1$ Hz, 1H), 1.73-1.06 (m, 23H), 1.04-0.86 (m, 1H), 0.75 (m, 4H), 0.59 (s, 3).

Example 73. Synthesis of Compound 132



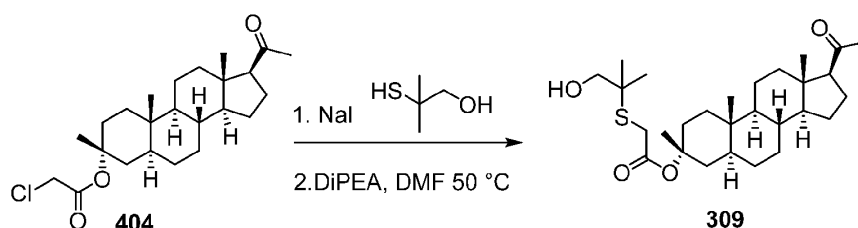
[0323] Compound **132** was prepared following a similar procedure as outlined in Example 69, using 2-amino-2-methyl-1-propanol (203 mg, 2.28 mmol) instead of benzyl-2-amino-2-methylpropanoate•HCl. Compound **132** was obtained as a solid (110.8 mg). HRMS (ESI⁺): calculated for $\text{C}_{28}\text{H}_{48}\text{NO}_4$ m/z $[\text{M}+\text{H}]^+$: 462.357787, observed 462.358015; ^1H NMR δ : 3.31-3.24 (m, 2H), 3.23-3.17 (m, 2H), 2.48 (t, $J = 8.8$ Hz, 1H), 2.22-2.02 (m, 5H), 2.01-1.83 (m, 2H), 1.71-1.51 (m, 4H), 1.50-0.98 (m, 23H), 0.97-0.81 (m, 4H), 0.55 (s, 3H).

Example 74. Synthesis of Compound 133



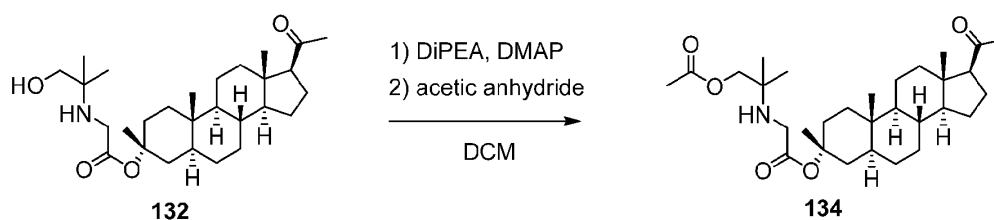
[0324] Compound **133** was prepared following a similar procedure as outlined in Example 69, using 2-(methylamino)ethanol (0.16 mL, 2.13 mmol) instead of benzyl-2-amino-2-methylpropanoate•HCl. Compound **133** was obtained as an oil (118.9 mg). HRMS (ESI⁺): calculated for $\text{C}_{27}\text{H}_{46}\text{NO}_4$ m/z $[\text{M}+\text{H}]^+$: 448.342135, observed 448.342812; ^1H NMR δ : 3.55 (d, $J = 4.7$ Hz, 2H), 3.42-3.21 (m, 2H), 3.13 (d, $J = 13.5$ Hz, 1H), 2.77-2.60 (m, 2H), 2.58-2.32 (m, 3H), 2.25-1.84 (m, 5H), 1.75-1.00 (m, 14H), 0.87 (dt, $J = 4.7, 11.7$ Hz, 1H), 0.72-0.58 (m, 3H), 0.57-0.36 (m, 3H).

Example 75. Synthesis of Compound 309



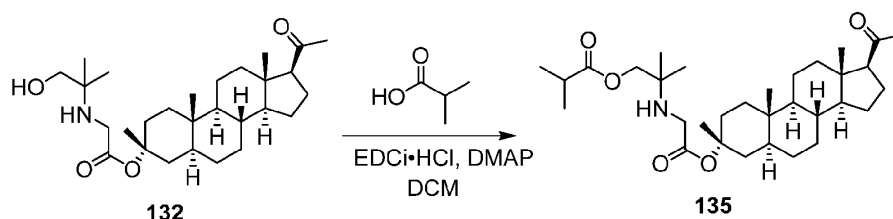
[0325] Compound **309** was prepared following a similar procedure as outlined in Example 69, using 2-methyl-2-sulfanylpropan-1-ol (0.25 mL, 2.35 mmol) instead of benzyl-2-amino-2-methylpropanoate•HCl. Compound **309** was obtained as an oil (172.6 mg). HRMS (ESI⁺): calculated for C₂₈H₄₇O₄S m/z [M+H]⁺: 479.318957, observed 479.318148; ¹H NMR δ: 3.32 (br. s, 2H), 3.27 (br. s, 1H), 3.19 (d, *J* = 1.2 Hz, 2H), 2.56-2.45 (m, 1H), 2.24-2.06 (m, 5H), 2.04-1.87 (m, 2H), 1.73-1.53 (m, 4H), 1.52-1.07 (m, 21H), 0.99-0.83 (m, 1H), 0.79-0.65 (m, 4H), 0.57 (s, 3H).

Example 76. Synthesis of Compound 134



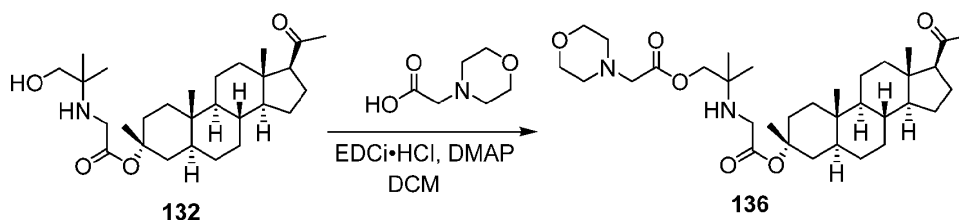
[0326] Acetic anhydride (0.023 mL, 0.24 mmol) was added to a solution of Compound **132** (from Example 73; 104 mg, 0.23 mmol), DMAP (3 mg, 0.03 mmol) and DiPEA (0.04 mL, 0.23 mmol) in DCM (5 mL), and the mixture was stirred at ambient temperature overnight. Water (10 mL) was added and the mixture was stirred for 15 minutes. The mixture was concentrated to remove the DCM, then acidified by the addition of 2 mL of 2N HCl. The mixture was stirred for 5 minutes, then transferred to a separatory funnel and extracted with EtOAc (2 x 25 mL). The combined EtOAc extracts were dried with Na₂SO₄, filtered and concentrated to provide Compound **134** (102.5 mg) as a oil. HRMS (ESI⁺): calculated for C₃₀H₅₀NO₅ m/z [M+H]⁺: 504.368350, observed 504.368827; ¹H NMR δ: 6.02 (br. s, 1H), 4.03-3.93 (m, 2H), 3.51-3.36 (m, 2H), 2.48 (t, *J* = 8.8 Hz, 1H), 2.20-2.07 (m, 9H), 2.02-1.83 (m, 4H), 1.69-1.03 (m, 24H), 0.99-0.80 (m, 1H), 0.77-0.67 (m, 4H), 0.55 (s, 3H).

Example 77. Synthesis of Compound 135



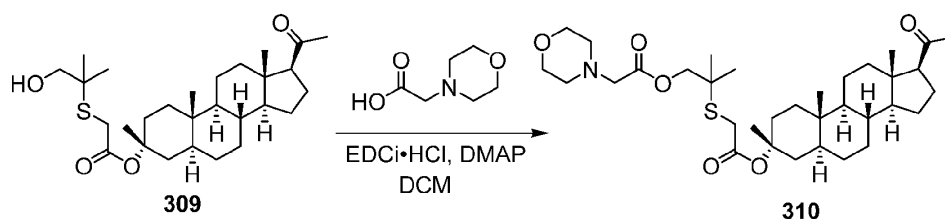
[0327] EDCi·HCl (79 mg, 0.41 mmol) was added to a solution of Compound **132** (from Example 73; 116 mg, 0.25 mmol), isobutyric acid (0.04 mL, 0.45 mmol), DMAP (6 mg, 0.05 mmol) in DCM (3 mL) and the reaction mixture was stirred overnight at ambient temperature. The reaction was worked up as follows: add 5 mL of H₂O and stir for 15 minutes. The reaction mixture was diluted with DCM (10 mL) and the aqueous phase was separated and discarded. The DCM phase was washed with saturated NaCl solution, dried (Na₂SO₄), filtered and concentrated. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **135** (97 mg) as an oil. HRMS (ESI⁺): calculated for C₃₂H₅₄NO₅ m/z [M+H]⁺: 532.399650, observed 532.398550; ¹H NMR δ: 3.93-3.86 (m, 2H), 3.33-3.26 (m, 2H), 2.64-2.43 (m, 2H), 2.21-2.03 (m, 5H), 2.01-1.83 (m, 3H), 1.70-1.50 (m, 4H), 1.49-1.01 (m, 27H), 0.98-0.80 (m, 1H), 0.77-0.64 (m, 4H), 0.56 (s, 3H).

Example 78. Synthesis of Compound 136



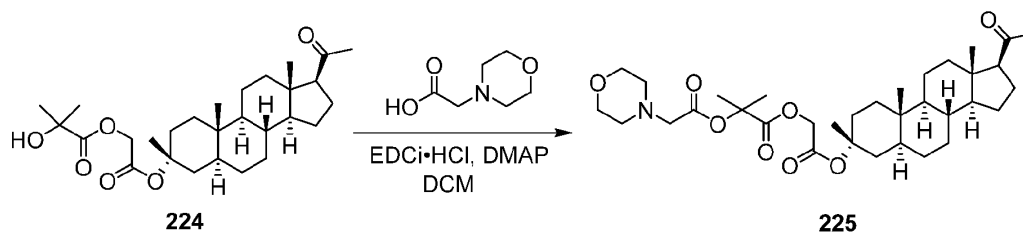
[0328] Following a similar procedure as in Example 77, except using morpholin-4-yl-acetic acid (29 mg, 0.20 mmol) instead of isobutyric acid, Compound **136** (172.6 mg) was obtained as a solid. HRMS (ESI⁺): calculated for C₃₄H₅₇N₂O₆ m/z [M+H]⁺: 589.421114, observed 589.420110; ¹H NMR δ: 4.03-3.91 (m, 2H), 3.81-3.69 (m, 4H), 3.30 (s, 2H), 3.25 (2, 2H), 2.64-2.46 (m, 5H), 2.23-2.06 (m, 5H), 2.05-1.85 (m, 3H), 1.73-1.04 (m, 25H), 1.02-0.84 (m, 1H), 0.81-0.67 (m, 4H), 0.58 (s, 3H).

Example 79. Synthesis of Compound 310

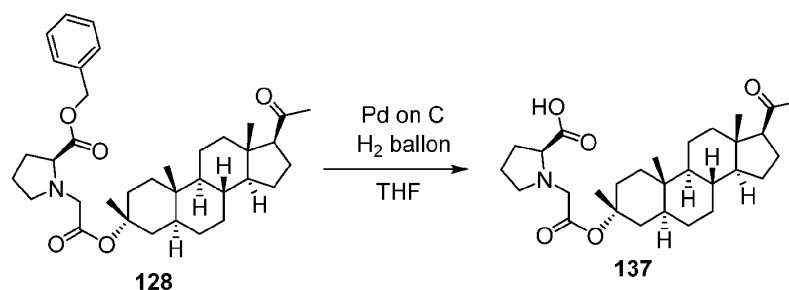


[0329] Following a similar procedure as in Example 77, except using morpholin-4-yl-acetic acid (29 mg, 0.20 mmol) instead of isobutyric acid, and using Compound **309** (from Example 75; 60 mg, 0.13 mmol) instead of Compound **132**, Compound **310** (42.0 mg) was obtained as a solid. HRMS (ESI+): calculated for C₃₄H₅₆NO₆S m/z [M+H]⁺: 606.382286, observed 606.382306; ¹H NMR δ: 4.13-4.06 (m, 2H), 3.77-3.66 (m, 6H), 3.29-3.20 (m, 2H), 2.63-2.43 (m, 5H), 2.21-2.10 (m, 2H), 2.08 (s, 3H), 2.02-1.85 (m, 2H), 1.70-1.53 (m, 4), 1.51-1.09 (m, 26H), 0.98-0.81 (m, 1H), 0.79-0.67 (m, 4H), 0.57 (s, 3H).

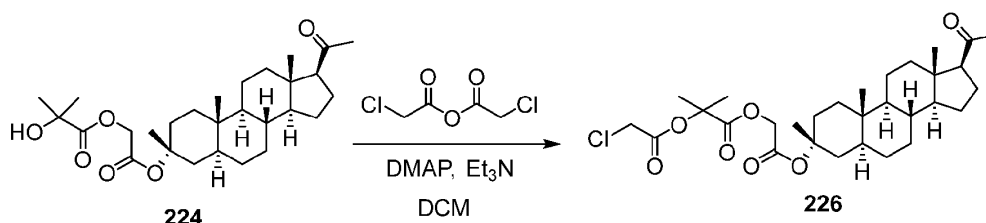
Example 80. Synthesis of Compound 225



[0330] EDCi•HCl (122 mg, 0.64 mmol) was added to a solution of Compound **224** (from Example 49; 40 mg, 0.08 mmol), morpholin-4-yl-acetic acid (86 mg, 0.59 mmol), and DMAP (5 mg, 0.04 mmol) in DCM (3 mL) and the reaction mixture was stirred overnight at ambient temperature. Water (5 mL) was added and the mixture was stirred for 15 minutes. The mixture was transferred to a separatory funnel, diluted with 10 mL of DCM, shaken and the layers were separated. The upper aqueous layer was discarded and the lower organic layer was washed with saturated NaCl solution. The organic layer was then dried with Na₂SO₄, filtered and concentrated using a rotatory evaporator. The crude material was purified by column chromatography using an ISCO™ chromatography system to afford Compound **225** (25.2 mg) as a solid. HRMS (ESI+): calculated for C₃₄H₅₄NO₈ m/z [M+H]⁺: 604.384394, observed 604.384184; ¹H NMR δ: 4.65-4.48 (m, 2H), 3.83-3.69 (m, 4H), 3.32-3.20 (m, 2H), 2.64-2.57 (m, 4H), 2.53 (t, *J* = 9.1 Hz, 1H), 2.30-2.10 (m, 6H), 2.00 (d, *J* = 11.7 Hz, 1H), 1.92-1.81 (m, 2H), 1.77-1.09 (m, 24H), 1.03-0.83 (m, 1H), 0.83-0.76 (m, 4H), 0.60 (s, 3H).

Example 81. Synthesis of Compound 137

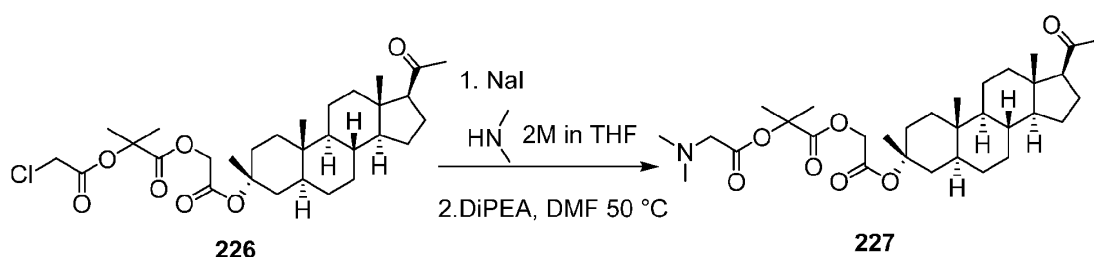
[0331] To a solution of Compound **128** (from Example 48; 54 mg, 0.09 mmol) in EtOAc (10 mL) was added 5 wt% wet Pd(C) (29 mg, 0.014 mmol) to produce a black slurry. The reaction was evacuated, then back filled with H₂. This was repeated 3 times, then the reaction was allowed to stir under a H₂ atmosphere until complete. The reaction was worked up as follows: filter the reaction through a plug of CELITE® to remove the catalyst. Rinse the flask with 3x15 mL of MeOH and run it through the CELITE® plug. The filtrate was concentrated to provide Compound **137** as an oil (17.4 mg). HRMS (ESI⁺): calculated for C₂₉H₄₆NO₅ m/z [M+H]⁺: 488.337050, observed 488.334346; ¹H NMR δ: 4.08 (s, 2H), 3.80 (br. s, 1H), 3.22 (d, *J* = 8.2 Hz, 1H), 2.62-2.41 (m, 3H), 2.38-1.79 (m, 12H), 1.75-1.10 (m, 18H), 0.97 (m, 1H), 0.85-0.70 (m, 4H), 0.60 (s, 3H).

Example 82. Synthesis of Compound 226

[0332] DMAP (5 mg, 0.04 mmol) was added to a solution of Compound **224** (from Example 49; 0.31 g, 0.66 mmol) in DCM (5 mL). After stirring for 10 minutes, Et₃N (0.6 mL, 4.3 mmol) was added dropwise over 1 minute. The resulting solution was stirred at ambient temperature for 5 mins. A solution of chloroacetic anhydride (632 mg, 3.69 mmol) in 5 mL of DCM (5 mL) was then added to the reaction mixture via a syringe. The addition took 2 min to complete and the reaction mixture was allowed to stir for 3 hours at ambient temperature. The reaction was quenched with 15 mL of 1M HCl and then stirred for 10 minutes. The reaction mixture was

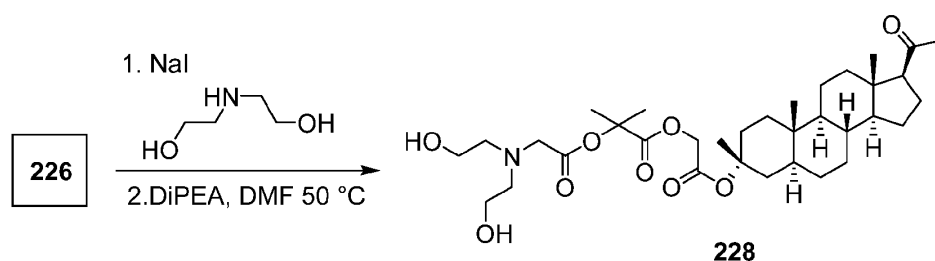
transferred to a 60 mL separatory funnel and the phases were separated. The lower organic phase was washed with 15 mL of HCl, then 15 ml of H₂O. The washed organic phase was dried with Na₂SO₄, filtered and concentrated, and the concentrate was purified by column chromatography using an ISCO™ chromatography system to provide Compound **226** (330.8 mg) as an oil. ¹H NMR δ: 4.64-4.48 (m, 2H), 4.10-4.04 (m, 2H), 2.54 (t, *J* = 8.8 Hz, 1H), 2.33-2.07 (m, 5H), 2.05-1.97 (m, 1H), 1.91-1.81 (m, 1H), 1.75-1.09 (m, 25H), 1.05-0.86 (m, 1H), 0.84-0.70 (m, 4H), 0.61 (s, 3H).

Example 83. Synthesis of Compound 227



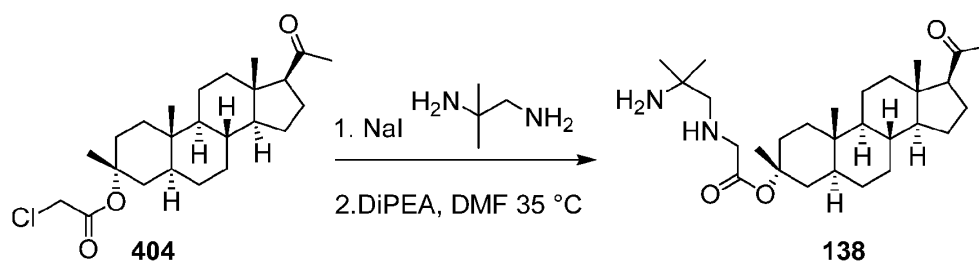
[0333] Dimethylamine 2M in THF (0.24 mL, 0.48 mmol) followed by DiPEA (0.1 mL, 0.57 mmol) was added to a solution of Compound **226** (from Example 82; 52 mg, 0.09 mmol) and sodium iodide (90 mg, 0.60 mmol) in DMF (4 mL) and the reaction mixture was stirred at 50 °C for 17 hours. The reaction was diluted with 25 mL of EtOAc, then quenched with 25 mL of water. It was transferred to a separatory funnel and the layers were separated. The EtOAc extract was washed with 2x25 mL of 1N HCl, followed by 15 mL of NaCl. The washed organic phase was then dried with Na₂SO₄, filtered and concentrated, and the concentrate was purified by column chromatography using an ISCO™ chromatography system to provide Compound **227** (39.8 mg) as an oil. HRMS (ESI+): calculated for C₃₂H₅₂NO₇ m/z [M+H]⁺: 562.373829, observed 562.372967; ¹H NMR CDCl₃ 300MHz δ: 4.66-4.47 (m, 2H), 3.26-3.14 (m, 2H), 2.59-2.48 (m, 1H), 2.35 (s, 6H), 2.31-2.08 (m, 5H), 1.99 (d, J = 11.7 Hz, 1H), 1.91-1.80 (m, 1H), 1.75-1.54 (m, 10H), 1.53-1.11 (m, 16H), 1.04-0.85 (m, 1H), 0.82-0.71 (m, 4H), 0.59 (s, 3H).

Example 84. Synthesis of Compound 228



[0334] Diethanolamine (0.1 mL, 1.04 mmol) followed by DiPEA (0.180 mL, 1.03 mmol) was added to a solution of Compound **226** (from Example 82; 96 mg, 0.17 mmol) and sodium iodide (89 mg, 0.49 mmol) in anhydrous DMF (4 mL) and the reaction mixture was stirred at 50 °C for 2 hours. The reaction was diluted with 25 mL of EtOAc, then quenched with 25 mL of water. It was transferred to a separatory funnel and the layers were separated. The EtOAc extract was washed with 2x25 mL of 1N HCl, followed by 15 mL of NaCl. The washed organic phase was then dried with Na₂SO₄, filtered and concentrated, and the concentrate was purified by column chromatography using an ISCOTM chromatography system to provide Compound **228** (18.5 mg) as an oil. HRMS (ESI⁺): calculated for C₃₄H₅₆NO₉ m/z [M+H]⁺: 622.394959, observed 622.394161; ¹H NMR CDCl₃ 300MHz δ : 4.70-4.49 (m, 2H), 3.60 (t, *J* = 5.0 Hz, 4H), 3.48 (s, 2H), 2.91-2.78 (m, 4H), 2.53 (t, *J* = 8.8 Hz, 1H), 2.34-2.08 (m, 5H), 2.00 (d, *J* = 11.7 Hz, 1H), 1.85 (d, *J* = 12.9 Hz, 1H), 1.74-1.56 (m, 8H), 1.55-1.08 (m, 19H), 1.05-0.84 (m, 2H), 0.84-0.70 (m, 4H), 0.60 (s, 3H).

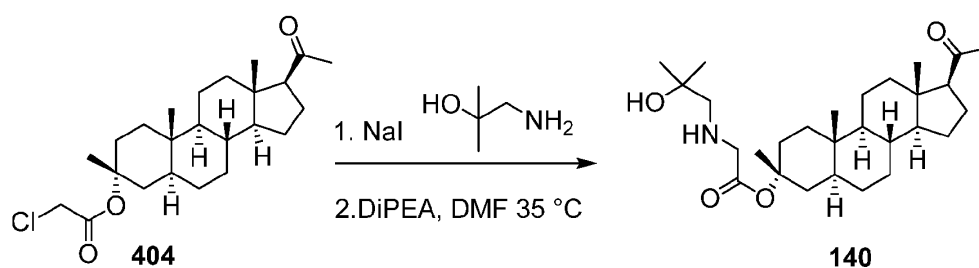
Example 85. Synthesis of Compound 138



[0335] Compound **404** (150 mg, 0.37 mmol) and sodium iodide (176 mg, 1.18 mmol) were added to a 40 mL capped vial with stir bar. The solids were dissolved with anhydrous DMF (4 mL) and stirred at ambient temperature for 15 minutes, then DiPEA (750 μ L, 4.31 mmol) was added in a single portion followed by 1,2-diamino-2-methylpropane (190 μ L, 1.86 mmol) and the resulting mixture was heated to 35 °C. After stirring for 22 hours the reaction mixture was

cooled and diluted with ethyl acetate (40 mL), then quenched with water (35 mL). The organic layer was washed with water (2x25 mL) then brine (25 mL), dried with Na₂SO₄ for 30 minutes, filtered and concentrated to provide crude product that was purified by column chromatography using an ISCOTM chromatography system to provide Compound **138** (69 mg) as an oil. HRMS (ESI⁺): calculated for C₂₈H₄₉N₂O₃ m/z [M+H]⁺: 461.3733, observed 461.3738; ¹H NMR δ: 3.42-3.30 (m, 2H), 3.12 (br. s, 4H), 2.62-2.42 (m, 3H), 2.26-2.03 (m, 5H), 2.02-1.82 (m, 2H), 1.71-1.00 (m, 22H), 0.98-0.80 (m, 2H), 0.78-0.66 (m, 5H), 0.61-0.51 (s, 3H).

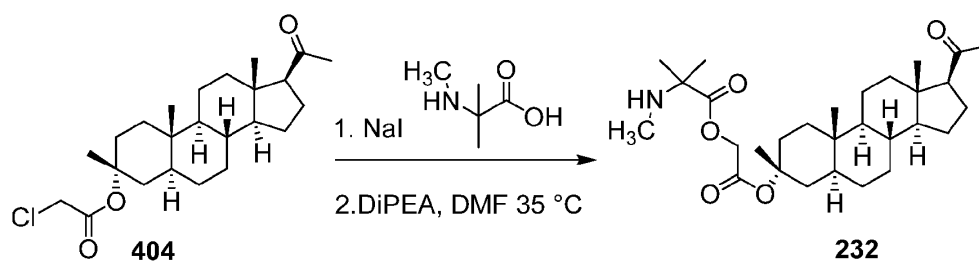
Example 86. Synthesis of Compound 140



[0336] Following a similar procedure as in Example 85, but using 1-amino-2-methylpropan-2-ol instead of 1,2-diamino-2-methylpropane, Compound **140** (164.2 mg) was obtained as an oil.

HRMS (ESI⁺): calculated for C₂₈H₄₈NO₄ m/z [M+H]⁺: 462.3578, observed 462.3573; ¹H NMR δ: 3.38-3.28 (m, 2H), 2.56-2.39 (m, 3H), 2.22-2.00 (m, 5H), 1.99-1.79 (m, 2H), 1.69-0.99 (m, 1.69-0.99 (m, 27H), 0.96-0.76 (m, 1H), 0.74-0.59 (m, 4H), 0.53 (s, 3H).

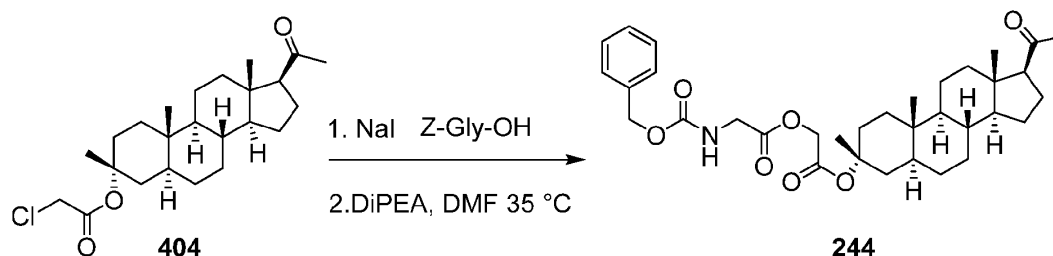
Example 87. Synthesis of Compound 232



[0337] Following a similar procedure as in Example 85, but using 2-(methylamino)isobutyric acid (215 mg, 2.01 mmol) instead of 1,2-diamino-2-methylpropane, Compound **232** (48.8 mg) was obtained as an oil. HRMS (ESI⁺): calculated for C₂₉H₄₈NO₅ m/z [M+H]⁺: 490.3527, observed 490.3523; ¹H NMR δ: 4.64-4.47 (m, 2H), 2.57-2.46 (m, 1H), 2.38-2.30 (m, 3H), 2.29-

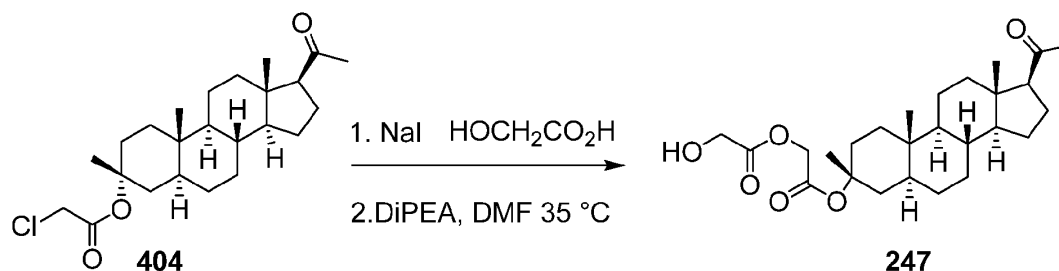
2.20 (m, 1H), 2.18-1.93 (m, 7H), 1.90-1.81 (m, 1H), 1.73-1.05 (m, 24H), 1.02-0.83 (m, 1H), 0.81-0.68 (m, 4H), 0.58 (s, 3H).

Example 88. Synthesis of Compound 244



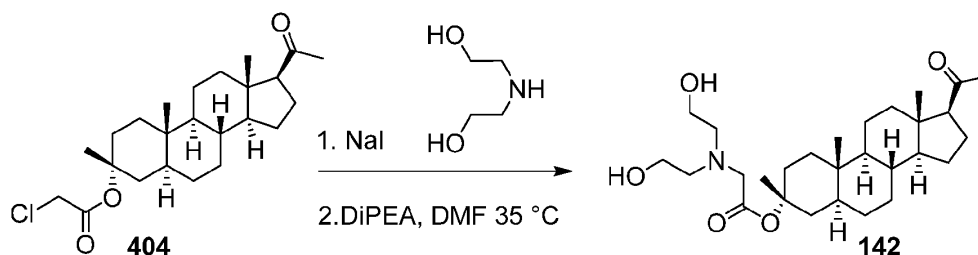
[0338] Following a similar procedure as in Example 85, but using Z-Gly-OH instead of 1,2-diamino-2-methylpropane, Compound **244** (135 mg) was obtained as a foam. ^1H NMR δ : 7.44-7.30 (m, 5H), 5.26 (br. s, 1H), 5.15 (s, 2H), 4.69-4.55 (m, 2H), 4.19-4.07 (m, 2H), 2.50 (t, $J = 8.8$ Hz, 1H), 2.28-2.07 (m, 5H), 2.05-1.96 (m, 1H), 1.89 (dd, $J = 2.9$ Hz, 11.1 Hz, 1H), 1.76-1.05 (m, 19H), 1.03-0.87 (m, 1H), 0.82-0.72 (m, 4H), 0.60 (s, 3H).

Example 89. Synthesis of Compound 247



[0339] Following a similar procedure as in Example 85, but using glycolic acid (159 mg, 2.09 mmol) instead of 1,2-diamino-2-methylpropane, Compound **247** (170 mg) was obtained as a solid. ^1H NMR CDCl_3 400MHz δ : 4.74-4.60 (m, 2H), 4.30 (br. s, 2H), 2.53 (t, $J = 9.0$ Hz, 1H), 2.32 (br. s, 1H), 2.28-2.09 (m, 5H), 2.06-1.98 (m, 1H), 1.94-1.86 (m, 1H), 1.76-1.09 (m, 18H), 1.04-0.82 (m, 1H), 0.78 (s, 3H), 0.61 (s, 3H).

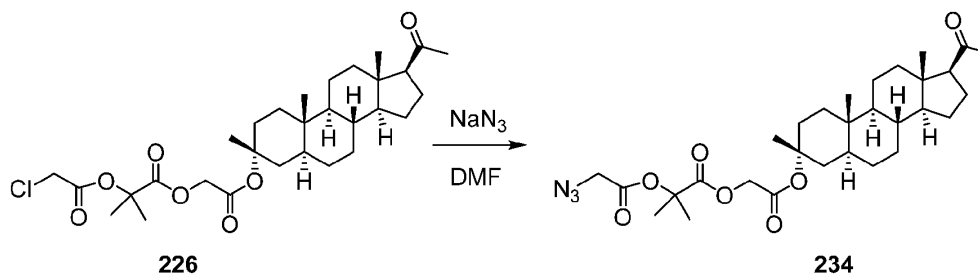
Example 90. Synthesis of Compound 142



Following a similar procedure as in Example 85, but using diethanolamine (180 μ L, 1.88 mmol) instead of 1,2-diamino-2-methylpropane, Compound **142** (108.6 mg) was obtained as an oil.

HRMS (ESI⁺): calculated for C₂₈H₄₈NO₅ m/z [M+H]⁺: 478.3527, observed 478.3534; ¹H NMR δ : 3.56 (t, J = 5.0 Hz, 6H), 3.41-3.31 (m, 2H), 2.86-2.75 (m, 4H), 2.54-2.43 (m, 1H), 2.25-2.06 (m, 5H), 2.00-1.92 (m, 1H), 1.71-1.08 (m, 18H), 0.97-0.80 (m, 2H), 0.72 (s, 3H), 0.71-0.62 (m, 1H), 0.55 (s, 3H).

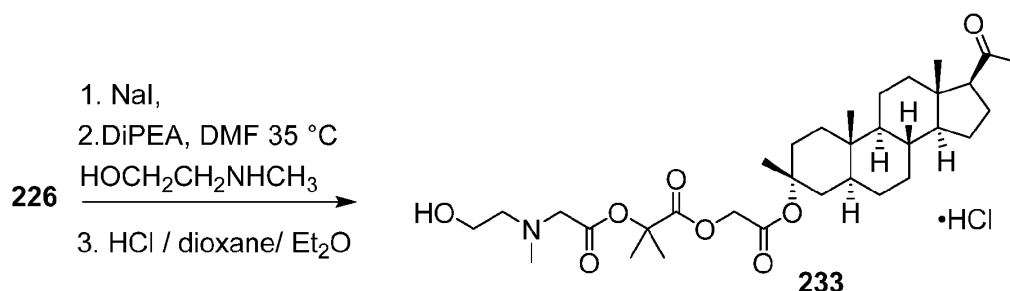
Example 91. Synthesis of Compound 234



[0340] Compound **226** (from Example 82; 122 mg, 0.22 mmol) was added to DMF (4 mL) in an aluminum foil-covered vial, and sodium azide (66.4 mg, 1.02 mmol) was added in a single portion. The mixture was stirred at ambient temperature overnight, then diluted with ethyl acetate (50 mL), extracted with water (2x25 mL) then brine (25 mL), and the organic layer was dried with Na₂SO₄, filtered and concentrated to provide Compound **234** as a solid in 93% yield.

¹H NMR δ : 4.65-4.48 (m, 2H), 3.93-3.84 (m, 2H), 2.57-2.44 (m, 1H), 2.31-2.03 (m, 5H), 2.01-1.91 (m, 1H), 1.88-1.78 (m, 1H), 1.73-1.02 (m, 25H), 1.00-0.80 (m, 1H), 0.79-0.67 (m, 4H), 0.56 (s, 3H).

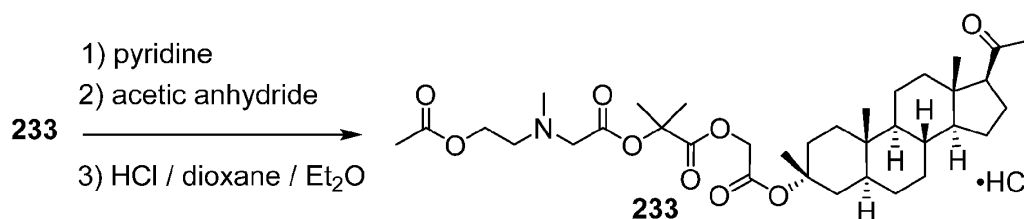
Example 92. Synthesis of Compound 233



[0341] Compound **226** (from Example 82; 103 mg, 0.19 mmol), and sodium iodide (202 mg, 1.35 mmol) were dissolved in anhydrous DMF (4 mL) and stirred at ambient temperature for 15 minutes. Then DiPEA (450 μ L, 2.58 mmol) was added in a single portion followed by 2-(methylamino)ethanol (80 μ L, 1.07 mmol) and the resulting mixture was heated to 35 °C. After stirring for 2.5 hours the reaction mixture was cooled and then diluted with ethyl acetate (40 mL), quenched with water (35 mL), extracted with water (2x25 mL) then brine (25 mL), and the organic layer was dried with Na₂SO₄ for 30 minutes, filtered and concentrated to provide a crude oil which was purified by column chromatography using an ISCOTM chromatography system to provide Compound **233** (free base; 58.8 mg) as an oil. ¹H NMR δ : 4.65-4.49 (m, 2H), 3.66-3.53 (m, 2H), 3.41-3.30 (m, 2H), 2.92-2.66 (m, 3H), 2.51 (t, J = 8.8 Hz, 1H), 2.48-2.37 (m, 3H), 2.30-2.05 (m, 5H), 1.97 (d, J = 11.7 Hz, 1H), 1.90-1.77 (m, 1H), 1.73-1.05 (m, 25H), 1.01-0.82 (m, 1H), 0.80-0.67 (m, 4H), 0.57 (s, 3).

[0342] The free base of Compound **233** (47.4 mg; 0.08 mmol) was then dissolved in a flask with 1,4-dioxane (2 mL), and a 1M solution of HCl in diethyl ether (90 μ L, 0.09 mmol) was added in single portion, and the solution was stirred at ambient temperature for 15 minutes. The flask was then placed in dry ice for 30 minutes and frozen to a solid, and then lyophilized to provide Compound **233** as a solid hydrochloride salt. HRMS (ESI⁺): calculated for C₃₃H₅₄NO₈ m/z [M+H]⁺: 592.3844, observed 592.3851; ¹H NMR δ : 5.05 (q, J = 5.1 Hz, 1H), 4.70-5.54 (m, 2H), 4.12 (br. s. 2H), 4.03 (br. s. 2H), 3.50 (br. s. 2H), 3.09 (s, 3H), 2.53 (t, J = 9.1 Hz, 1H), 2.29-2.08 (m, 5H), 2.01 (d, J = 11.7 Hz, 1H), 1.84 (d, J = 8.8 Hz, 1H), 1.79-1.04 (m, 28H), 1.02-0.82 (m, 1H), 0.82-0.69 (m, 4H), 0.61 (s, 3H).

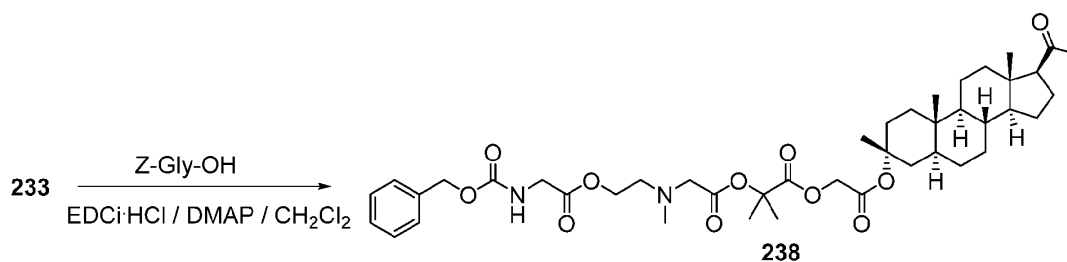
Example 93. Synthesis of Compound 242



[0343] Compound **233** (from Example 92; 142 mg, 0.24 mmol) was dissolved in DCM (5 mL) and pyridine (250 μ L) was added, and the mixture was then cooled to 0 °C in an ice water bath. After stirring for 5 minutes acetic anhydride (500 μ L, 5.3 mmol) was added dropwise over ~5 minutes. The resulting mixture was warmed to ambient temperature and stirred overnight. The reaction mixture was then concentrated under reduced pressure to provide an oil, which was then placed under high vacuum for a period of time to remove residual pyridine and acetic anhydride. The residue was purified by column chromatography using an ISCOTM chromatography system to provide Compound **242** (free base) as an oil in 68% yield. ¹H NMR δ : 4.63-4.46 (m, 2H), 4.20-4.10 (m, 2H), 3.40-3.32 (m, 2H), 2.82 (t, J = 5.6 Hz, 2H), 2.50 (t, J = 8.8 Hz, 1H), 2.45-2.40 (m, 3H), 2.30-2.16 (m, 1H), 2.16-2.03 (m, 6H), 2.02-1.93 (m, 1H), 1.88-1.76 (m, 1H), 1.71-1.53 (m, 8H), 1.52-1.04 (m, 18H), 1.01-0.81 (m, 1H), 0.80-0.67 (m, 4H), 0.57 (s, 3H).

[0344] The free base of Compound **242** (112.9 mg) was converted to the hydrochloride salt following the same procedure outlined in Example 92. HRMS (ESI⁺): calculated for C₃₅H₅₆NO₉ m/z [M+H]⁺: 634.3950, observed 634.3955; ¹H NMR δ : 5.04 (d, J = 5.3 Hz, 1H), 4.61 (d, J = 2.9 Hz, 2H), 4.54 (d, J = 4.7 Hz, 2H), 3.98 (br. s, 2H), 3.55 (br. s, 2H), 3.00 (br. s, 3H), 2.53 (t, J = 8.5 Hz, 1H), 2.29-2.09 (m, 9H), 2.0 (d, 10.5 Hz, 1H), 1.84 (d, J = 11.1 Hz, 1H), 1.76-1.08 (m, 22H), 0.90 (br. s, 1H), 0.80-0.75 (m, 4H), 0.60 (s, 3).

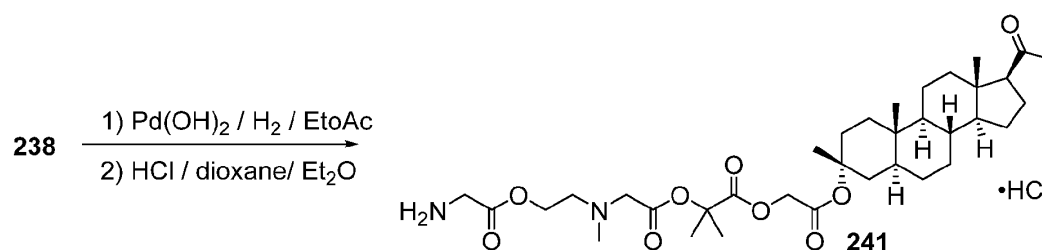
Example 94. Synthesis of Compound 238



[0345] Compound **233** (from Example 92; 46.5 mg, 0.079 mmol), Z-Gly-OH (24.3 mg, 0.12 mmol) and DMAP (5.1 mg, 0.042 mmol) were stirred in DCM (3 mL). EDCi·HCl (24.4 mg,

0.13 mmol) was then added to the mixture to provide a solution that was stirred overnight at ambient temperature. The mixture was then diluted with water (10 mL) and stirred for 10 minutes, then transferred to a separatory funnel and the upper aqueous was discarded. The organic phase was then dried with Na₂SO₄, filtered and concentrated to provide a crude product which was purified by column chromatography using an ISCOTM chromatography system to provide Compound **238** (101.5 mg) as an oil. ¹H NMR δ: 7.44-7.22 (m, 5H), 5.70-5.65 (m, 1H), 5.18-5.02 (m, 2), 4.65-4.45 (m, 2H), 4.34-4.03 (m, 4H), 2.58-2.39 (m, 1H), 2.31-1.93 (m, 9H), 1.90-1.78 (m, 1H), 1.75-1.06 (m, 1H), 0.82-0.68 (m, 4), 0.58 (s, 3).

Example 95. Synthesis of Compound 241

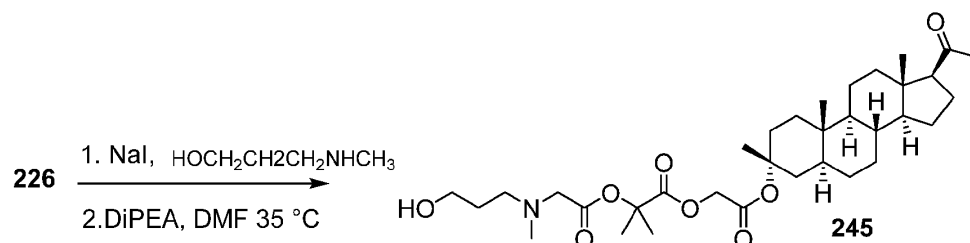


[0346] Compound **238** (from Example 94; 72 mg, 0.094 mmol) was dissolved in EtOAc (10 mL), and 20wt% Pd(OH)₂ (17.8 mg, 0.025 mmol) was then added to the solution. The reaction was evacuated and back filled with hydrogen (H₂) gas three times, and then the mixture was stirred under an H₂ atmosphere for 22 hours. The reaction mixture was then filtered through a plug of Celite[®], and the reaction vessel was rinsed with ethyl acetate (3x15 mL) and the washings were also passed through the Celite[®] plug. The filtrate was concentrated to a residue and purified by column chromatography using an ISCOTM chromatography system to provide Compound **241** (free base; 18.2 mg) as a solid. ¹H NMR δ: 4.67-4.48 (m, 2H), 4.32-4.20 (m, 2H), 3.51-3.43 (m, 1H), 3.43-3.30 (m, 2H), 2.86 (t, *J* = 5.3 Hz, 2H), 2.74-2.60 (m, 1H), 2.58-2.49 (m, 1H), 2.49-2.40 (m, 3H), 2.26 (d, *J* = 13.5 Hz, 1H), 2.16-2.09 (m, 3H), 2.07-1.95 (m, 2H), 1.75-1.06 (m, 26H), 1.03-0.82 (m, 2H), 0.81-0.70 (m, 4H), 0.60 (s, 3H).

[0347] The free base of Compound **241** was converted to the hydrochloride salt (solid; 12.7 mg) using the procedure in Example 92. HRMS (ESI⁺): calculated for C₃₅H₅₇N₂O₉ *m/z* [M+H]⁺: 649.4059, observed 649.4070; ¹H NMR CDCl₃ 400MHz δ: 4.72-4.45 (m, 4H), 4.30-3.97 (m, 4H), 3.88-3.66 (m, 1H), 3.24-3.00 (m, 4H), 2.55 (t, *J* = 8.8 Hz, 1H), 2.33-2.08 (m, 6H), 2.00 (d, *J*

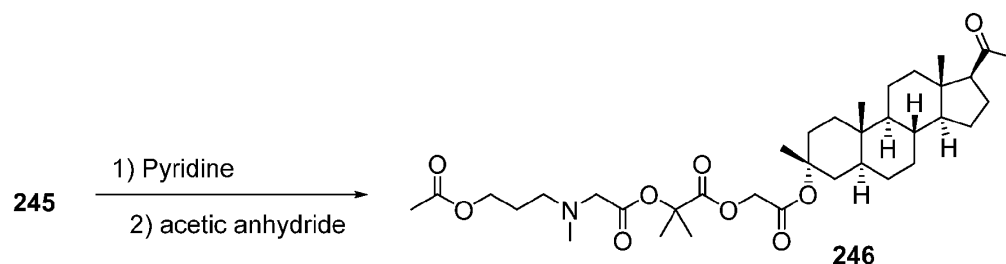
= 12.1 Hz, 1H), 1.91-1.81 (m, 1H), 1.79-1.59 (m, 8H), 1.57-1.06 (m, 18H), 1.03-0.88 (m, 1H), 0.84-0.72 (m, 4H), 0.61 (s, 3H).

Example 96. Synthesis of Compound 245



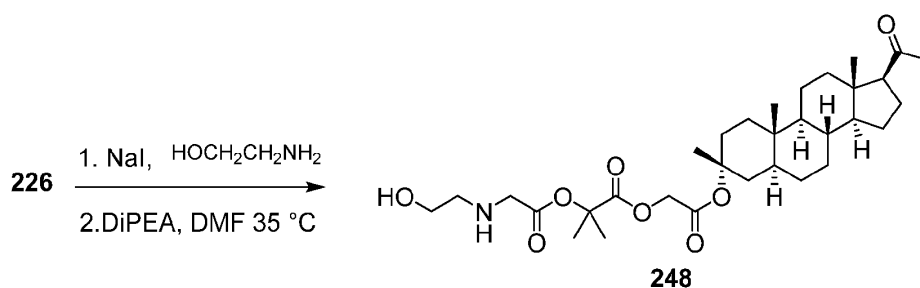
[0348] Following a similar procedure as in Example 92, but using 3-methylamino-1-propanol instead of 2-(methylamino)ethanol, Compound **245** was obtained as a foam in 78% yield. ^1H NMR CDCl_3 400MHz δ : 4.60-4.45 (m, 2H), 3.78-3.70 (m, 2H), 3.29-3.19 (m, 2H), 2.70-2.60 (m, 2H), 2.48 (t, $J = 9.0$ Hz, 1H), 2.34 (s, 3H), 2.25-2.16 (m, 1H), 2.15-2.03 (m, 4H), 1.98-1.91 (m, 1H), 1.85-1.75 (m, 1H), 1.71-1.04 (m, 28H), 0.99-0.81 (m, 1H), 0.78-0.64 (m, 4H), 0.55 (s, 3H).

Example 97. Synthesis of Compound 246



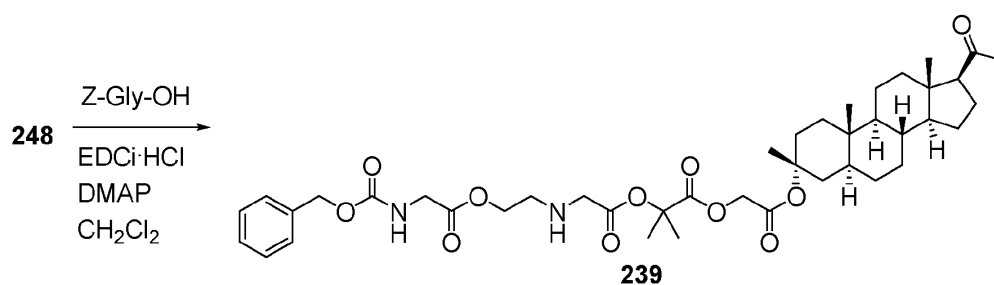
[0349] Following a similar procedure as in Example 93, but using Compound **245** (from Example 96) instead of Compound **233**, Compound **246** was obtained as an oil. HRMS (ESI⁺): calculated for $\text{C}_{36}\text{H}_{58}\text{NO}_9$ m/z $[\text{M}+\text{H}]^+$: 648.4106, observed 648.4123; ^1H NMR CDCl_3 400MHz δ : 4.61-4.45 (m, 2H), 4.14-4.02 (m, 2H), 3.31-3.20 (m, 2H), 2.62-2.53 (m, 2H), 2.49 (t, $J = 9.0$ Hz, 1H), 2.35 (s, 3H), 2.22 (dd, $J = 2.7, 14.4$ Hz, 1H), 2.16-2.04 (m, 4H), 2.02-1.91 (m, 4H), 1.85-1.72 (m, 3H), 1.70-1.52 (m, 9H), 1.51-1.04 (m, 16H), 0.98-0.84 (m, 1H), 0.79-0.65 (m, 4H), 0.56 (s, 3H).

Example 98. Synthesis of Compound 248



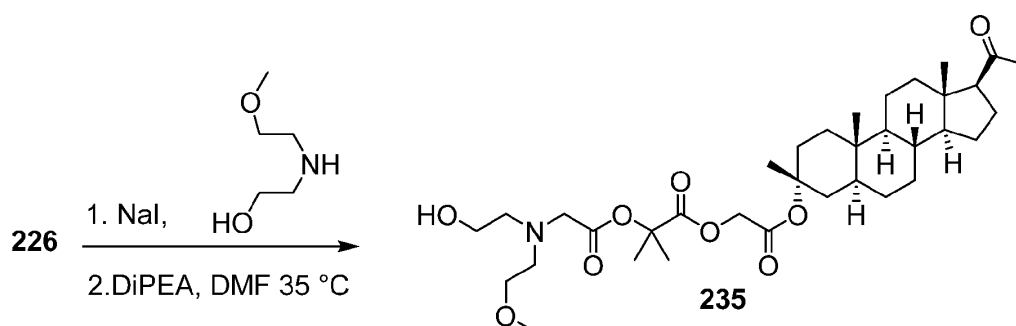
[0350] Following a similar procedure as in Example 92, but using aminoethanol instead of 2-(methylamino)ethanol, Compound **248** was obtained as an oil in 95% yield. ^1H NMR δ : 4.65-4.47 (m, 2H), 3.67-3.53 (m, 2H), 3.49-3.38 (m, 2H), 2.82-2.74 (m, 2H), 2.59-2.38 (m, 3H), 2.30-2.04 (m, 6H), 2.02-1.92 (m, 1H), 1.73-1.53 (m, 8H), 1.53-1.03 (m, 17H), 1.00-0.82 (m, 1H), 0.80-0.67 (m, 4H), 0.57 (s, 3H).

Example 99. Synthesis of Compound 239



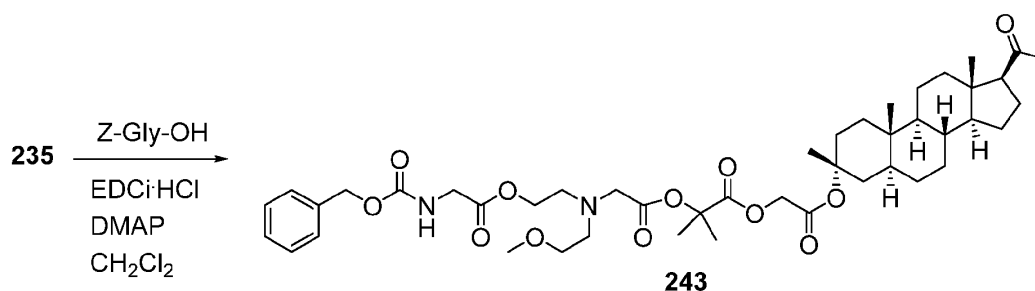
[0351] Following a similar procedure as in Example 94, but using Compound **248** instead of Compound **233**, Compound **239** was obtained as a solid in 39% yield. ^1H NMR δ : 7.44-7.26 (m, 5H), 5.43 (br. s, 1H), 5.18-5.08 (m, 2H), 4.65-4.48 (m, 2H), 4.25 (t, $J = 5.3$ Hz, 2H), 4.00 (d, $J = 5.3$ Hz, 2H), 3.36 (s, 2H), 2.84 (t, $J = 5.6$ Hz, 2H), 2.57-2.36 (m, 4H), 2.31-2.06 (m, 5H), 2.04-1.94 (m, 1H), 1.90-1.78 (m, 1H), 1.74-1.04 (m, 24H), 1.02-0.68 (m, 6H), 0.59 (s, 3).

Example 100. Synthesis of Compound 235



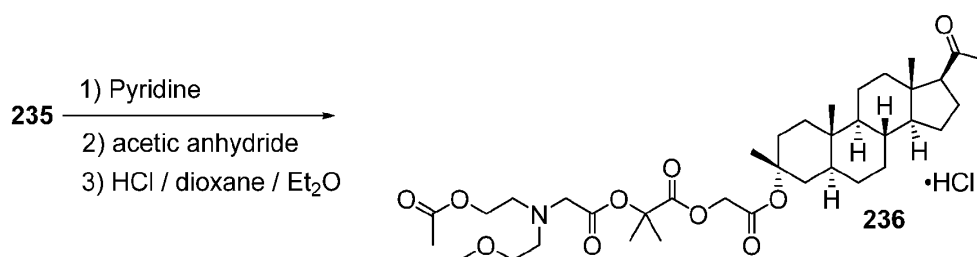
[0352] Following a similar procedure as in Example 92, but using 2-[(2-methoxyethyl)amino]ethan-1-ol instead of 2-(methylamino)ethanol, Compound **235** was obtained as an oil in 97% yield. ^1H NMR δ : 4.66-4.48 (m, 2H), 3.58-3.49 (m, 4H), 3.49-3.42 (m, 2H), 3.34 (s, 3H), 2.98-2.81 (m, 8H), 2.52 (t, $J = 9.1$ Hz, 1H), 2.31-2.07 (m, 5H), 1.99 (d, $J = 11.7$ Hz, 1H), 1.89-1.80 (m, 1H), 1.73-1.07 (m, 22H), 0.99-0.86 (m, 1H), 0.81-0.69 (m, 4H), 0.59 (s, 3H).

Example 101. Synthesis of Compound **243**



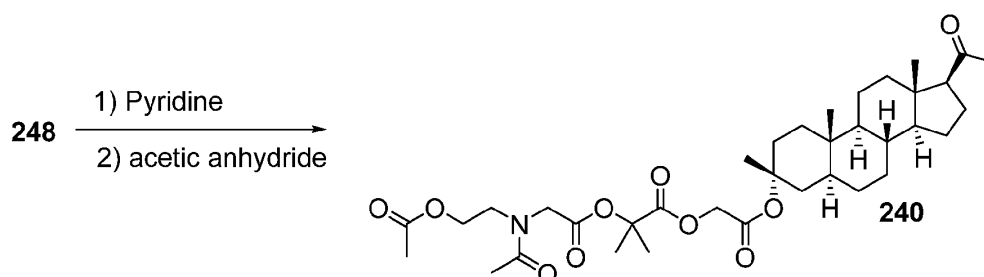
[0353] Following a similar procedure as in Example 94, but using Compound **235** (from Example 100) instead of Compound **233**, Compound **243** was obtained as a solid in 88% yield. ^1H NMR δ : 7.44-7.29 (m, 5H), 5.38 (br. s, 1H), 5.14 (s, 2H), 4.66-4.50 (m, 2H), 4.24 (t, $J = 5.6$ Hz, 2H), 4.01 (d, $J = 5.3$ Hz, 2H), 3.59-3.40 (m, 4H), 3.33 (s, 3H), 3.04-2.85 (m, 4H), 2.60-2.48 (m, 1H), 2.32-2.08 (m, 5H), 2.08-1.96 (m, 1H), 1.85 (d, $J = 10.5$ Hz, 1H), 1.76-1.09 (m, 25H), 1.05-0.85 (m, 1H), 0.80-0.76 (m, 4H), 0.61 (s, 3H).

Example 102. Synthesis of Compound **236**



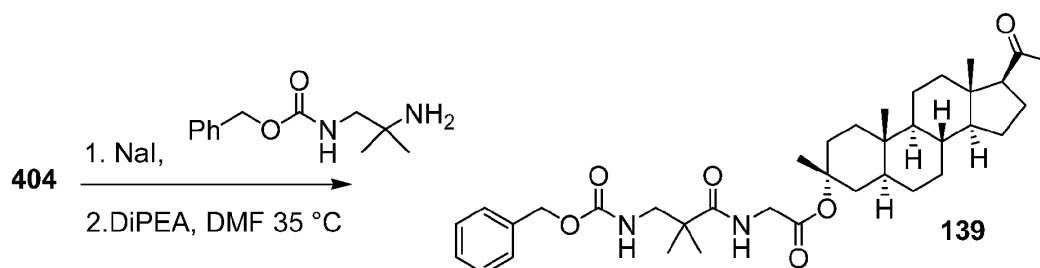
[0354] Following a similar procedure as in Example 93, but using Compound **235** (from Example 100) instead of Compound **233**, Compound **236** (free base) was obtained as an oil. ^1H NMR δ : 4.65-4.48 (m, 2H), 4.13 (t, $J = 6.2$ Hz, 2H), 3.61-3.52 (m, 2H), 3.46 (t, $J = 5.6$ Hz, 2H), 2.94 (td, $J = 5.8, 16.4$ Hz, 4H), 2.52 (t, $J = 8.8$ Hz, 1H), 2.34-1.94 (m, 10H), 1.90-1.79 (m, 1H), 1.76-1.05 (m, 24H), 1.02-0.83 (m, 1H), 0.83-0.69 (m, 4H), 0.59 (s, 3H). The free base of Compound **236** was converted to the hydrochloride salt (solid; 79% yield) following the procedure used in Example 92. HRMS (ESI $^{+}$): calculated for $\text{C}_{37}\text{H}_{59}\text{NO}_{10}$ m/z $[\text{M}+\text{H}]^{+}$: 678.4212, observed 678.4208; ^1H NMR CDCl_3 400MHz δ : 4.67-4.51 (m, 2H), 4.44 (t, $J = 5.1$ Hz, 2H), 4.05-3.91 (m, 2H), 3.79 (d, $J = 4.3$ Hz, 2H), 3.55-3.26 (m, 4H), 2.57-2.47 (m, 1H), 2.31-2.06 (m, 9H), 2.03-1.94 (m, 1H), 1.90-1.80 (m, 1H), 1.76-1.57 (m, 9H), 1.54-1.05 (m, 19H), 1.00-0.86 (m, 1H), 0.83-0.71 (m, 4H), 0.59 (s, 3H).

Example 103. Synthesis of Compound 240



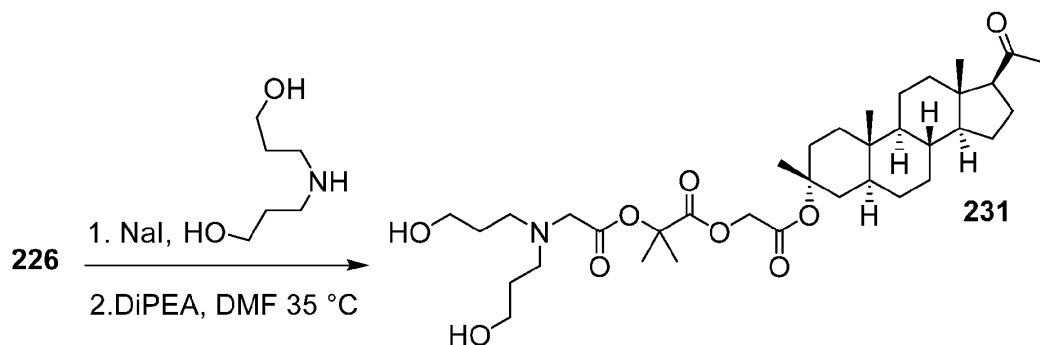
[0355] Following a similar procedure as in Example 93, but using Compound **248** (from Example 98) instead of Compound **233**, Compound **240** (75.4 mg) was obtained. HRMS (ESI $^{+}$): calculated for $\text{C}_{36}\text{H}_{56}\text{NO}_{10}$ m/z $[\text{M}+\text{H}]^{+}$: 662.3899, observed 662.3910; ^1H NMR δ : 4.63-4.46 (m, 2H), 4.25-4.03 (m, 5H), 3.62 (q, $J = 5.7$ Hz, 2H), 2.50 (t, $J = 8.8$ Hz, 1H), 2.30-2.03 (m, 11H), 2.03-1.90 (m, 1H), 1.91-1.77 (m, 2H), 1.77-1.06 (m, 24H), 1.02-0.72 (m, 5H), 0.57 (s, 3).

Example 104. Synthesis of Compound 139



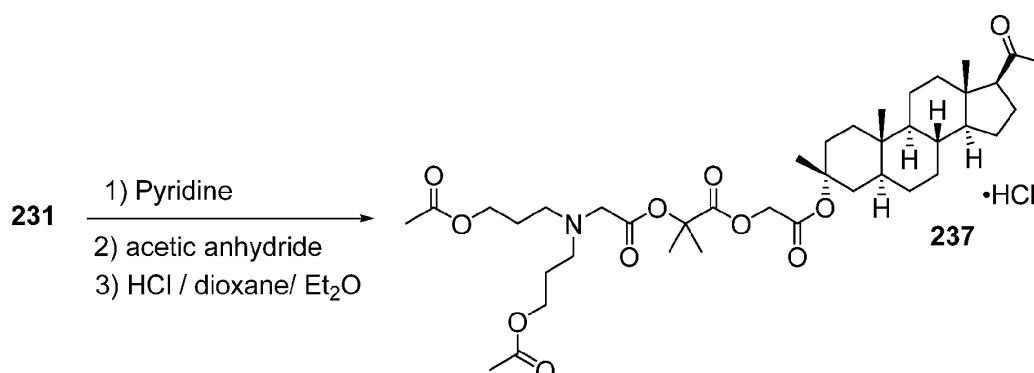
[0356] Following a similar procedure as in Example 85, but using benzyl (2-amino-2-methylpropyl)carbamate instead of 1,2-diamino-2-methylpropane, Compound **139** was obtained as an oil in 71% yield. HRMS (ESI⁺): calculated for C₃₆H₅₅N₂O₅ m/z [M+H]⁺: 595.4105, observed 595.4121; ¹H NMR δ : 7.40-7.19 (m, 5H), 5.50 (t, J = 5.6 Hz, 1H), 5.16-4.97 (m, 2H), 3.25 (s, 2H), 3.04 (d, J = 5.9 Hz, 2H), 2.57-2.39 (m, 1H), 2.24-1.80 (m, 6H), 1.73-0.80 (m, 28H), 0.77-0.64 (m, 4H), 0.55 (s, 3H).

Example 105. Synthesis of Compound 231



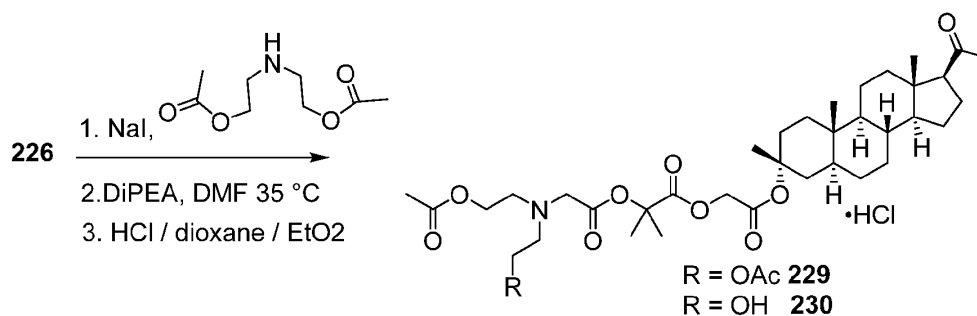
[0357] Following a similar procedure as in Example 92, but using 1,2-diamino-2-methylpropane instead of 2-(methylamino)ethanol, Compound **231** was obtained as an oil in 41% yield. ¹H NMR δ : 3.42-3.30 (m, 2H), 3.12 (br. s, 4H), 2.62-2.42 (m, 3H), 2.26-2.03 (m, 5H), 2.02-1.82 (m, 2H), 1.71-1.00 (m, 22H), 0.98-0.80 (m, 2H), 0.78-0.66 (m, 5H), 0.61-0.51 (s, 3H).

Example 106. Synthesis of Compound 237



[0358] Following a similar procedure as in Example 93, but using Compound **231** (from Example 105) instead of Compound **233**, Compound **237** (free base) was obtained as an oil in 91% yield. $^1\text{H NMR } \delta$: 4.65-4.50 (m, 2H), 4.12 (t, $J = 6.4$ Hz, 4H), 3.37 (s, 2H), 2.70 (t, $J = 7.0$ Hz, 4H), 2.54 (t, $J = 8.8$ Hz, 1H), 2.34-1.98 (m, 13H), 1.92-1.09 (m, 29H), 1.05-0.87 (m, 1H), 0.83-0.71 (m, 4H), 0.61 (s, 3H). The free base of Compound **237** was converted to the hydrochloride salt (solid; 98% yield) using the procedure in Example 92. HRMS (ESI $^{+}$): calculated for $\text{C}_{40}\text{H}_{64}\text{NO}_{11}$ m/z $[\text{M}+\text{H}]^{+}$: 734.4474, observed 734.4452; $^1\text{H NMR } \delta$: 4.70-4.53 (m, 2H), 4.17 (t, $J = 5.9$ Hz, 4H), 3.92 (br. s, 2H), 3.35 (br. s, 4H), 2.58-2.48 (m, 1H), 2.37-2.15 (m, 4H), 2.12 (s, 3H), 2.08-1.97 (m, 8H), 1.85 (d, $J = 8.8$ Hz, 1H), 1.78-1.07 (m, 24H), 1.03-0.82 (m, 1H), 0.78-0.72 (m, 4H), 0.61 (s, 3H).

Example 107. Synthesis of Compounds **229** and **230**



[0359] Following a similar procedure as in Example 92, but using 2-[(2-acetoxyethyl)amino]ethyl acetate HCl instead of 2-(methylamino)ethanol, a mixture of Compound **229** (free base) and Compound **230** (free base) was obtained. The mixture was purified by ISCO chromatography (gradient 0% EtOAc for 2 minutes, then ramping to 30% over

12 minutes, then holding at 30% until the product eluted, then ramping to 100% EtOAc) to provide:

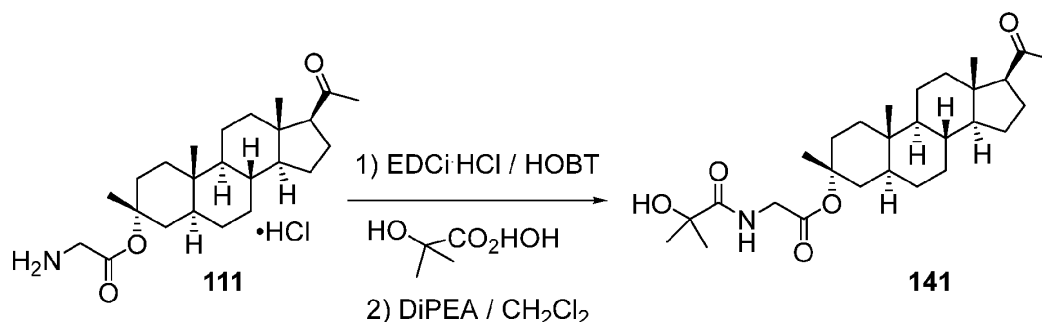
[0360] Compound **229** (free base) as an oil in 31% yield. ^1H NMR δ : 4.62-4.54 (m, 2H), 4.12 (t, $J = 5.9$ Hz, 4H), 3.56-3.50 (m, 2H), 2.98 (t, $J = 5.9$ Hz, 4H), 2.52 (t, $J = 8.8$ Hz, 1H), 2.32-2.13 (m, 2H), 2.11 (s, 3H), 2.08-2.04 (m, 5H), 1.99 (d, $J = 11.7$ Hz, 1H), 1.88-1.80 (m, 1H), 1.76-1.54 (m, 10H), 1.54-1.06 (m, 17H), 1.01-0.84 (m, 1H), 0.81-0.68 (m, 4H), 0.59 (s, 3H); and

[0361] Compound **230** (free base) as an oil in 16% yield. ^1H NMR δ : 4.66-4.50 (m, 2H), 4.20-4.11 (m, 2H), 3.59-3.47 (m, 4H), 2.98 (t, $J = 5.6$ Hz, 2H), 2.87 (t, $J = 5.0$ Hz, 2H), 2.52 (t, $J = 8.8$ Hz, 1H), 2.31-2.09 (m, 5H), 2.07 (s, 3H), 2.04-1.95 (m, 1H), 1.89-1.79 (m, 1H), 1.73-1.05 (m, 26H), 1.00-0.84 (m, 1H), 0.81-0.70 (m, 4H), 0.59 (s, 3H).

[0362] The free base of Compound **229** was converted to the hydrochloride salt (solid; 83% yield) using the procedure in Example 92. HRMS (ESI $^+$): calculated for $\text{C}_{38}\text{H}_{60}\text{NO}_{11}$ m/z $[\text{M}+\text{H}]^+$: 706.4161, observed 706.4151; ^1H NMR δ : 4.69-4.54 (m, 2H), 4.43 (br. s. 4H), 3.91 (br. s. 2H), 3.38 (br. s. 4H), 2.53 (t, $J = 8.8$ Hz, 1H), 2.31-2.14 (m, 2H), 2.12-2.09 (m, 8H), 2.07 (d, $J = 2.9$ Hz, 1H), 2.03 (br. s. 1H), 1.90-1.86 (m, 1H), 1.83 (br. s. 1H), 1.77-1.63 (m, 10H), 1.63-1.46 (m, 8H), 1.45-1.09 (m, 10H), 1.01-0.84 (m, 1H), 0.80-0.76 (m, 4H), 0.61 (s, 3H).

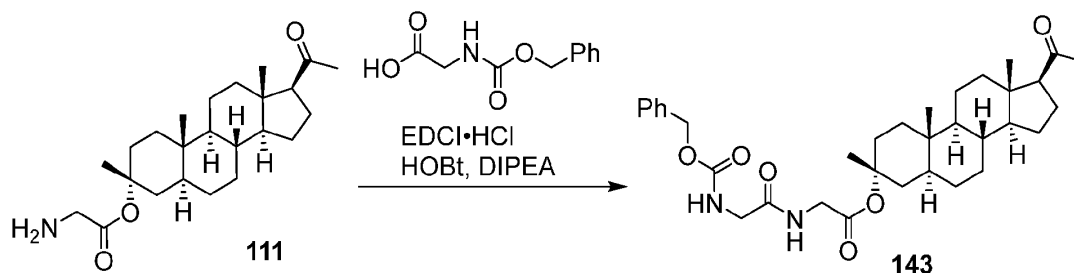
[0363] The free base of Compound **230** was converted to the hydrochloride salt (solid; 97% yield) using the procedure in Example 92. HRMS (ESI $^+$): calculated for $\text{C}_{36}\text{H}_{58}\text{NO}_{10}$ m/z $[\text{M}+\text{H}]^+$: 664.4055, observed 664.4072; ^1H NMR δ : 4.62 (d, $J = 2.9$ Hz, 2H), 4.54 (d, $J = 4.1$ Hz, 2H), 4.13 (s, 2H), 3.97 (d, $J = 5.3$ Hz, 2H), 3.59 (d, $J = 4.1$ Hz, 2H), 3.44 (d, $J = 5.9$ Hz, 2H), 2.53 (t, $J = 9.1$ Hz, 1H), 2.28-2.17 (m, 1H), 2.15-2.12 (m, 6H), 2.06-1.97 (m, 2H), 1.83 (br. s. 1H), 1.80-1.65 (m, 8H), 1.54-1.08 (m, 18H), 1.01-0.84 (m, 1H), 0.82-0.72 (m, 4H), 0.61 (s, 3H).

Example 108. Synthesis of Compound 141



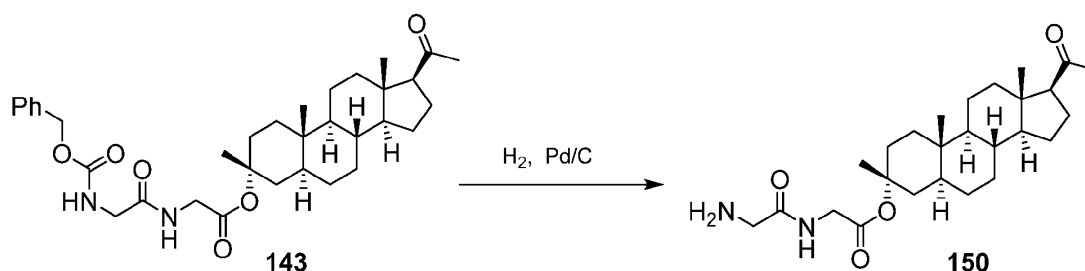
[0364] A mixture of Compound **111** (HCl salt, 81.4 mg, 0.19 mmol) and 2-hydroxyisobutyric acid (74.7 mg, 0.72 mmol) was stirred in DCM (4 mL) at 0 °C, then EDCI·HCl (79.4 mg, 0.41 mmol) and then HOBt (41.4 mg, 0.31 mmol) were added, followed by DIPEA (150 µL, 0.86 mmol). The resulting pale-yellow solution was slowly warmed to ambient temperature overnight, then diluted with EtOAc (25 mL) and quenched with a 1N solution of HCl (25 mL). The organic phase was washed with saturated NaHCO₃ (25 mL) followed by saturated NaCl (25 mL), and then dried with Na₂SO₄, filtered and concentrated. The crude product was purified by column chromatography using an ISCOTM chromatography system to provide Compound **141** (19.5 mg) as a solid. HRMS (ESI⁺): calculated for C₂₈H₄₆NO₅ m/z [M+H]⁺: 476.3370, observed 476.3373; ¹H NMR δ: 7.18 (br. s, 1H), 4.03-3.95 (m, 2H), 2.68 (br. s, 1H), 2.53 (t, *J* = 9.1 Hz, 1H), 2.29-2.06 (m, 7H), 1.99 (d, *J* = 11.7 Hz, 1H), 1.92-1.07 (m, 21H), 1.03-0.83 (m, 3H), 0.83-0.69 (m, 5H), 0.60 (s, 3H).

Example 109. Synthesis of Compound 143



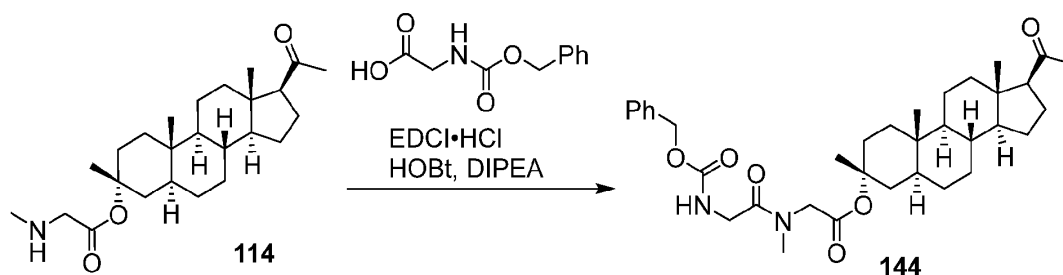
[0365] Following a similar procedure as in Example 35, but using Z-Gly-OH instead of 4-morpholinylacetic acid, Compound **143** will be obtained.

Example 110. Synthesis of Compound 150



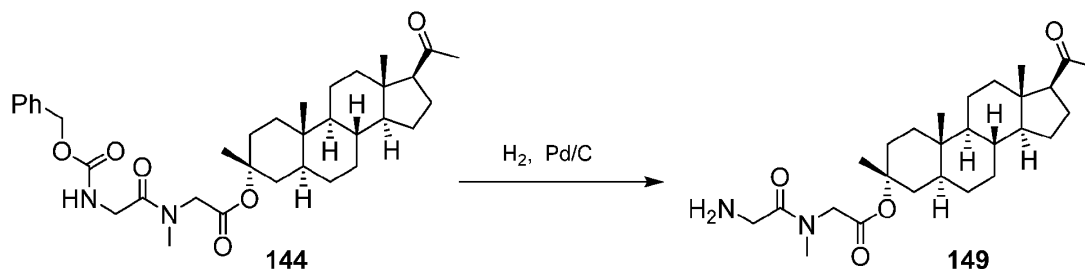
[0366] Following a similar procedure as in Example 81, but using Compound **143** (from Example 109) instead of Compound **128**, Compound **150** will be obtained.

Example 111. Synthesis of Compound 144



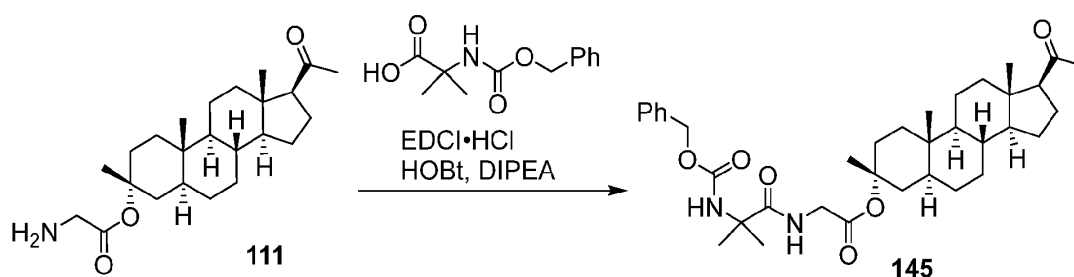
[0367] Compound **114** (From Example 36; 133.8 mg, 0.33 mmol), Z-Gly-OH (90.8 mg, 0.43 mmol) and DMAP (10.1 mg, 0.083 mmol) were dissolved in DCM (10 mL), and the mixture was cooled to 0 °C. EDCI·HCl (98.7 mg, 0.51 mmol) was then added in a single portion, and the resulting solution was warmed to ambient temperature overnight. The mixture was then diluted with EtOAc (40 mL) and quenched with water (35 mL). The aqueous phase was separated, and the organic phase was washed with water (2x25 mL) then brine (25 mL), dried with Na₂SO₄ for 30 minutes, filtered and concentrated to provide an oil, which was purified by column chromatography using an ISCOTM chromatography system to provide Compound **144** (133.2 mg) as an oil. LCMS (ESI+): R_f = 7.57, (M+H)⁺ = 595.41; ¹H NMR 400MHz δ: 7.42-7.29 (m, 5H), 5.79 (br. s., 1H), 5.18-5.10 (m, 2H), 4.16-3.99 (m, 4H), 3.10-3.30 (s, 22.51-2.44 (m, 1H), 2.28-2.20 (m, 1H), 2.20-2.07 (m, 4H), 1.99 (d, J = 12.1 Hz, 1H), 1.74-1.04 (m, 19H), 1.00-0.87 (m, 1H), 0.81-0.69 (m, 4H), 0.59 (s, 3H).

Example 112. Synthesis of Compound 149



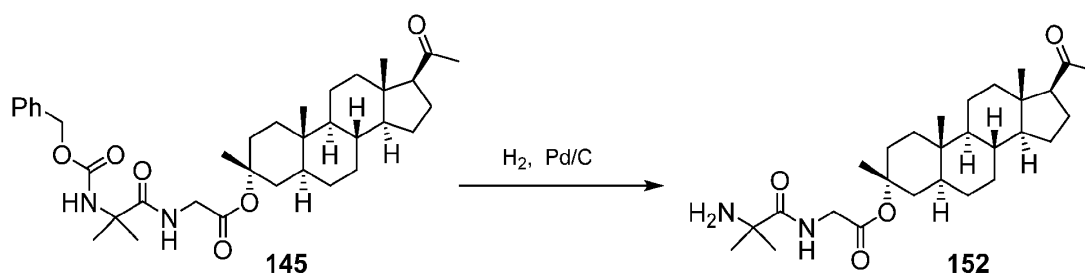
[0368] Following a similar procedure as in Example 81, but using Compound **144** (from Example 111) instead of Compound **128**, Compound **149** will be obtained.

Example 113. Synthesis of Compound 145



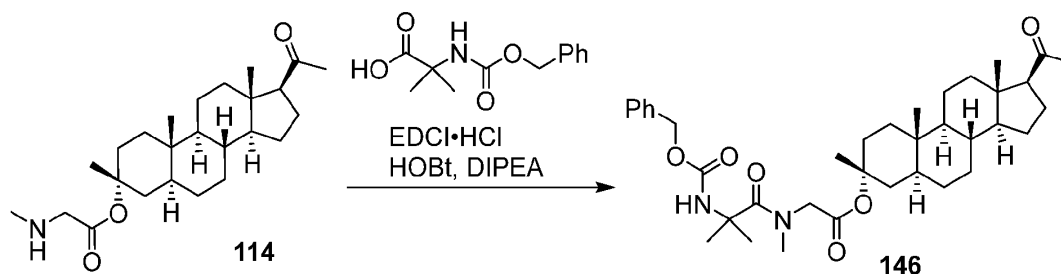
[0369] Following a similar procedure as in Example 35, but using Z-Aib-OH instead of 4-morpholinylacetic acid, Compound **144** will be obtained.

Example 114. Synthesis of Compound 152



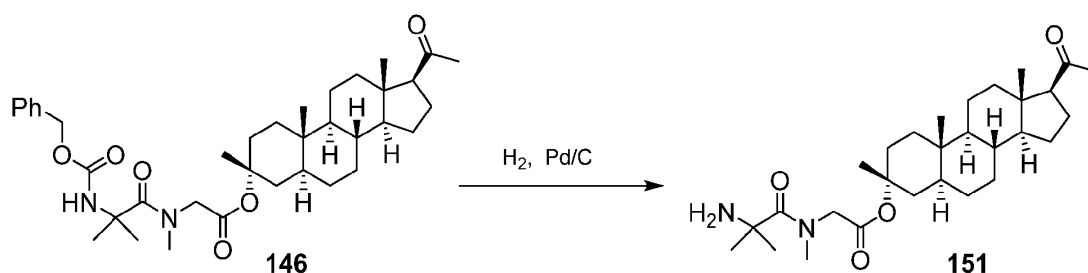
[0370] Following a similar procedure as in Example 81, but using Compound **145** (from Example 113) instead of Compound **128**, Compound **152** will be obtained.

Example 115. Synthesis of Compound 146



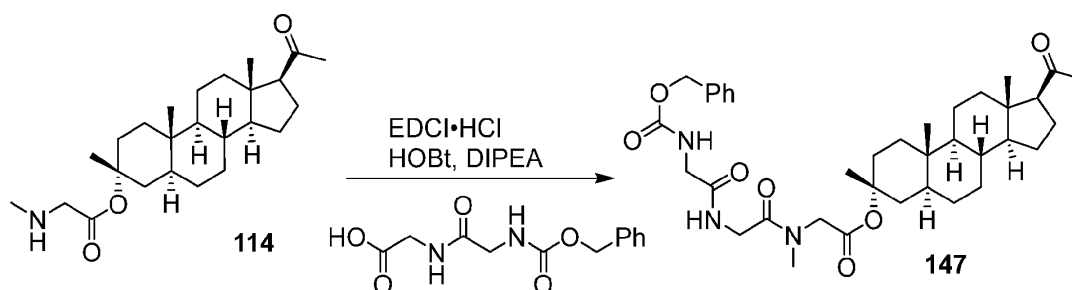
[0371] Following a similar procedure as in Example 35, but using Z-Aib-OH instead of 4-morpholinylacetic acid, and Compound **114** instead of Compound **111**, Compound **146** will be obtained.

Example 116. Synthesis of Compound 151



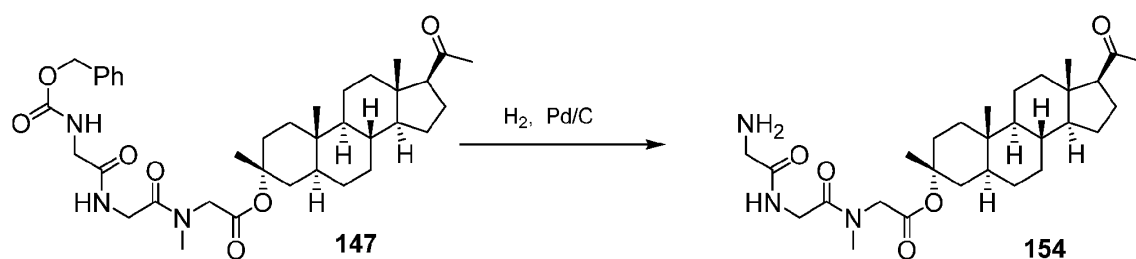
[0372] Following a similar procedure as in Example 81, but using Compound **146** (from Example 115) instead of Compound **128**, Compound **151** will be obtained.

Example 117. Synthesis of Compound 147



[0373] Following a similar procedure as in Example 35, but using (2-benzyloxycarbonylamino)-acetyl-amino)-acetic acid instead of 4-morpholinylacetic acid, and Compound **114** instead of Compound **111**, Compound **147** will be obtained.

Example 118. Synthesis of Compound 154



[0374] Following a similar procedure as in Example 81, but using Compound **147** (from Example 117) instead of Compound **128**, Compound **154** will be obtained.

Example 119. Physicochemical properties of compounds.

[0375] The physicochemical properties of the compounds (Log S, Log D, Log P, TPSA, acid pKa and base pKa) disclosed herein were calculated using commercially available software (ChemAxon), and provided below in Table 2.1.

Table 2.1. Calculated physicochemical properties of exemplary compounds.

Compound No.	Salt	Log S pH 7.4	Log S pH 2.0	Log D pH 7.4	LogP	TPSA	acid pKa	base pKa
ganaxolone	-	-5.38	-5.38	4.27	4.27	37	19.1	-1.0
100	HCl	NC	NC	6.18	6.18	59	19.4	5.4
101	HCl	NC	NC	4.38	4.38	56	19.4	4.6
102	HCl	NC	NC	4.15	4.45	50	19.4	7.4
103	HCl	NC	NC	4.20	4.20	82	19.4	2.7
104	HCl	NC	NC	4.52	4.55	56	19.4	6.3
105	HCl	NC	NC	4.58	4.58	73	19.4	4.1
106	HCl	NC	NC	4.41	4.41	82	19.4	2.8
107	HCl	NC	NC	4.89	3.53	76	15.6	6.0
108	HCl	NC	NC	5.30	5.30	82	19.4	3.1
109	-	NC	NC	4.01	4.89	82	19.4	2.7
110	HCl	NC	NC	3.84	3.84	82	19.4	2.7
111	HCl	-5.61	-0.70	3.61	3.78	69	19.4	7.1
112	HCl	-5.61	NC	3.27	3.28	85	12.62	5.2
113	-	NC	NC	4.27	4.28	85	12.6	5.8
114	HCl	-5.54	NC	4.17	4.22	55	19.4	6.4
115	HCl	-5.41	NC	3.50	3.50	76	19.4	5.4
116	-	-4.60	NC	2.37	3.51	88	14.9	8.5
117	-	NC	NC	5.19	5.19	140	12.2	-4.3
118	-	NC	NC	6.30	6.30	111	12.5	-4.6
119	-	NC	NC	7.40	7.40	82	13.6	-7.0
120	-	-4.04	-5.01	1.60	3.39	93	3.1	5.3
121	-	NC	NC	6.52	6.52	82	13.5	-7.0
122	HCl	-6.20	NC	2.16	3.03	128	12.4	8.2
124	-	NC	NC	0.56	2.50	93	3.0	5.2
125	-	NC	NC	4.84	4.84	82	19.4	2.9
126	-	NC	NC	5.90	5.90	82	19.4	2.9
127	-	NC	NC	6.57	6.57	82	19.4	2.9
128	-	NC	NC	6.57	6.57	73	19.4	4.7
129	-	NC	NC	6.13	6.13	82	19.4	2.8
130	-	NC	NC	4.41	4.41	82	19.4	2.8
131	-	-6.88	NC	1.15	3.02	93	3.0	5.3
132	-	-5.97	-1.67	4.20	4.22	76	14.8	6.1
133	-	NC	NC	3.87	3.91	67	15.6	6.3
134	-	NC	NC	4.66	4.67	82	19.4	5.68
135	-	-5.63	-3.21	5.90	5.91	82	19.4	5.7
136	-	-5.63	NC	4.33	4.34	94	19.4	5.7
137	-	NC	NC	1.59	2.85	84	3.1	5.9
138	-	-3.46	0.00	1.77	4.12	81	19.4	9.8
139	-	NC	NC	6.27	6.28	94	14.8	5.9
140	-	-5.78	-1.53	4.19	4.22	76	15.0	6.3
141	-	-6.27	-6.27	3.79	3.79	93	12.4	-3.5
142	-	-5.02	-0.91	3.20	3.22	87	15.3	6.1

143	-	-7.66	-7.66	4.84	4.84	111	12.4	-5.2
144	-	-7.44	-7.44	5.07	5.07	102	13.5	-5.0
145	-	-8.02	-8.02	5.84	5.84	111	12.4	-4.7
146	-	-7.80	-7.80	6.07	6.07	102	13.4	-4.5
147	-	-7.42	-7.42	3.96	3.96	131	12.5	-4.5
148	-	-7.65	-7.65	3.74	3.74	140	12.1	-4.6
149	-	-5.76	0.00	2.10	2.90	90	19.4	8.1
150	-	-5.95	0.00	1.87	2.68	98	12.7	8.1
151	-	-6.18	0.00	2.65	3.90	90	19.4	8.6
152	-	-6.37	0.00	2.42	3.68	98	12.7	8.6
153	-	-6.06	-0.22	1.00	1.57	128	12.3	7.8
154	-	-5.86	-0.02	1.22	1.80	119	12.7	7.8
200	HCl	-5.53	-3.17	3.89	4.01	82	19.4	4.4
201	-	-5.69	-5.69	3.89	3.89	64	13.1	-3.6
202	HCl	-5.64	NC	4.16	4.22	73	19.4	6.6
203	-	NC	NC	4.75	4.75	79	19.4	-4.1
204	-	NC	NC	4.11	4.11	88	19.4	-3.7
205	-	-5.54	-5.54	4.06	4.06	97	19.4	-3.7
206	-	NC	NC	8.11	8.11	137	12.2	-3.7
207	-	NC	NC	5.03	5.03	137	12.1	-4.9
208	bis HCl	NC	NC	3.78	4.07	76	19.4	7.4
209	-	NC	NC	5.92	5.92	137	12.2	-4.6
210	-	NC	NC	6.41	6.41	99	19.4	-6.9
211	HCl	-5.85	NC	4.57	4.57	82	19.4	4.6
212	HCl	-5.85	NC	4.57	4.57	82	19.4	4.6
213	HCl	-6.09	NC	5.01	5.01	82	19.4	4.9
214	HCl	-5.86	NC	2.62	3.76	125	12.4	8.5
215	HCl	-7.75	NC	4.88	5.95	125	12.4	8.4
216	HCl	-5.25	NC	1.85	2.87	125	12.3	8.4
217	HCl	NC	NC	3.10	4.24	85	14.8	8.5
218	-	-5.89	-0.71	4.00	4.41	96	19.4	7.6
219	-	NC	NC	5.55	5.56	70	9.1	-6.8
220	HCl	NC	NC	3.92	4.97	82	19.4	8.4
221	-	NC	NC	5.76	5.76	108	19.4	-5.6
222	TFA	NC	NC	3.48	4.48	91	19.4	8.4
223	-	NC	NC	6.57	6.57	108	13.2	-6.9
224	-	-6.2	-6.2	4.52	4.52	90	12.8	-3.7
225	-	-6.04	-3.62	4.63	4.63	108	19.4	4.4
226	-	NC	NC	5.50	5.50	96	19.4	-6.8
227	-	-6.14	-1.63	4.79	4.85	99	19.4	6.6
228	-	-5.52	-1.41	3.45	3.47	140	15.3	6.1
229	-	-6.06	-2.96	4.35	4.35	152	19.4	5.1
230	-	-5.89	-2.20	3.90	3.91	146	15.6	5.6
231	-	-5.56	-1.00	3.52	3.59	140	15.6	6.6
232	-	-6.01	-1.42	4.77	4.84	82	19.4	6.7
233	-	-5.84	-1.54	4.12	4.16	119	15.6	6.3
234	-	-6.58	-6.58	4.85	4.96	125	19.4	-6.8
235	-	-5.64	-1.58	4.09	4.11	129	15.6	6.1
236	-	-5.92	-2.36	4.55	4.55	135	19.4	5.6
237	-	-6.01	-1.07	4.25	4.47	152	19.4	7.2
238	-	NC	NC	5.83	5.84	163.84	13.2	5.8
239	-	NC	NC	5.45	5.46	172.63	13.2	5.5
240	-	-6.39	-6.39	3.83	3.83	142.58	19.4	-2.0

241	-	-5.82	0.00	3.49	3.68	152	19.4	7.1
242	-	-6.16	-2.36	4.59	4.60	126	19.4	5.8
243	-	-6.94	-3.38	5.79	5.79	173	13.1	5.6
244	-	NC	NC	5.57	5.57	108	13.2	-6.8
245	-	-5.85	-1.21	4.14	4.22	119	15.9	6.7
246	-	-6.20	-1.44	4.55	4.66	126	19.4	6.9
247	-	-5.78	-5.78	3.52	3.52	90	13.1	-3.6
248	-	-6.20	-1.44	4.55	4.66	126	19.4	6.9
300	-	NC	NC	5.76	5.76	82	15.1	-7.0
301	-	NC	NC	4.37	4.37	64	15.5	-2.6
302	HCl	NC	NC	2.04	4.27	69	19.4	9.7
303	TFA	NC	NC	4.49	4.49	82	19.4	4.3
304	HCl	-3.81	NC	2.18	4.51	93	19.4	10.5
305	-	NC	NC	2.37	5.49	81	4.1	-7.0
306	-	NC	NC	1.34	4.49	81	4.0	-7.0
307	HCl	-6.26	-0.89	3.79	4.93	76	15.5	8.5
308	-	NC	NC	5.64	5.64	70	19.4	-6.8
309	-	NC	NC	5.02	5.02	64	14.8	-2.9
310	-	NC	NC	5.13	5.13	82	19.4	4.2
400	-	NC	NC	4.71	4.71	43	19.4	-6.8
401	-	NC	NC	5.41	5.41	43	19.4	-6.9
402	-	NC	NC	5.85	5.85	43	19.4	-6.9
403	-	NC	NC	6.76	6.76	43	19.4	-6.8
404	-	NC	NC	5.25	5.25	43	19.4	-7.0
405	-	NC	NC	6.91	6.91	43	19.4	-6.8
406	-	NC	NC	5.65	5.65	43	19.4	-7.0
407	-	-2.26	NC	1.49	4.53	81	4.2	-6.9
408	-	-2.60	NC	1.61	4.71	81	4.1	-6.9
409	HCl	-4.26	NC	3.64	4.70	73	19.4	8.4
410	TFA	NC	NC	2.83	3.97	76	15.7	8.5
411	TFA	NC	NC	3.01	4.15	76	15.6	8.5
412	TFA	NC	NC	3.93	5.07	76	15.7	8.5
413	TFA	NC	NC	4.74	5.80	73	19.4	8.4
414	TFA	NC	NC	1.43	1.45	107	2.0	8.6
415	-	NC	NC	3.88	3.88	81	19.4	-6.5
416	TFA	-5.67	-5.33	1.73	1.74	107	2.1	9.5
417	HCl	-2.74	NC	1.72	4.31	69	19.4	10.2
418	HCl	-2.97	NC	2.15	4.75	69	19.4	10.2
419	HCl	-4.63	NC	4.29	5.35	56	19.4	8.4
420	-	NC	NC	2.62	5.63	81	4.2	-6.9
500	-	NC	NC	5.61	5.61	26	19.4	-4.2
501	-	NC	NC	5.04	5.15	56	19.2	-4.3
502	-	NC	NC	6.01	6.01	91	13.3	-4.3
503	-	-5.41	-5.41	4.50	4.50	80	19.4	-3.6
504	-	-5.40	NC	4.44	4.44	65	19.4	4.6

TPSA = Topological Polar Surface Area; HCl = hydrochloride; TFA = trifluoroacetate; NC = not calculated.

[0376] The solubility of exemplary compounds of the present disclosure, and ganaxolone, were measured by the following protocol and provided in Table 2.2. Each test compound was

weighed and placed in 1.5 mL glass vial to which an appropriate amount of 50 mM phosphate buffer at pH 7.4 was added to yield a mixture of more than 10 mg/mL. The mixture was vortexed and a magnetic stirring bar was subsequently added to the vial. The vial was placed on a magnetic stirrer with constant stirring for 16-24 hours at room temperature. The pH of the top layer solution was measured. Subsequently, 200 μ L of the top layer solution was placed in a 1.5 mL microcentrifuge tube and centrifuged at 18,000 g for 10 min at room temperature. A 10 μ L aliquot of supernatant was added to 990 μ L of methanol:water (1/1, v/v) and vortexed. Then, one volume of acetonitrile containing internal standard was added to one volume of the above 100-fold diluted solution and the resulting solution was vortexed and placed in 96-well plate for LC-MS/MS analysis. Calibration standards were made in a concentration range of 10 ng/mL to 10 μ g/mL in methanol:water (1/1, v/v) to which one volume of acetonitrile containing internal standard was also added, vortexed, and placed in a 96-well plate along with the solubility samples for LC-MS/MS analysis. LC-MS-MS analysis was performed utilizing multiple reaction monitoring for detection of characteristic ions for each test compound, additional related analytes and internal standard.

Table 2.2. Measured solubility of exemplary compounds.

Compound No.	Solubility	
	pH 2.0, mg/mL	pH 7.4, μ g/mL
ganaxolone	0.002	4
111	1.52	29.1
120	0.039	35
200	11.8	29
201	0.036	33
218	16.9	152
224	0.024	26
229	0.022	11

Example 120. Stability of Compounds in simulated gastric fluid and simulated intestinal fluid.

[0377] The stability of exemplary compounds in simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) was tested according to the following protocol. For each test compound, samples at a final concentration of 2 μ g/mL were prepared in respective blank simulated gastric fluid (SGF) with pepsin (pH 1.2) and simulated intestinal fluid (SIF) with pancreatin (pH 6.8). All samples are incubated at 37 °C on a 150-RPM orbital shaker, and an aliquot was removed at

pre-determined time points (0 to 180 minutes). Samples were precipitated with three volumes of acetonitrile containing propranolol as an internal standard, and centrifuged for 10 min at 2000g before LC-MS/MS analysis of the supernatant solutions.

[0378] Percent prodrug compound remaining was determined relative to 0-minute incubation samples. If a sufficient number of time points was available, the degradation half-life was obtained, based on the natural log of % compound remaining vs. time plot. The following parameters were calculated to estimate the compound stability in *in vitro* SGF and SIF:

1. T₉₀ = time to reach 90% prodrug compound remaining.
2. t_{1/2} = the half-life (min), where t_{1/2} is equal to 0.693/slope .

[0379] The results of the study, and general observations, are provided in Table 3 below.

Table 3. Stability of exemplary compounds in SGF and SIF.

Compound No.	SGF t _{1/2} (min)	SGF (% remain, 60 min)	Conversion in SGF (60 min)	SIF t _{1/2} (min)	SIF (% remain, 60 min)	Conversion in SIF (60 min)
ganaxolone		95.6	N/A		94.6	N/A
100		90.8			93.2	
101		90.5			90.2	
102		56.3			74.7	
103		98.4			75.9	
106		2.80				
109		96.2			92.9	
111	746	95	conversion to GNX	256	79.0	no conversion to GNX
120	250	83	no conversion to GNX	199	74	no conversion to GNX
200		99.0	no conversion to GNX		31	converted to Compound 201
201				1583	98.0	very little conversion to GNX
218	2099	97	no conversion to GNX	1363	95	no conversion to GNX
224	365	88	no conversion to GNX	98	60	no conversion to GNX
228	511	89	no conversion to GNX	32	1.7	no conversion to GNX
242	4595	99.1	no conversion to GNX	146	29	no conversion to GNX
503	118.0	68	conversion to GNX	~30	~90	conversion to GNX

504	7.41	0.4	small amount GNX produced	88.4	49.0	small amount GNX produced
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GNX = ganaxolone.

Example 121. Liver microsomal stability of compounds.

[0380] The liver microsomal stability of exemplary compounds was tested using rat, mice, dog, and human liver microsomes according to the following protocol. For several compounds only human liver microsomal stability was tested. For each test compound, samples at a final concentration of 1 μ M were prepared in 25 mM potassium phosphate buffer with liver microsomes of each species at a final concentration of 0.5 mg/mL. The microsomal assays were carried out with and without the addition of NADPH at a final concentration of 1 mM. For negative control samples, NADPH reagent was not added. All samples were incubated at 37 °C on a 100-RPM orbital shaker, and an aliquot was removed at pre-determined time points. Samples were precipitated with three volume of acetonitrile containing propranolol as internal standard, and centrifuged for 10 min at 2000 g before LC/MS/MS analysis of the supernatant solutions. Note that compounds undergo only Phase I metabolism in liver microsomes.

[0381] Percent prodrug compound remaining was determined relative to 0-minute incubation samples, from which the elimination half-life was calculated based on the natural log of % compound remaining vs. time plot. The following parameters were calculated to estimate the compounds *in vitro* metabolic stability:

1. Cmp= concentration of microsomal proteins (mg/mL);
2. $t_{1/2}$ = the half-life (min), where $t_{1/2}$ is equal to $0.693/\text{slope}$.
3. CL_{int} = the intrinsic hepatic clearance (uL/min/mg), where CL_{int} is equal to $0.693/(t_{1/2} \times \text{Cmp})$

[0382] Concentrations of each compound were 0.5 μ M in all liver microsome assays. Results of the assay and general observations are provided in Table 4.

Table 4. Rat liver microsomal stability and human liver microsomal stability results.

Comp. No.	Rat Liver Microsomal Stability			Human Liver Microsomal Stability			Comments
	$t_{1/2}$ (min)	CL _{int} (uL/min/mg liver)	no NADPH, % remain 1 h	$t_{1/2}$ (min)	CL _{int} (uL/min/mg liver)	no NADPH, % remain 1 h	
GNX	12.0	116.0	98.0	12.6	110.0	99.0	

100	12.7	109.0	98.0	11.9	116.0	100.0	GNX not produced in human or rat
101	6.8	204.0	100.0	10.2	137.0	99.0	GNX not produced in human or rat
104	7.41	187	99	12	116	98	GNX not produced in human or rat
106				4.57	303	3.05	GNX not produced in human
107	21.9	63	98	64.7	21.4	99	GNX not produced in human or rat
108				12.2	114	98	GNX not produced in human
110				4.15	344	1.5	In human GNX not produced
111	335	4.13	99.7	190	7.28	82.6	In rat no GNX produced; In human GNX produced
112				46.7	29.6	98.6	In human no GNX produced
114				277	5.00	99.5	In human GNX produced
115				13.8	100	99	In human no GNX produced
120	36	38	72	16	86	8	In rat no GNX produced; In human GNX produced
122				345	4.02	99	In human no GNX produced
124				532	2.61	99	In human small amount of GNX produced
125				3.9	354	1	In human GNX produced
128				9	153	20	In human no GNX produced
131				207	6.7	82	In human no GNX produced
132				11.7	118	1	In human GNX produced
135				3.6	385	1.3	In human GNX produced
136				3	457	0.5	In human GNX produced, Compounds 132 and 120 also produced
137				908	0.5	95	In human no GNX produced
138				33.2	41.8	95.3	In human small amount of GNX produced
140				39.1	35.5	99	In human GNX produced
141				38.3	36.2	99.7	In human no GNX produced
142				32.3	42.9	99	In human GNX produced
200	12.1	115	7.5	6	229	1	In rat and human, both GNX and Compound 201 produced
201	32.4	42.7	99.5	17.4	79.5	70	In rat, may be converted to GNX very slowly In human, GNX produced
202				2.62	529	1.85	In human GNX produced
203				2.24	618	0.79	In human GNX produced
204				4.12	337	10.5	In human GNX produced
205				3.58	387	5.7	In human GNX produced
208				37	37.4	72	In human GNX not produced
211				10.5	132	27	In human GNX produced, more Compound 201 produced than GNX
212				14.3	96.9	99	In human small amount of GNX produced
213				27.3	50.7	98	In human small amount of GNX produced
214				161	8.6	79.5	In human both GNX and Compound 201 produced
215				257	5.39	88	In human small amounts of Compound 201 and GNX produced
216				192	7.22	80	In human both GNX and Compound 201 produced
217				316	4.39	99.7	In human small amount of GNX produced
218	56.4	26	83	14.4	95.3	10.0	In rat no GNX produced; In human GNX produced

220				11.8	117	4	In human small amount of GNX produced, small amount of Compound 201 produced
222				63.7	21.8	61	In human no GNX produced
224	9.8	142	1.4	1.67	828	0.4	In rat no GNX produced; In human GNX produced
227				23.9	58.1	71	In human no GNX produced
228	16.4	84.4	15	6.2	225	6	In rat no GNX produced; In human GNX produced.
229				6.1	227	1	In human GNX produced
230				2.94	771	1	In human GNX produced
231				5.30	261	98	In human GNX produced
232				13.5	103	27	In human GNX produced
233				5.3	261	5	In human GNX produced
235				5.2	269	36	In human GNX produced
236				3.72	372	<1	In human GNX produced
237				5.18	267	<1	In human GNX produced
241				3.9	356	3.68	In human GNX produced
242				1.41	982	0.26	In human GNX produced
245				11.4	122	69.7	In human GNX produced
247				2.01	689	1.1	In human GNX produced
302				248	5.59	99	In human GNX not produced
303				2.48	599	90	In human GNX not produced
304				173	8.03	83.8	In human small amount of GNX produced
305				171	812	98.8	In human small amount of GNX produced
307				391	3.55	99	In human no GNX produced
310				2.9	474	1	In human no GNX produced
407				79.8	17.4	99	In human no GNX produced
408				143	9.72	76	In human no GNX produced
409				12.8	108	7	In human small amount of GNX produced
410				439	3.16	99	In human no GNX produced
411				444	3.12	99	In human small amount of GNX produced
412				273	5.07	94	In human small amount of GNX produced
413				126	11	89	In human no GNX produced
414				178	7.81	82	In human no GNX produced
415				8.2	969	99	In human small amount of GNX produced
416				273	5.08	99	In human no GNX produced
417				494	2.08	99	In human no GNX produced
418				451	3.08	99	In human no GNX produced
419				39.5	35.1	88	In human small amount of GNX produced
420				445	3.11	97.4	In human no GNX produced
503				5.65	245	11.6	In human GNX produced
504				2.5	554	0.8	In human GNX produced

GNX = ganaxolone.

[0383] Certain compounds were also tested in mice and dog liver microsome assays according to the protocol outlined above. The concentration of the compound was 0.5 μ M in the assay. Results and general observations are provided in Table 5.

Table 5. Mouse liver microsomal stability and dog liver microsomal stability results.

Comp. No.	Mouse Liver Microsomal Stability	Dog Liver Microsomal Stability	Comments
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	t _{1/2} (min)	CL _{int} (uL/min/mg liver)	no NADPH, % remain 1 h	t _{1/2} (min)	CL _{int} (uL/min/mg liver)	no NADPH, % remain 1 h	
GNX				49.8	27.8	43.6	
111	118	11.8	92.7	280	4.95	92.3	In mouse small amount of GNX produced In dog GNX produced.
120				81	17	83	In dog GNX produced
218				20.1	69.0	44.4	In dog GNX produced
224				7.1	196	0.6	In dog GNX produced
228				10.7	129	12.9	In dog GNX produced
229				6.2	224	1	In dog GNX produced
242				2.07	668	0.89	In dog GNX produced

GNX = ganaxolone.

Example 122. Plasma stability of compounds.

[0384] The plasma stability of exemplary compounds was tested using rat, mice, dog, and human plasma, according to the following protocol. For each test compound, samples at a final concentration of 2 µg/mL were prepared in blank plasma of selected species. All samples were incubated at 37 °C on a 150-RPM orbital shaker, and an aliquot was removed at pre-determined time points (0, 15, 30, 60, and 120 minutes). Samples were precipitated with three volumes of acetonitrile containing propranolol as internal standard, and centrifuged for 10 min at 2000 g before LC/MS/MS analysis of the supernatant solutions. Percent prodrug compound remaining was determined relative to 0-minute incubation samples for each replicate, from which the degradation half-life was calculated based on the natural log of % compound remaining vs. time plot. The following parameters were calculated to estimate the compounds *in vitro* plasma stability:

1. t₉₀ = time to reach 90% prodrug compound remaining.
2. t_{1/2} = the half-life (min), where t_{1/2} is equal to 0.693/slope.

[0385] Results and general observations of the assay are provided in Table 6.

Table 6. Rat, human, mouse, and dog plasma stability assay.

Compound No.	Rat	Human	Mouse	Dog	Observations
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	Half life (t _{1/2}) (min)	t ₉₀ (min)	Half life (t _{1/2}) (min)	t ₉₀ (min)	Half life (t _{1/2}) (min)	t ₉₀ (min)	Half life (t _{1/2}) (min)	t ₉₀ (min)	
ganaxolone	625.0	94.2	1401.0	211.0			3745	564	
100	185.0	27.9	184.0	27.8					Stable in human, GNX not apparent in metabolites
101	2269.0	342.0	1616.0	243.0					Stable in human
111	876	132	3602	542	446	67.2	1611	243	GNX is produced in rat and mouse Very stable in human and dog (no GNX)
120	520	78	1488	218			583	88	No GNX produced in rat, human, or dog;
200	9.5	1.4	14.6	2.19					In rat, compound converted to GNX, not Compound 201. In human, compound not converted to GNX, but is converted to Compound 201
201	543	82	2076	313					In rat and human, compound very slowly converted to GNX
208			177	26.6					No GNX produced in human
218	56.3	8.5	56.9	8.6			5198	783	No GNX produced in human or dog; GNX produced in rat
220			21.1	3.18					In human no GNX produced
224	14.4	2.16	43	6.5			838	126	No GNX produced in human or dog; GNX produced in rat
228	12	1.8	9	1.4			20	3	No GNX produced in human or dog; Compound 224 produced in human GNX produced in rat
242			33	4.99			3842	578	No GNX produced in human or dog

503			<<30						In human amount of Compound 503 at start: 3883 nM. Amount at end: 0.2 nM. Amount of GNX at start 349 nM. Amount at end 2469 nM
504			17.1	2.54					In human very small amount of GNX produced

GNX = ganaxolone

Example 123. Pharmacokinetic Study with Compound 111

[0386] A pharmacokinetic study was carried out using Compound 111, comparing intravenous administration (5 mg/kg; n=3) and oral (PO) administration (25 mg/kg; n=3) in fasted male beagle dogs. A single dose of Compound 111 was administered either orally or intravenously, with the compound formulated in the following vehicle: 1% DMA, 48% CAPTISOL[®] (30% concentration), 1% TWEEN-20[®] (10% concentration), 25% CAPTISOL[®] (30% concentration), and 25% PEG-300. Analysis time points for the IV arm were 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose and analysis time points for the PO arm were 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose. Pharmacokinetic parameters were obtained for both Compound 111 (prodrug) and ganaxolone (metabolite), with the expectation of observing the appearance of ganaxolone in the dog plasma following conversion of Compound 111 by metabolic processes.

[0387] The results are provided below in Tables 7 and 8, and in the plasma concentration-over-time curves provided as FIGS. 1A and 1B.

Table 7. Pharmacokinetic parameters for Compound 111 after IV (5 mg/kg) or oral (25 mg/kg) administration of Compound 111.

Compound 111 PK (after IV admin. of Compound 111)								
	t _{1/2} (hr)	C ₀ (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	V _z (L/kg)	V _{ss} (L/kg)	CL (mL/min/kg)	MRT _{inf} (hr)
Mean	3.54	1505	2743	2786	9.47	6.71	31.7	3.68
Compound 111 PK (after oral admin. of Compound 111)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	MRT _{inf} (hr)	AUC _{inf} /D (hr*kg*ng/ mL/mg)	F (%)
Mean	7.15	2.67	177	1566	1716	10.6	68.7	11.4

Table 8. Pharmacokinetic parameters for ganaxolone after IV (5 mg/kg) or oral (25 mg/kg) administration of Compound 111.

Ganaxolone PK (after IV admin. of Compound 111)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	C _{max} ratio (metabolite/prodrug)	AUC _{last} ratio (metabolite/prodrug)
Mean	13.7	0.0833	81.1	521	567	15.9	0.0599	0.201
Ganaxolone PK (after oral admin. of Compound 111)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	C _{max} ratio (metabolite/prodrug)	AUC _{last} ratio (metabolite/prodrug)
Mean	10.1	1.33	150	1724	1802	14.3	0.859	1.21

Example 124. Pharmacokinetic Study with Compound 224

[0388] A pharmacokinetic study was carried out using Compound 224, comparing intravenous (IV) administration (2 mg/kg; n=3) and oral (PO) administration (10 mg/kg; n=3) in fasted male beagle dogs. A single dose of Compound 224 was administered either orally or intravenously, with the compound formulated in the following vehicle: 1%DMA/1% of 10% Tween-20/25% of PEG400/73% of 30% kleptose. Analysis time points for the IV arm were 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose and analysis time points for the PO arm were 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose. Pharmacokinetic parameters were obtained for both Compound 224 (prodrug) and ganaxolone (metabolite), with the expectation of observing the appearance of ganaxolone in the dog plasma following conversion of Compound 224 by metabolic processes.

[0389] The results are provided below in Tables 9 and 10, and in the plasma concentration-over-time curves provided as FIGS. 2A, 2B, 3A, and 3B.

Table 9. Pharmacokinetic parameters for Compound 224 after IV (2 mg/kg) or oral (10 mg/kg) administration of Compound 224.

Compound 224 PK (after IV admin. of Compound 224)								
	t _{1/2} (hr)	C ₀ (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	V _z (L/kg)	V _{ss} (L/kg)	CL (mL/min/kg)	MRT _{Inf} (hr)
Mean	.0595	833	105	109	16.1	5.92	340	0.289
Compound 224 PK (after oral admin. of Compound 224)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	AUC _{Inf} /D (hr*kg*ng/ mL/mg)	F (%)
Mean	NA	0.5	38.3	19.3	NA	NA	NA	3.67

Table 10. Pharmacokinetic parameters for ganaxolone after IV (2 mg/kg) or oral (10 mg/kg) administration of Compound **224**.

Ganaxolone PK (after IV admin. of Compound 224)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/ mL)	AUC _{last} (hr*ng/ mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	C _{max} ratio (metabolite/prodrug)	AUC _{last} ratio (metabolite/ prodrug)
Mean	13.3	.0833	149	419	475	14.6	0.467	4.36
Ganaxolone PK (after oral admin. of Compound 224)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/ mL)	AUC _{last} (hr*ng/ mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	C _{max} ratio (metabolite/ prodrug)	AUC _{last} ratio (metabolite/ prodrug)
Mean	15.5	.0833	265	1761	1960	18.8	7.61	100

Example 125. Pharmacokinetic Study with Compound 218

[0390] A pharmacokinetic study was carried out using Compound **218**, comparing intravenous (IV) administration (5 mg/kg; n=3) and oral (PO) administration (25 mg/kg; n=3) in fasted male beagle dogs. A single dose of Compound **218** was administered either orally or intravenously, with the compound formulated in the following vehicle: 1%DMA/1% of 1% Tween-20/25% of PEG400/ 73% of 30% Captisol. Analysis time points for the IV arm were 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose and analysis time points for the PO arm were 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose. Pharmacokinetic parameters were obtained for both Compound **218** (prodrug) and ganaxolone (metabolite), with the expectation of observing the appearance of ganaxolone in the dog plasma following conversion of Compound **218** by metabolic processes.

[0391] The volume of distribution (V_d) (dose/Co) was 1.82 L/kg.

[0392] The results are provided below in Tables 11 and 12, and in the plasma concentration-over-time curves provided as FIGS. 4A and 4B.

Table 11. Pharmacokinetic parameters for Compound **218** after IV (5 mg/kg) or oral (25 mg/kg) administration of Compound **218**.

Compound 218 PK (after IV admin. of Compound 218)								
	t _{1/2} (hr)	C ₀ (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	V _z (L/kg)	V _{ss} (L/kg)	CL (mL/min/kg)	MRT _{Inf} (hr)
Mean	17.7	2754	2127	2204	57.5	11.4	37.9	5.03
Compound 218 PK (after oral admin. of Compound 218)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/mL)	AUC _{last} (hr*ng/mL)	AUC _{Inf} (hr*ng/mL)	MRT _{Inf} (hr)	F (%)	-
Mean	6.13	1.17	89.8	359	415	6.38	3.76	-

Table 12. Pharmacokinetic parameters for ganaxolone after IV (5 mg/kg) or oral (25 mg/kg) administration of Compound **218**.

Ganaxolone PK (after IV admin. of Compound 218)								
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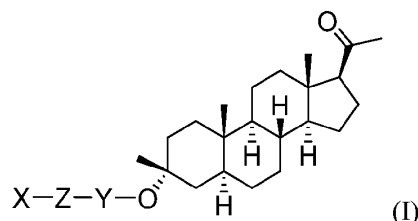
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/ mL)	AUC _{last} (hr*ng/ mL)	AUC _{inf} (hr*ng/mL)	MRT _{inf} (hr)	C _{max} ratio (metabolite/prodrug)	AUC _{last} ratio (metabolite/prodrug)
Mean	29.4	0.0833	507	1348	1715	27.8	0.23	0.633
Ganaxolone PK (after oral admin. of Compound 218)								
	t _{1/2} (hr)	T _{max} (hr)	C _{max} (ng/ mL)	AUC _{last} (hr*ng/ mL)	AUC _{inf} (hr*ng/mL)	MRT _{inf} (hr)	C _{max} ratio (metabolite/prodrug)	AUC _{last} ratio (metabolite/prodrug)
Mean	17.6	1	441	3839	4397	20.1	5.58	10.8

Example 126. Pharmacokinetic Study with Compound 242

[0393] A pharmacokinetic study will be carried out using Compound **242**, comparing intravenous (IV) administration (3 mg/kg; n=3) and intramuscular (IM) administration (2.5 mg/kg; n= 3) in fasted male beagle dogs. A single dose of Compound **242** will be administered either intramuscular or intravenously, with the compound formulated in the following vehicle: 2% DMA, 1% of 1% tween, 32% of PEG400, 65% of 8% captisol. Analysis time points for the IV and IM arms will be 0.083, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 and 48 hours post dose. Pharmacokinetic parameters will be obtained for both Compound **242** (prodrug) and ganaxolone (metabolite), with the expectation of observing the appearance of ganaxolone in the dog plasma following conversion of Compound **242** by metabolic processes.

What is claimed is:

1. A compound of Formula (I):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

Y is $-\text{C}(\text{O})-$ or $-\text{C}(\text{R}^{\text{A}})(\text{R}^{\text{B}})-$ (e.g., $-\text{CH}_2-$);

Z is absent, alkylene, alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, heteroarylene, $-\text{NR}^1-$, $-\text{O}-$, or $-\text{S}-$, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

X is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, heterocyclylene-heteroalkyl, $-\text{OC}(\text{O})$ -alkyl, $-\text{C}(\text{O})\text{O}$ -alkyl, $-\text{OC}(\text{O})$ -heteroalkyl, $-\text{C}(\text{O})\text{O}$ -heteroalkyl, $-\text{N}_3$, $-\text{NR}^1\text{R}^2$, $-\text{OR}^3$, or $-\text{SR}^4$, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^1 and R^2 are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

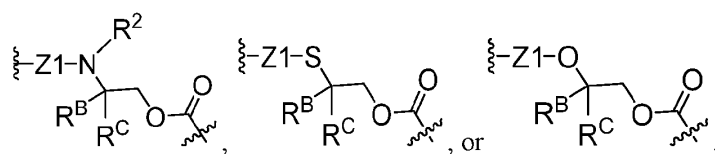
R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

2. The compound of claim 1, wherein Y is $-C(O)-$.

3. The compound of claim 1 or 2, wherein Z is methylene (e.g., unsubstituted methylene),



wherein

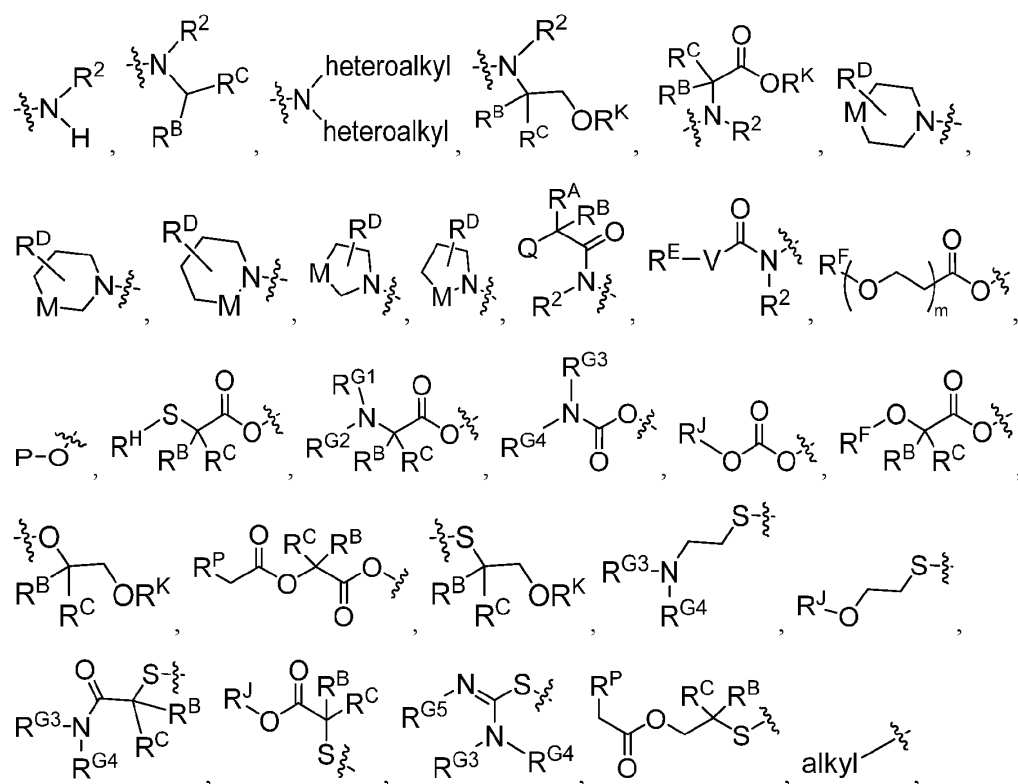
Z1 is absent, alkylene (e.g., methylene, e.g., unsubstituted methylene), alkenylene, alkynylene, heteroalkylene, cycloalkylene, heterocyclylene, arylene, or heteroarylene, wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

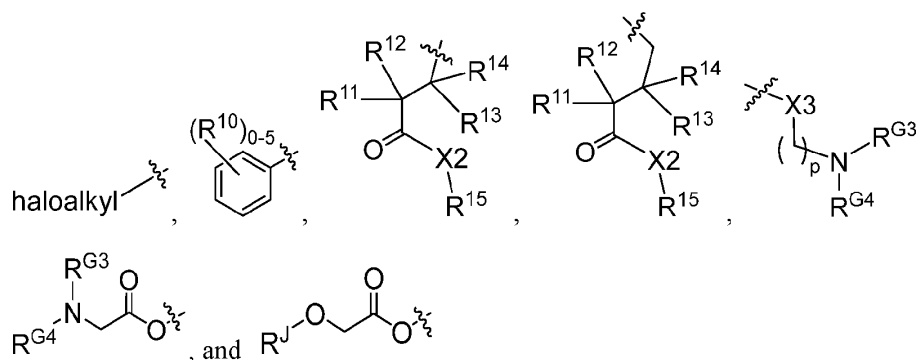
R^2 is hydrogen or alkyl;

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

each ζ denotes the point of attachment of Z to X or Y .

4. The compound of any one of the preceding claims, wherein X is a moiety selected from the group consisting of





wherein

R^2 is hydrogen or alkyl;

M is $-C(H)(R^D)-$ (e.g., $-CH_2-$), $-O-$, or $-N(R^D)-$ (e.g., $-N(Me)-$);

P is an amino acid residue (e.g., glycine, alanine, valine, leucine, or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

Q is heteroalkyl or heterocyclyl, wherein the heteroalkyl or heterocyclyl is optionally substituted;

V is $-O-$, $-N(H)-$, or $-N(Me)-$;

X_2 and X_3 are each independently $-CH_2-$, $-O-$, $-S-$, or $-N(R^{G3})-$ (e.g., $-NH-$);

R^A , R^B , R^C , R^D , R^E , and R^K are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

R^P is halo, $-NH$ -alkyl, $-NH$ -heteroalkyl, $-N$ -(alkyl)₂ (e.g., $-N(Me)_2$), $-N$ -(heteroalkyl)₂ (e.g., $-N(CH_2CH_2OH)_2$), or heterocyclyl (e.g., morpholinyl);

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$, $-NO_2$, $-CN$, or $-NC$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-N(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

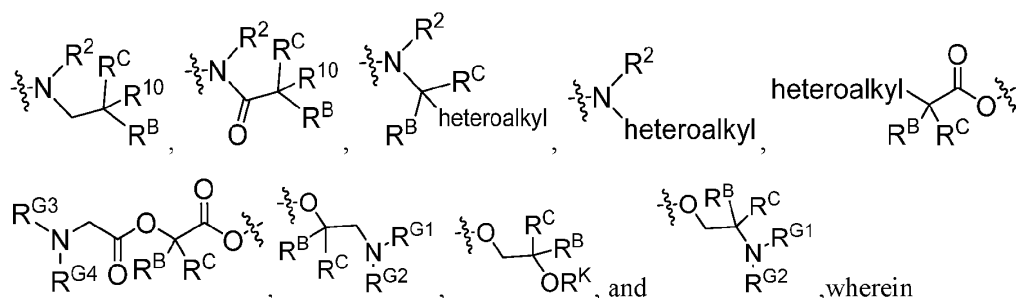
R^{15} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted; and

m is an integer of 1-5;

p is an integer between 0 and 4; and

$\{$ denotes the point of attachment of X to Z , or X to Y when Z is absent.

5. The compound of any one of the preceding claims, wherein X is a moiety selected from the group consisting of



R^B , R^C , and R^K are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

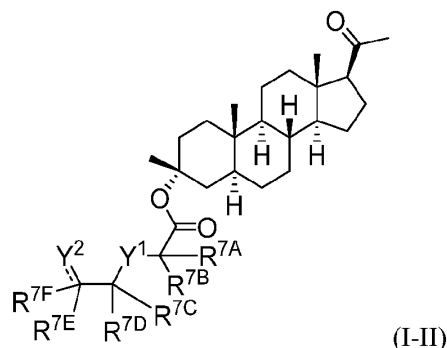
R^2 is hydrogen or alkyl; and

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$, $-NO_2$, $-CN$, or $-NC$.

6. The compound of any one of the preceding claims, wherein Y is $-C(O)-$ and Z is alkylene (e.g., methylene).

7. The compound of any one of the preceding claims, wherein R^1 and R^2 are not both hydrogen.

8. A compound of Formula (I-II):



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein:

$\text{--}\text{Y}\text{--}$ denotes a single bond or a double bond;

Y¹ is alkylene (e.g., methylene), alkenylene, alkynylene, heteroalkylene, --C(O)-- , --OC(O)-- , --C(O)O-- , $\text{--NR}^1\text{--}$, --O-- , or --S-- , wherein the alkylene, alkenylene, alkynylene, or heteroalkylene is optionally substituted;

Y² is heteroalkyl, heterocyclyl, heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, $\text{--NR}^1\text{R}^2$, --OR^3 , --SR^4 , =NR^1 , or =O , wherein the heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R¹ and R² are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R¹ and R², together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R³ is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-

heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

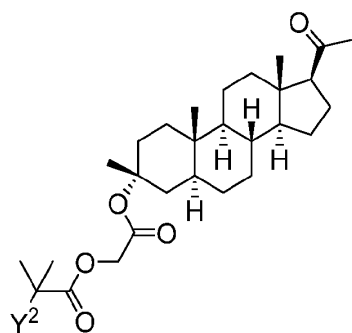
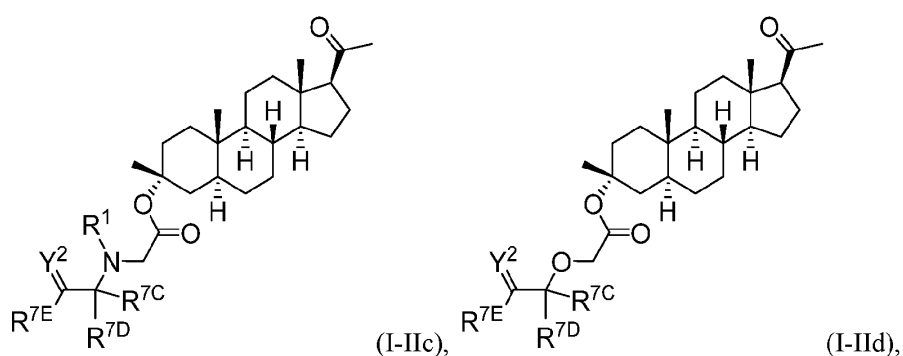
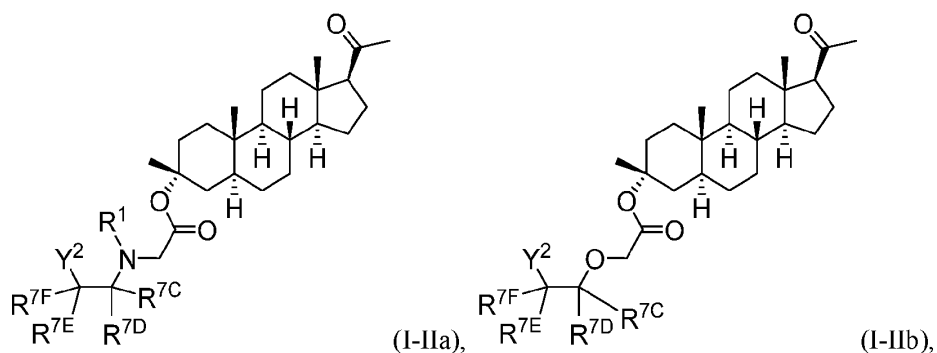
R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl, or one of R^{7A} and R^{7B} is bonded to Y^1 through one or more carbon atoms or heteroatoms to form a cyclic moiety (e.g., cycloalkyl, heterocyclyl, aryl, or heteroaryl, e.g., pyrrole), and the other of the R^{7A} and R^{7B} groups is hydrogen or optionally substituted alkyl;

R^{7C} and R^{7D} are each independently hydrogen or optionally substituted alkyl, or R^{7C} and R^{7D} are each bonded to the same oxygen atom to form an oxo group; and R^{7E} and R^{7F} are each independently absent, hydrogen, alkyl, heteroalkyl, $-NR^1R^2$, $-OR^3$, or $-SR^4$, wherein the alkyl or heteroalkyl is optionally substituted, or R^{7E} and R^{7F} are each bonded to the same oxygen to form an oxo group, with the proviso that when  is a double bond, one of R^{7E} and R^{7F} is absent.

9. The compound of claim 8, wherein Y^1 is $-O-$ or $-N(R^1)-$ (e.g., $-N(H)-$, $-N(alkyl)-$, or $-N(heteroalkyl)-$).

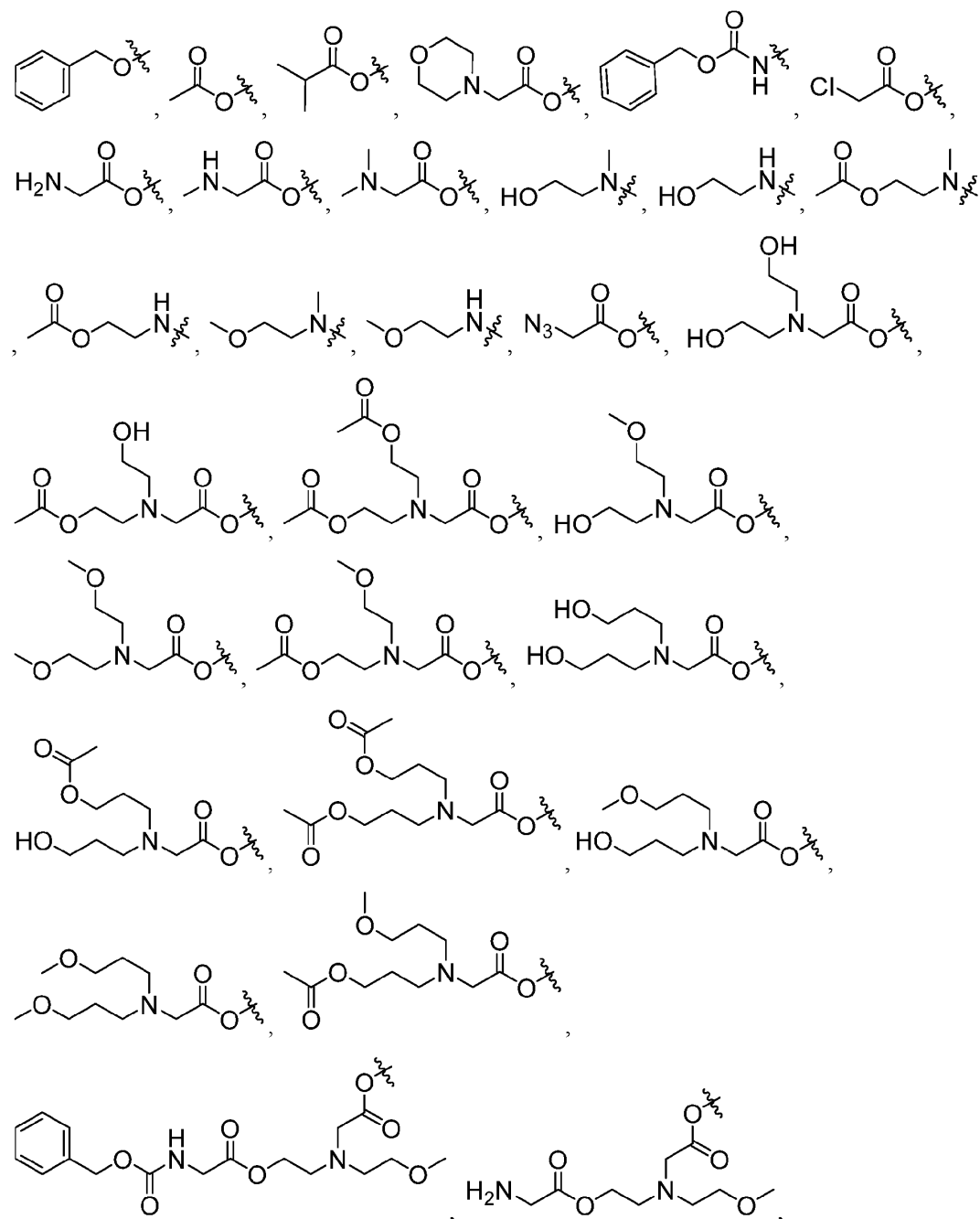
10. The compound of claim 8 or 9, selected from the group consisting of:



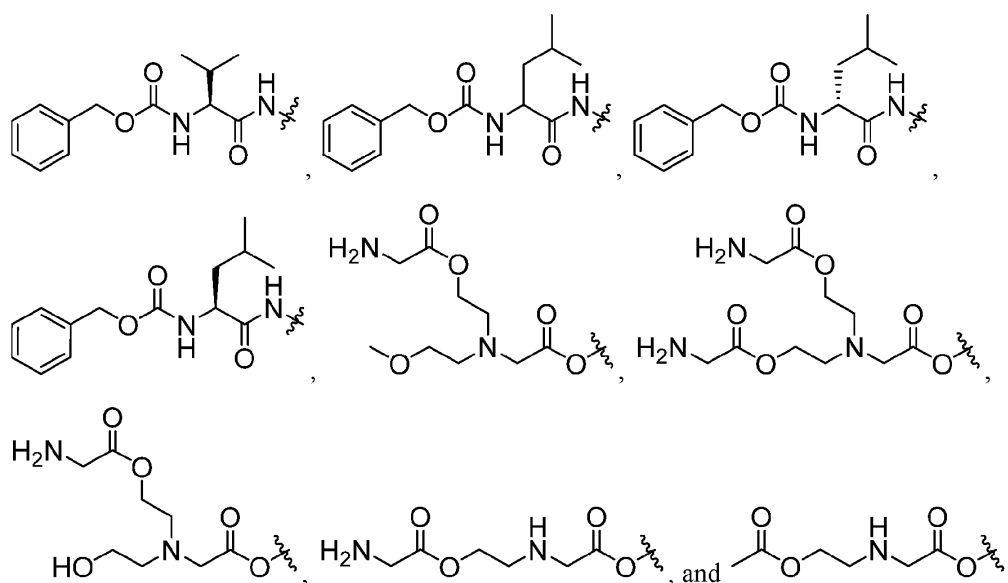
and pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomer thereof, wherein Y^2 , R^1 , R^{7C} , R^{7D} , R^{7E} , and R^{7F} are as defined in claim 8.

11. The compound of any one of claims 8-10, wherein Y^2 , or R^{7E} when $\text{\\textbackslash\\textbackslash}$ is a double bond, is optionally substituted heteroalkyl, $-\text{NR}^1\text{R}^2$ (e.g., $-\text{NH}_2$, $-\text{NHMe}$, or $-\text{NMe}_2$), $-\text{OR}^3$ (e.g., $-\text{OH}$, $-\text{OMe}$, $-\text{OEt}$, or $-\text{OBu}$), or $=\text{O}$, wherein R^1 , R^2 , and R^3 are as defined in claim 8.

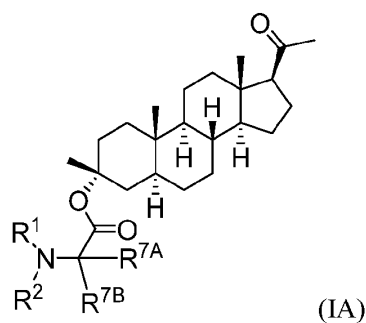
12. The compound of any one of claims 8-11, wherein Y², or R^{7E} when  is a double bond, is selected from the group consisting of:







13. A compound of Formula (IA)



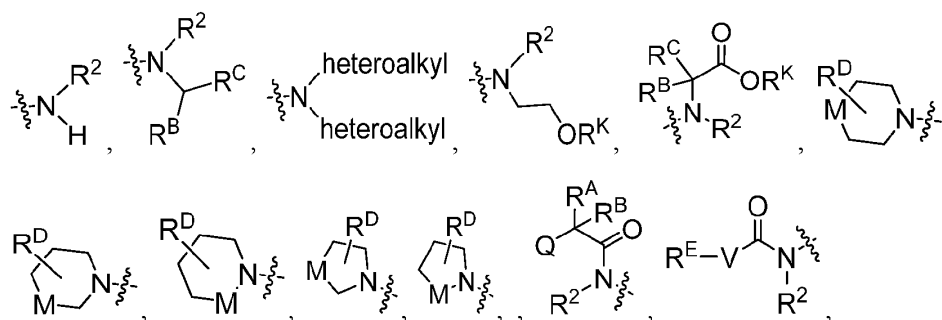
or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R¹ and R² are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted;

or R^1 and R^2 , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

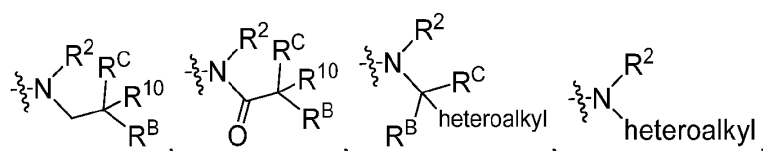
R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

14. The compound of claim 13, wherein the $-N(R^1)(R^2)$ group is a moiety selected from the group consisting of



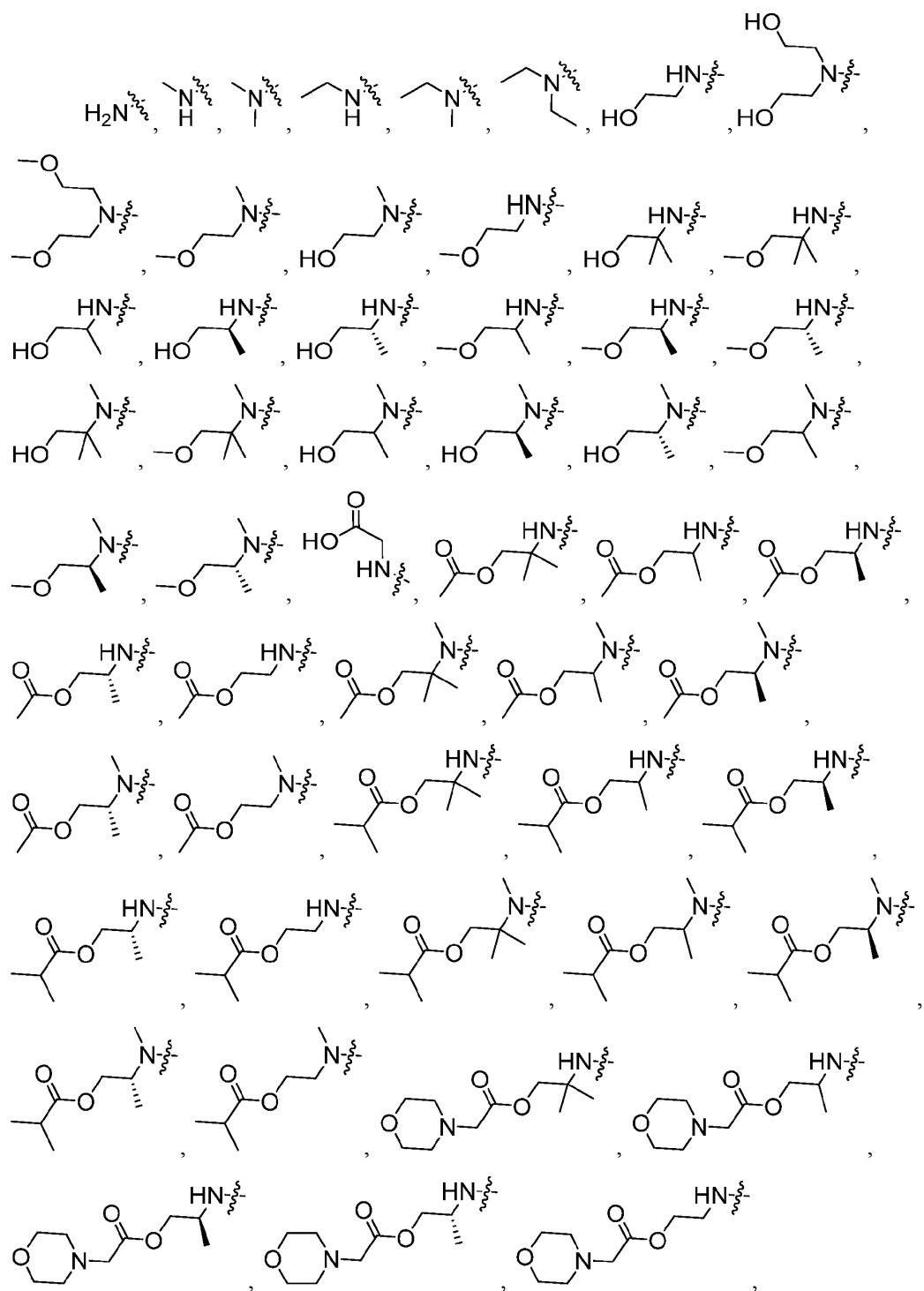
wherein R^2 , M, Q, V, R^A , R^B , R^C , R^D , R^E and R^K are as described in claim 1, and $\sim$ denotes the point of attachment of the nitrogen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group.

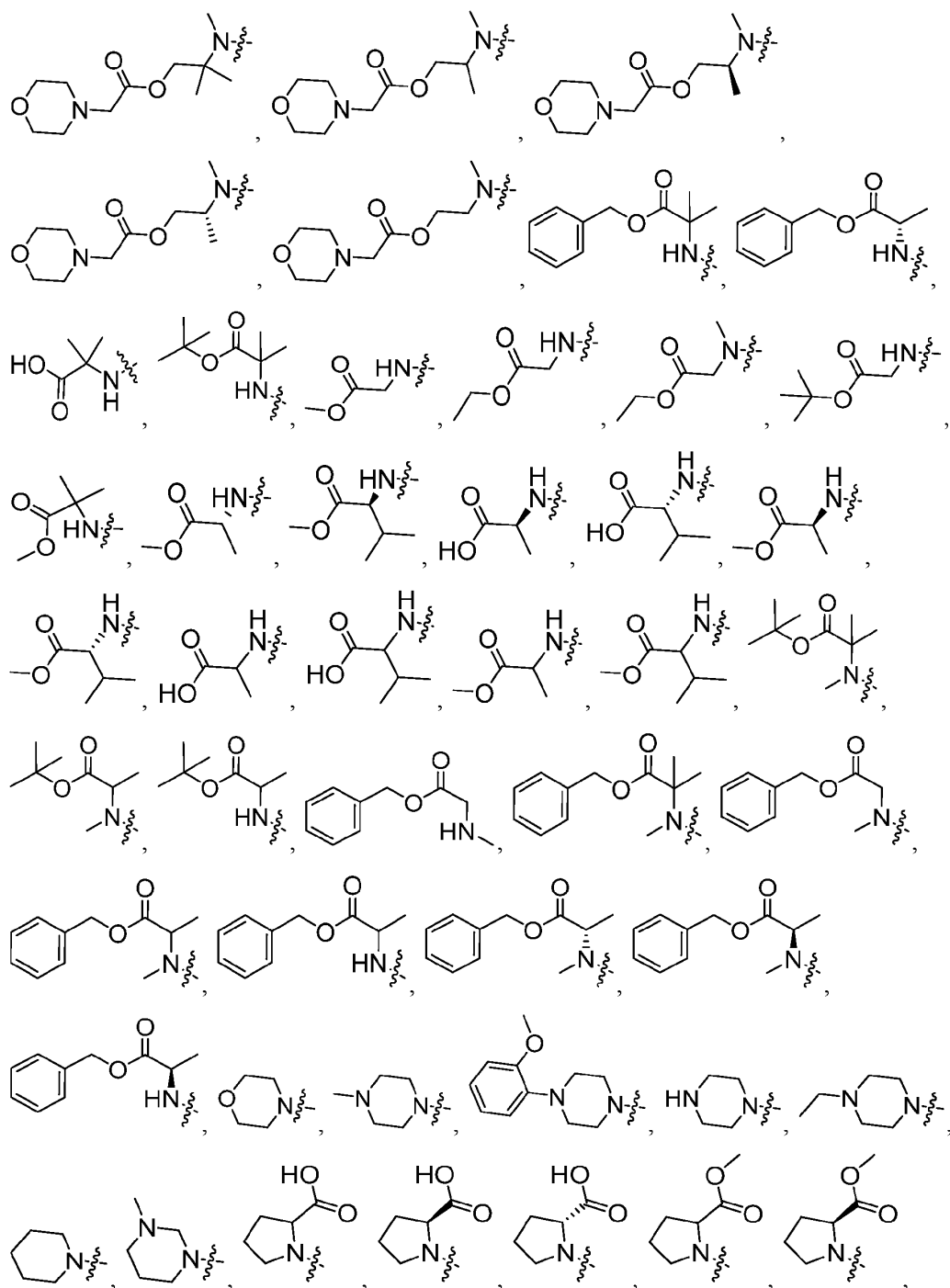
15. The compound of claim 13, wherein the $-N(R^1)(R^2)$ group is a moiety selected from the group consisting of

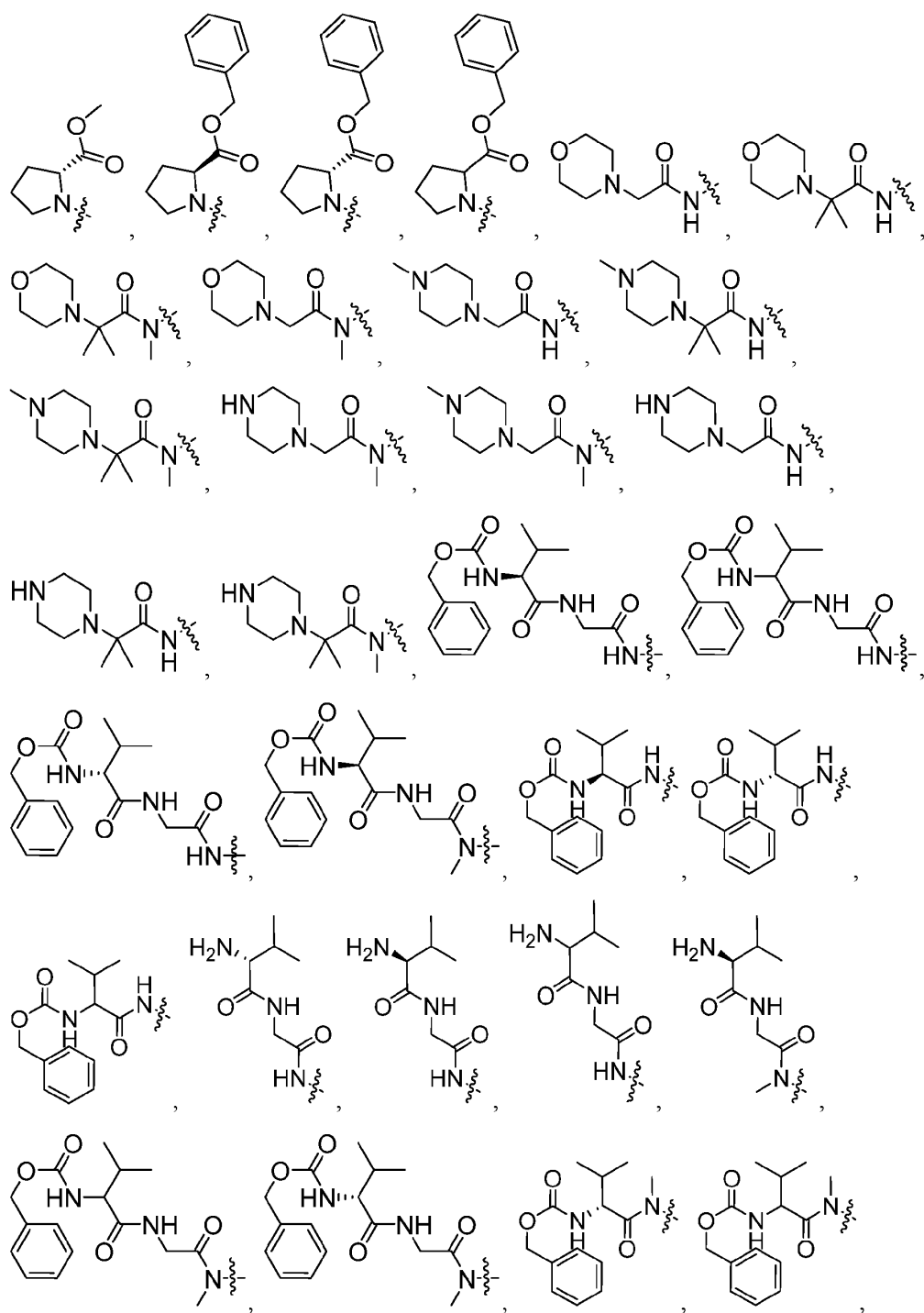


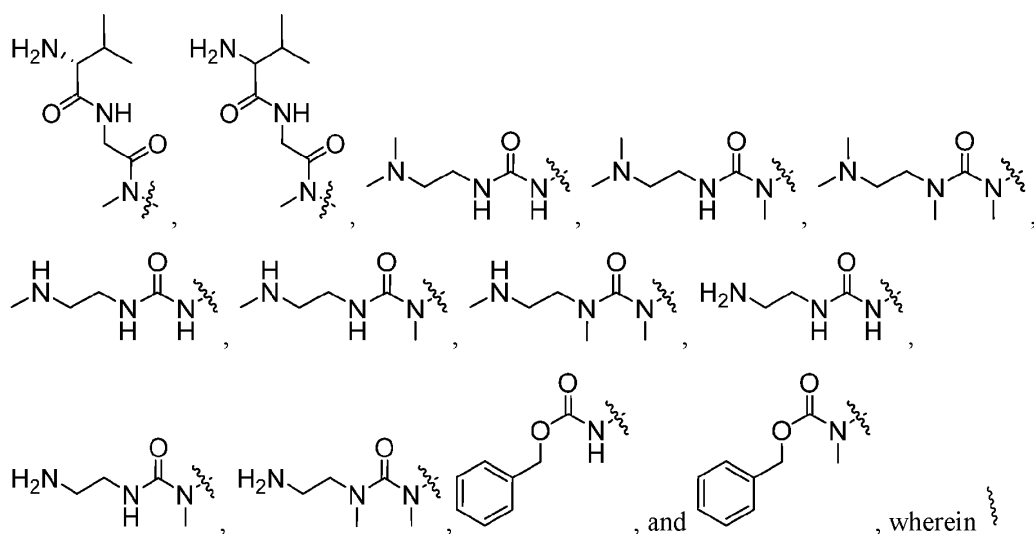
wherein R^2 , R^{10} , R^B , R^C , R^D , R^E and R^K are as described in claim 1, and $\sim$ denotes the point of attachment of the nitrogen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group.

16. The compound of any one of claims 1-6 or 13-15, wherein the X group of Formula (I), or the $-N(R^1)(R^2)$ group of Formula (IA), is a moiety selected from the group consisting of



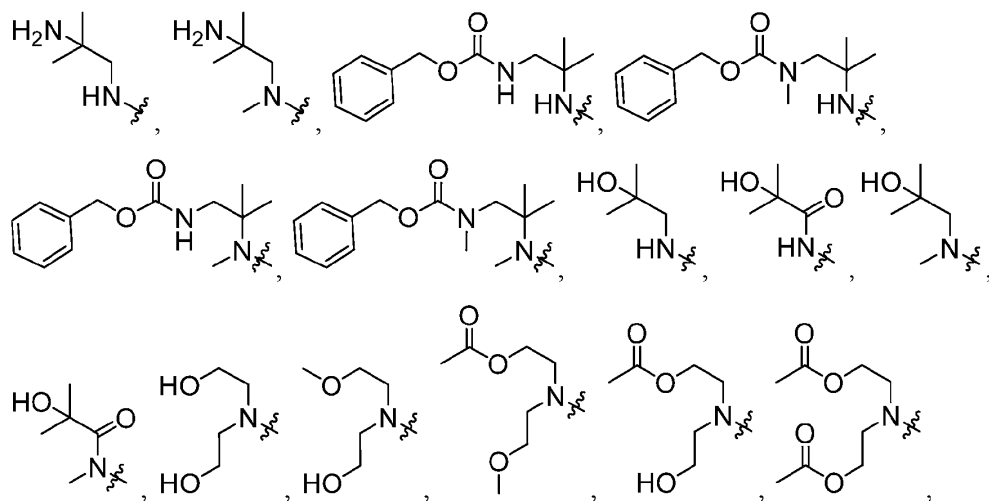


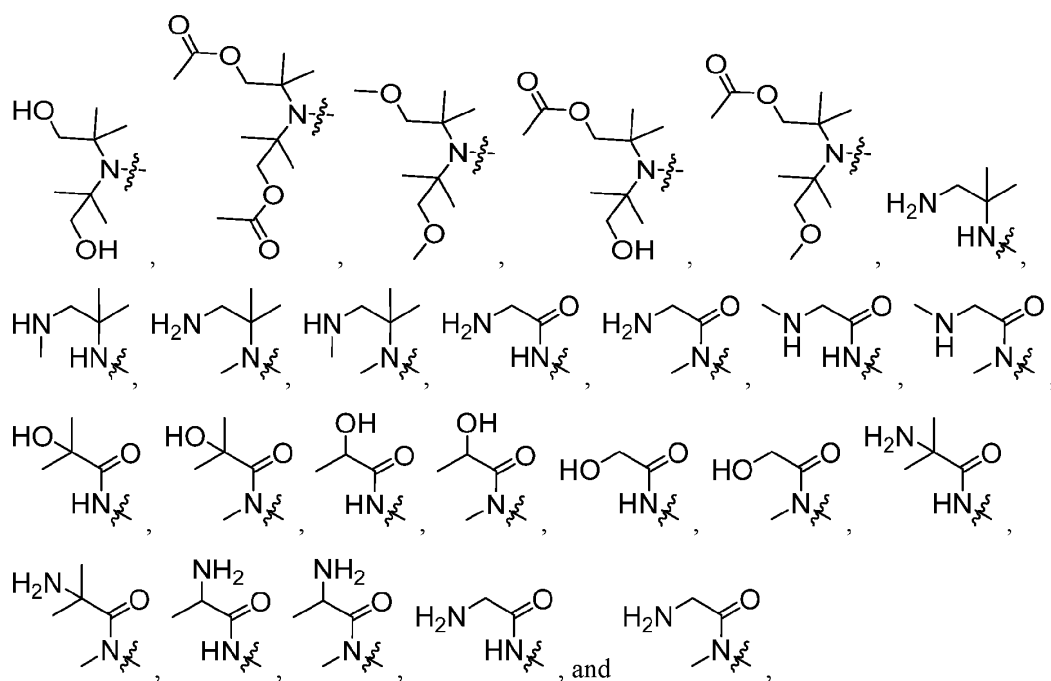




denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the nitrogen atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (IA).

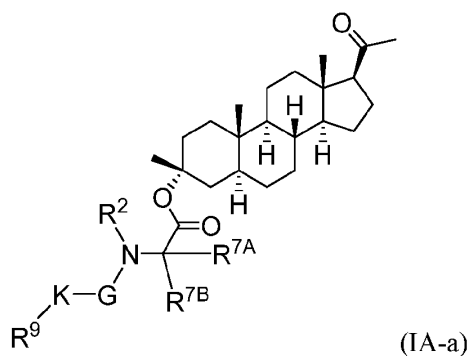
17. The compound of any one of claims 1-6 or 13-15, wherein the X group of Formula (I), or the $-N(R^1)(R^2)$ group of Formula (IA), is a moiety selected from the group consisting of





wherein $\overset{?}{\text{Z}}$ denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the nitrogen atom to the carbon atom of the $-\text{C}(\text{R}^{7\text{A}})(\text{R}^{7\text{B}})$ group in Formula (IA).

18. A compound of any one of the preceding claims, wherein the compound is a compound of Formula (IA-a)



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

G is absent, $-\text{C}(\text{O})-$, or $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$ (e.g., $-\text{CH}_2-$),

K is alkylene, heteroalkylene, $-\text{C}(\text{O})-$, $-\text{OC}(\text{O})-$, $-\text{C}(\text{O})\text{O}-$, $-\text{O}-$, $-\text{O}-(\text{CH}_2)-$, or $-(\text{CH}_2)-\text{O}-$, wherein the alkylene or heteroalkylene is optionally substituted;

R^2 , $\text{R}^{7\text{A}}$, $\text{R}^{7\text{B}}$, $\text{R}^{8\text{A}}$, and $\text{R}^{8\text{B}}$ are each independently hydrogen or optionally substituted alkyl; and

R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

19. The compound of claim 18, wherein

G is $-\text{C}(\text{R}^{8\text{A}})(\text{R}^{8\text{B}})-$;

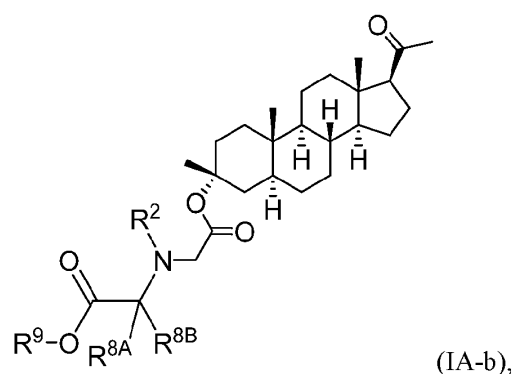
K is $-\text{OC}(\text{O})-$;

R^2 , $\text{R}^{7\text{A}}$, $\text{R}^{7\text{B}}$, and R^9 are each hydrogen; and

$\text{R}^{8\text{A}}$ and $\text{R}^{8\text{B}}$ are each independently hydrogen or alkyl (e.g., methyl),

wherein the carbon atom of the carbonyl group in $-\text{OC}(\text{O})-$ is bonded to G.

20. The compound of any one of the preceding claims, wherein the compound is a compound of Formula (IA-b)



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^2 , $\text{R}^{8\text{A}}$, and $\text{R}^{8\text{B}}$ are each independently hydrogen or optionally substituted alkyl; and

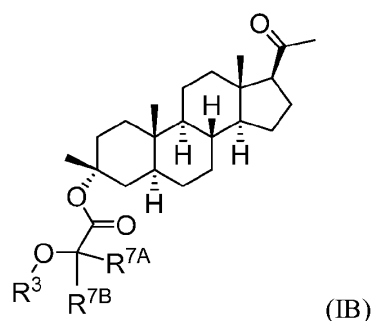
R^9 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

21. The compound of any one of claims 18-20, wherein

R^2 is hydrogen; and

R^{8A} and R^{8B} are each independently methyl.

22. A compound of Formula (IB):

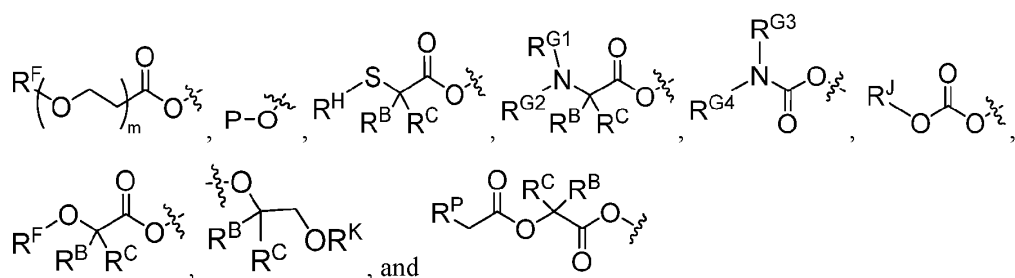


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^3 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

23. The compound of claim 22, wherein the $-O-(R^3)$ group is a moiety selected from the group consisting of



wherein

P is an amino acid residue (e.g., glycine, alanine, valine, leucine, or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or P is a dipeptide moiety (e.g., a leucine-leucine moiety) that may comprise D-amino acids, L-amino acids, or a combination thereof, and is optionally substituted (e.g., at one or more nitrogen atoms, e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group);

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^F and R^H are each independently hydrogen or alkyl;

R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

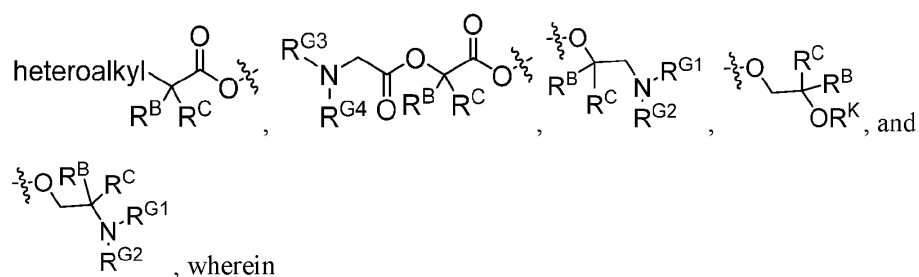
R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^P is halo, $-\text{NH-alkyl}$, $-\text{NH-heteroalkyl}$, $-\text{N-(alkyl)}_2$ (e.g., $-\text{N(Me)}_2$), $-\text{N-(heteroalkyl)}_2$ (e.g., $-\text{N(CH}_2\text{CH}_2\text{OH)}_2$), or heterocyclyl (e.g., morpholinyl);

m is an integer of 1-5; and

$\sim$ denotes the point of attachment of the oxygen atom to the carbon atom of the $-\text{C(R}^{7A}\text{)(R}^{7B}\text{)}$ group.

24. The compound of claim 22, wherein the $-\text{O-(R}^3\text{)}$ group is a moiety selected from the group consisting of



R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

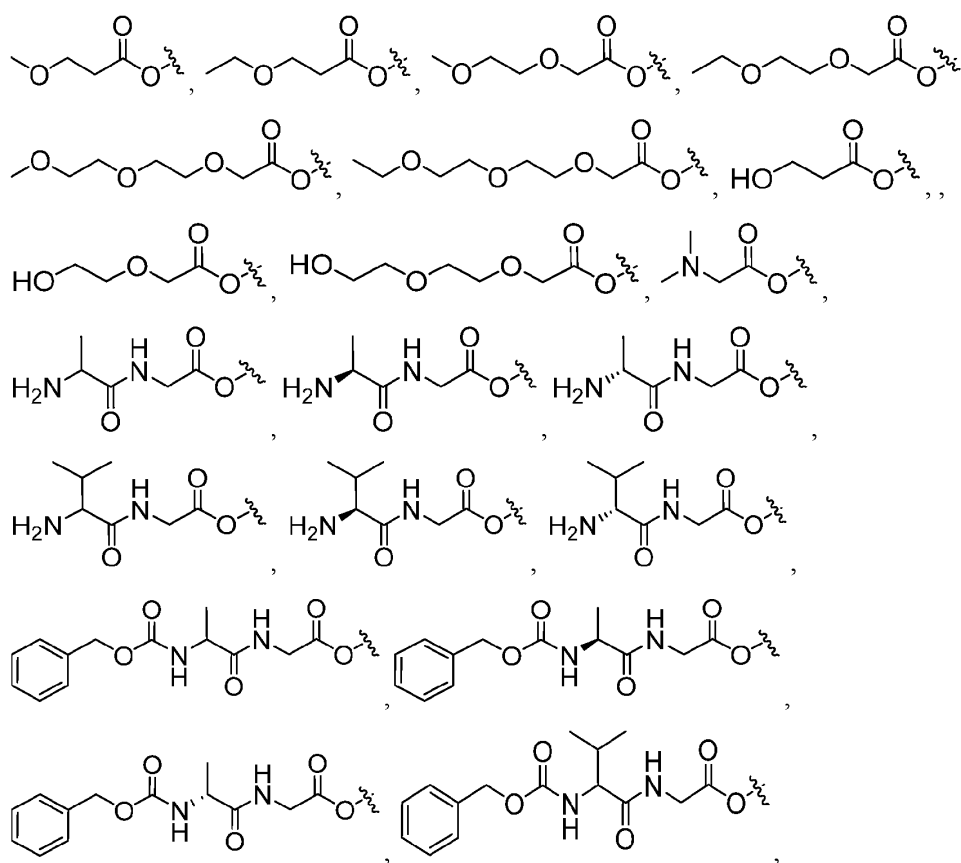
R^{G1} and R^{G2} are each independently hydrogen, alkyl, or an amino acid residue (e.g., glycine, alanine, valine, leucine or proline), that may be a D-amino acid residue or L-amino acid residue, and is optionally substituted (e.g., at a terminal nitrogen atom, e.g., by a carbonate group, e.g., a carboxybenzyl (Cbz) group),

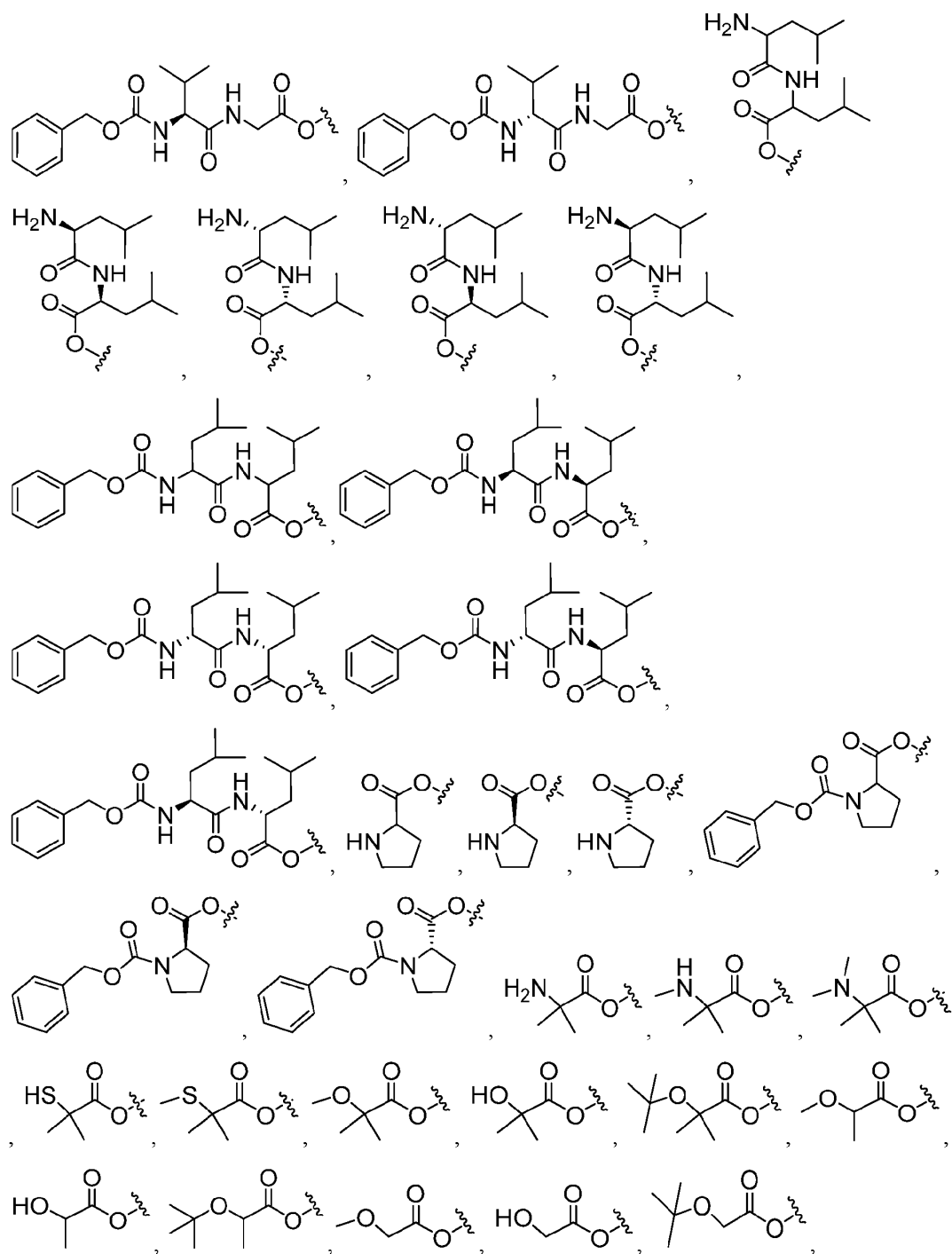
or R^{G1} and R^{G2} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

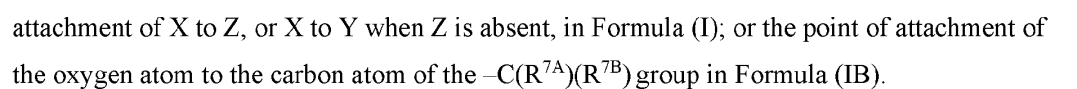
R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

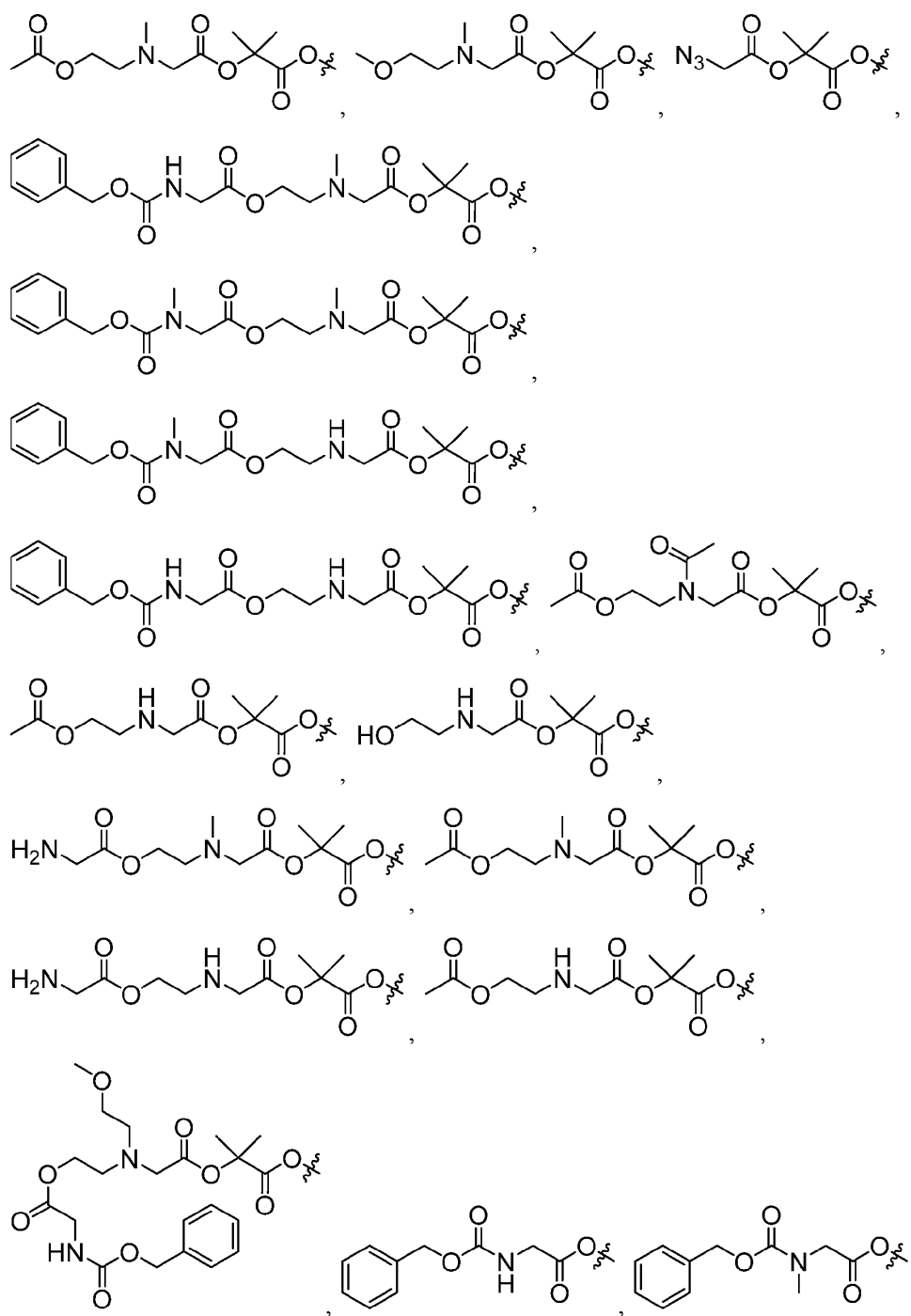
or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

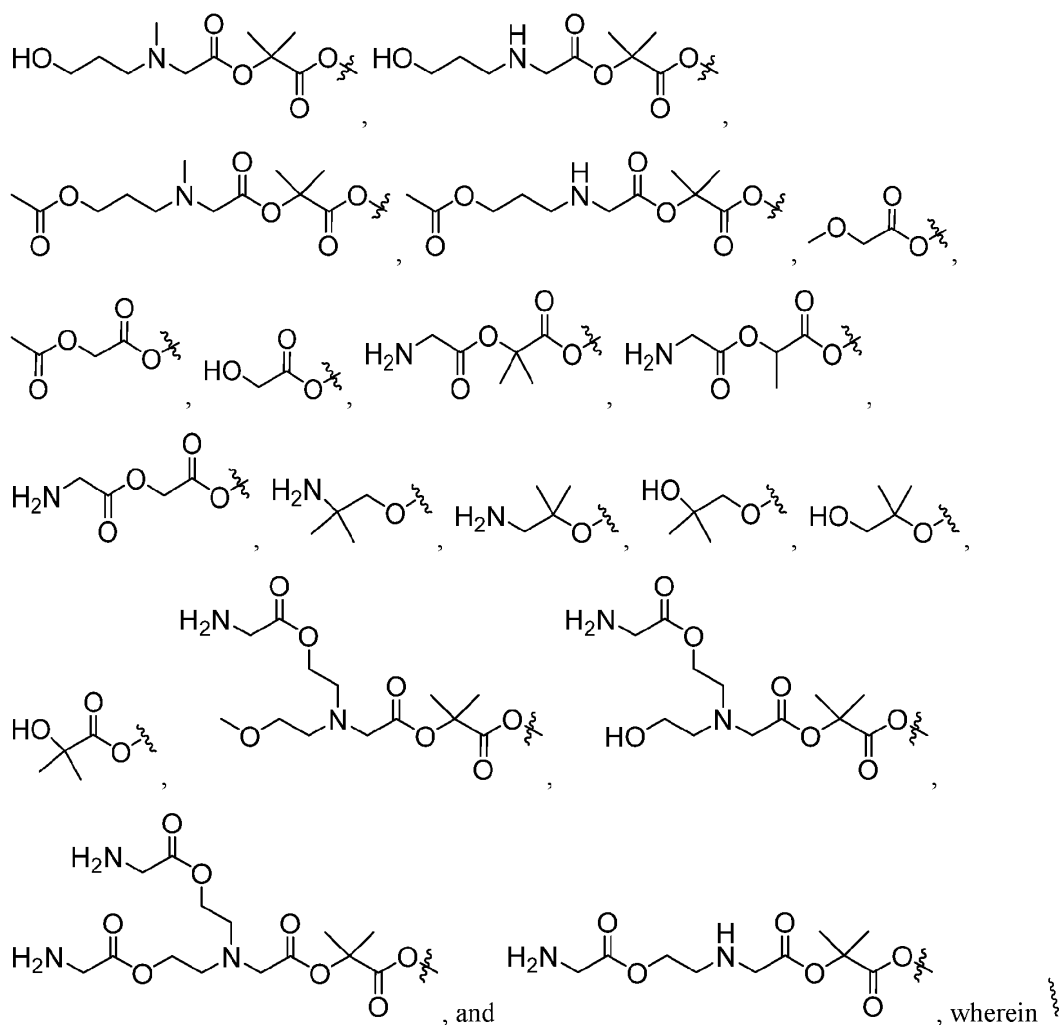
25. The compound of any one of claims claim 1, 2, or 22-24, wherein the X group of Formula (I), or the $-O-R^3$ group of Formula (IB), is a moiety selected from the group consisting of





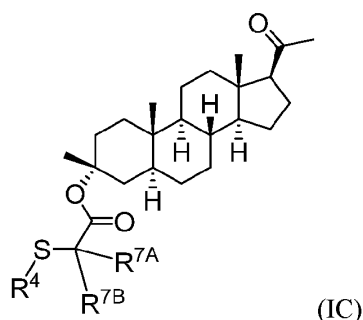






denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the oxygen atom to the carbon atom of the $-\text{C}(\text{R}^{7\text{A}})(\text{R}^{7\text{B}})$ group in Formula (IB).

27. A compound of Formula (IC)

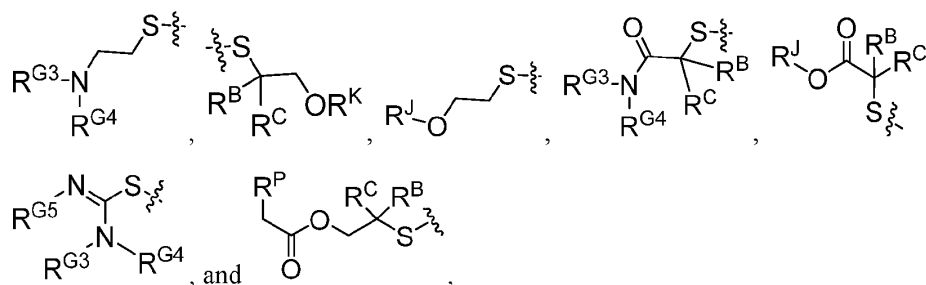


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^4 is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, or heteroalkylene-heteroaryl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted; and

R^{7A} and R^{7B} are each independently hydrogen or optionally substituted alkyl.

28. The compound of claim 27, wherein the $-S-(R^4)$ group is a moiety selected from the group consisting of



wherein

R^B and R^C are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{G5} is hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

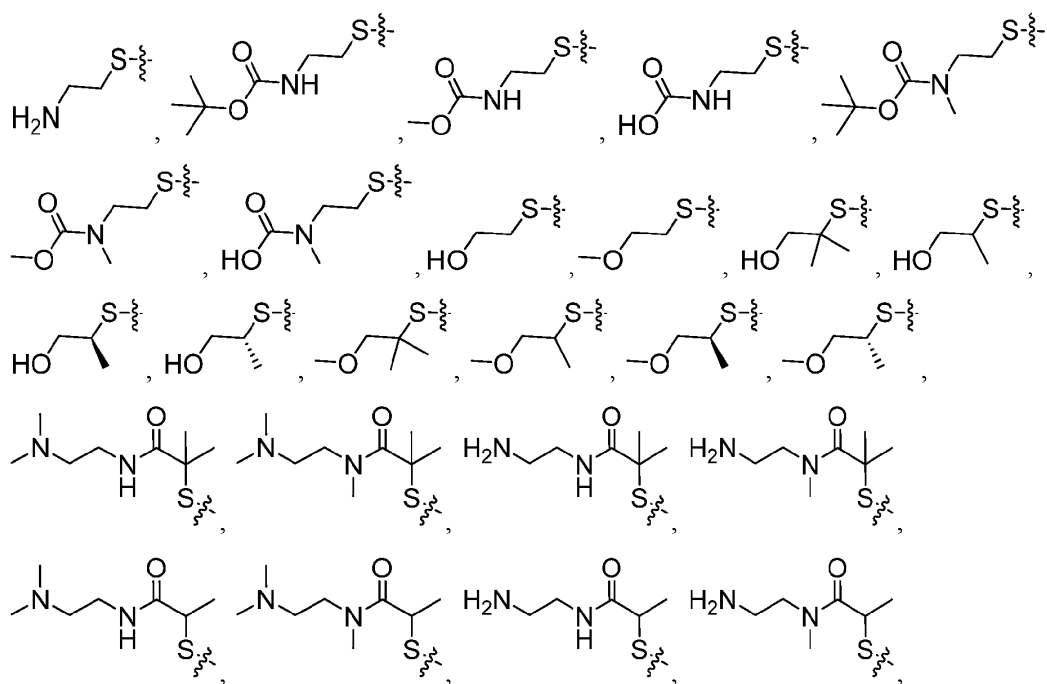
R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

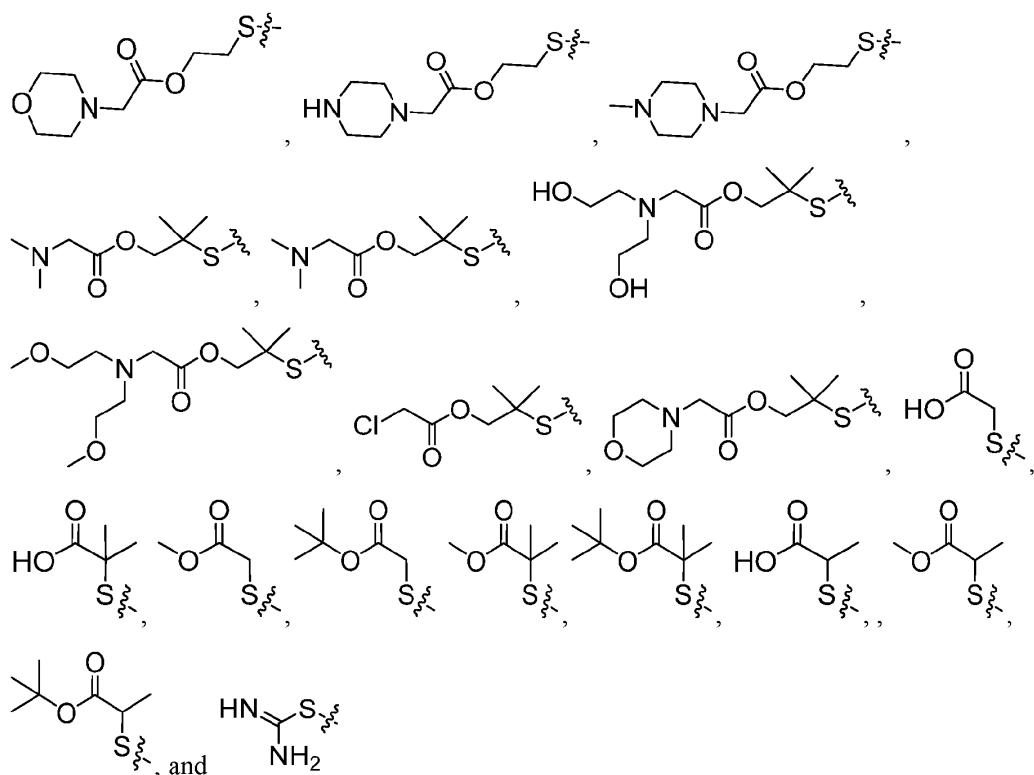
R^K is hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^P is halo, $-\text{NH-alkyl}$, $-\text{NH-heteroalkyl}$, $-\text{N-(alkyl)}_2$ (e.g., $-\text{N(Me)}_2$), $-\text{N-(heteroalkyl)}_2$ (e.g., $-\text{N(CH}_2\text{CH}_2\text{OH)}_2$), or heterocyclyl (e.g., morpholinyl); and

$\sim$ denotes the point of attachment of the sulfur atom to the carbon atom of the $-\text{C(R}^{7A}\text{)(R}^{7B}\text{)}$ group.

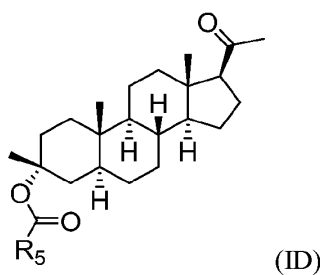
29. The compound of any one of claims 1, 2, 27 or 28, wherein the X group of Formula (I), or the $-\text{S-R}^4$ group of Formula (IC), is a moiety selected from the group consisting of





wherein $\sim$ denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the sulfur atom to the carbon atom of the $-C(R^{7A})(R^{7B})$ group in Formula (IC).

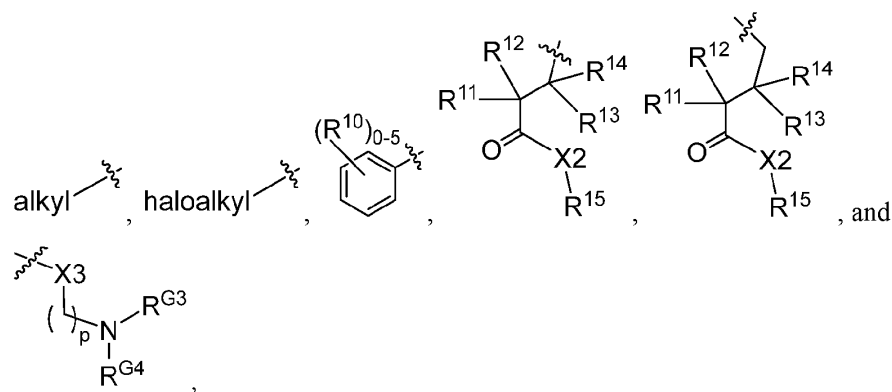
30. A compound of Formula (ID)



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof,
wherein

R^5 is alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, cycloalkylene-alkyl, cycloalkylene-heteroalkyl, heterocyclylene-alkyl, or heterocyclylene-heteroalkyl, wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, cycloalkylene, heterocyclyl, heterocyclylene, aryl, or heteroaryl is optionally substituted.

31. The compound of claim 30, wherein R^5 comprises a moiety selected from group consisting of



wherein

X_2 and X_3 are each independently $-CH_2-$, $-O-$, $-S-$, or $-N(R^{G3})-$ (e.g., $-NH-$);

R^{10} is alkyl, alkenyl, alkynyl, haloalkyl, halo, $-OR^J$, $-N(R^{G3})(R^{G4})$, $-NO_2$, $-CN$, or $-NC$;

R^{11} , R^{12} , R^{13} , and R^{14} are each independently hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, halo, or $-N(R^{G3})(R^{G4})$, wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted,

or one of R^{11} and R^{12} , and one of R^{13} and R^{14} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^{15} is hydrogen, alkyl, alkenyl, alkynyl, heteroalkyl, haloalkyl, or halo; wherein the alkyl, alkenyl, alkynyl, heteroalkyl, or haloalkyl is optionally substituted;

R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

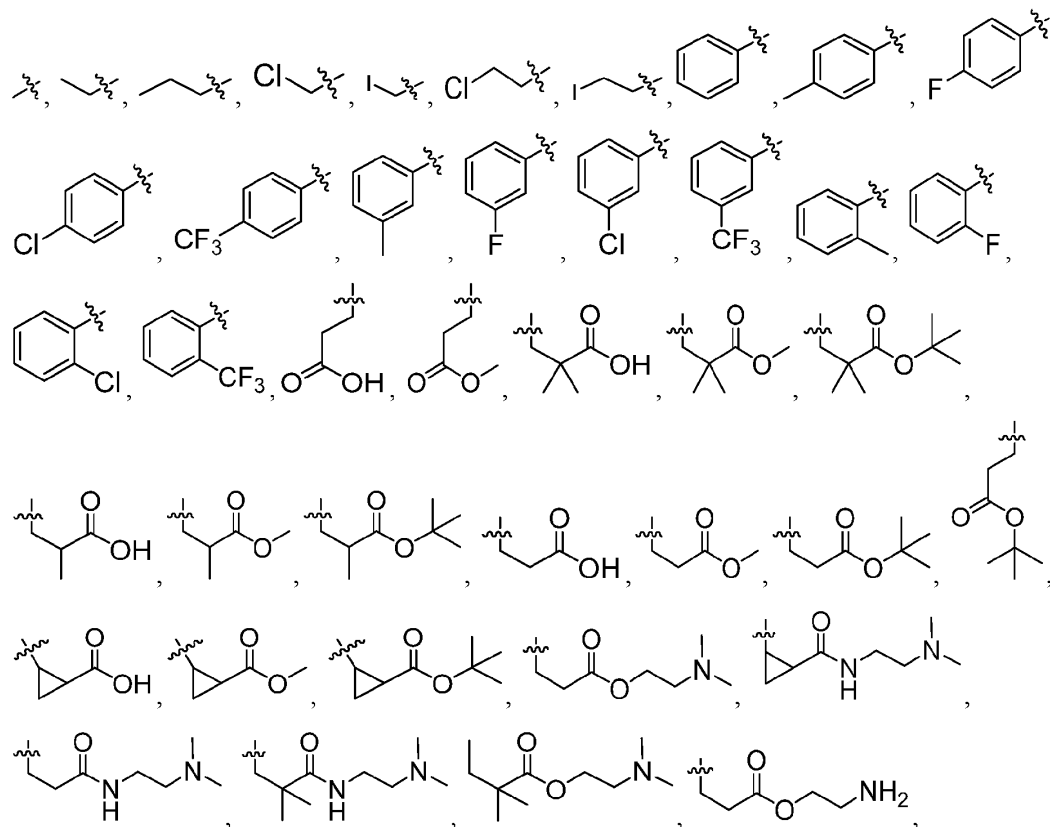
R^I is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

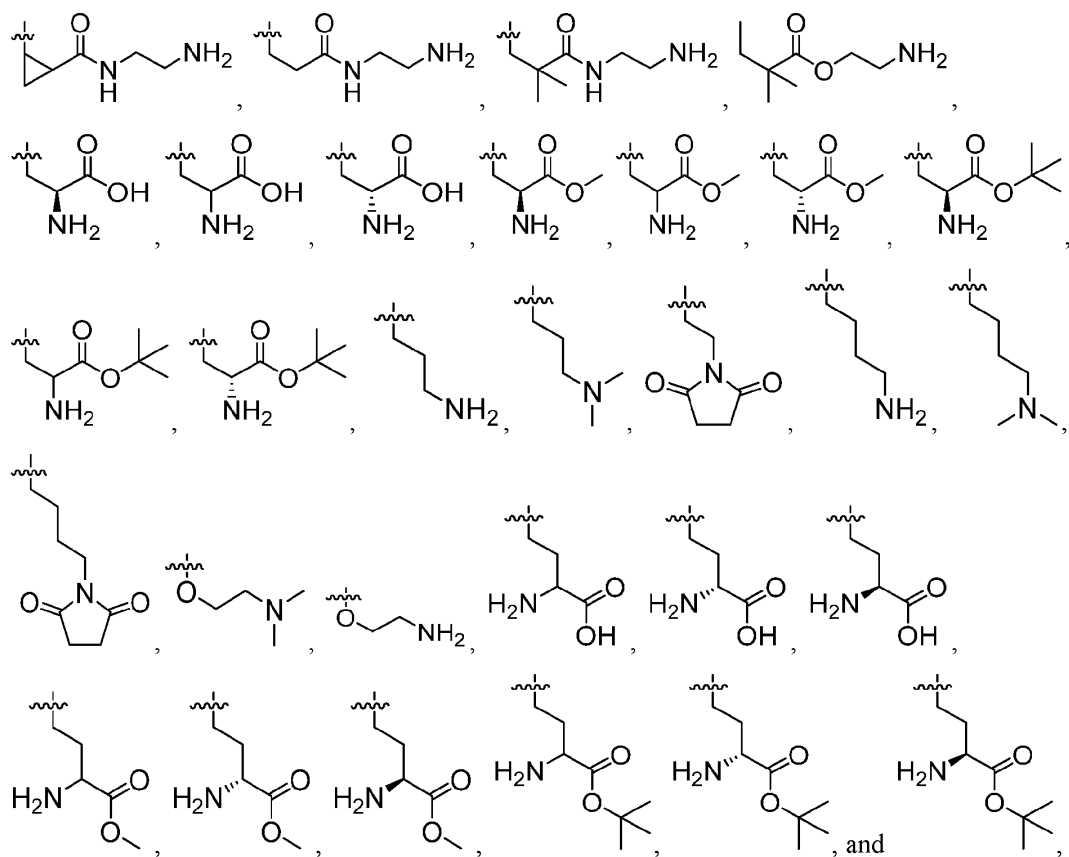
and

p is an integer between 0 and 4; and

~ denotes the point of attachment of the R^5 group to the carbon atom of the $-C(O)-$ group.

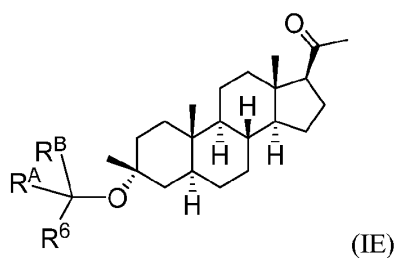
32. The compound of any one of claims 1, 2, 30, or 31, wherein the X group of Formula (I), or the R^5 group of Formula (ID), is a moiety selected from the group consisting of





wherein  denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the R⁵ group to the carbon atom of the –C(O)– group in Formula (ID).

33. A compound of Formula (IE)

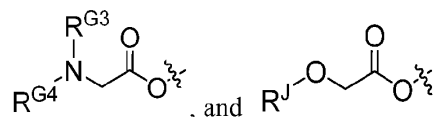


or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof, wherein

R^6 is alkyl, alkenyl, alkynyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, heteroaryl, haloalkyl, alkylene-cycloalkyl, alkylene-heterocyclyl, alkylene-aryl, alkylene-heteroaryl, heteroalkylene-cycloalkyl, heteroalkylene-heterocyclyl, heteroalkylene-aryl, heteroalkylene-heteroaryl, $-OC(O)$ -alkyl, $-C(O)O$ -alkyl, $-OC(O)$ -heteroalkyl, $-C(O)O$ -heteroalkyl, $-N_3$, $-SH$, or $-S$ -alkyl (e.g., $-S$ -Me), wherein the alkyl, alkylene, alkenyl, alkynyl, heteroalkyl, heteroalkylene, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted; and

R^A and R^B are each independently hydrogen, alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the alkyl, heteroalkyl, cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted.

34. The compound of claim 33, wherein R^6 is a moiety selected from the group consisting of



wherein

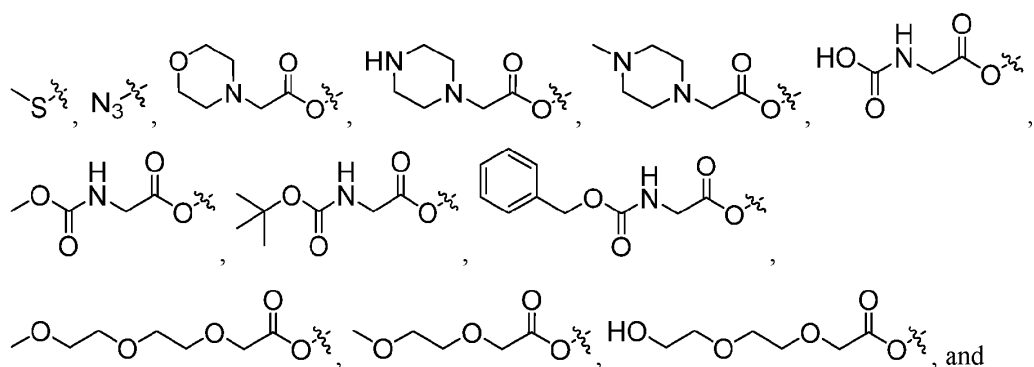
R^{G3} and R^{G4} are each independently hydrogen, alkyl, or heteroalkyl, wherein the alkyl or heteroalkyl is optionally substituted;

or R^{G3} and R^{G4} , together with the atoms to which they are attached, form a 3-7 membered cycloalkyl, heterocyclyl, aryl, or heteroaryl, wherein the cycloalkyl, heterocyclyl, aryl, or heteroaryl is optionally substituted;

R^J is hydrogen, alkyl, alkylene-heterocyclyl, heteroalkyl, or heterocyclyl, wherein the alkyl, alkylene, heteroalkyl, or heterocyclyl is optionally substituted;

and $\sim$ denotes the point of attachment of the R^6 group to the carbon atom of the $-C(R^A)(R^B)-$ group.

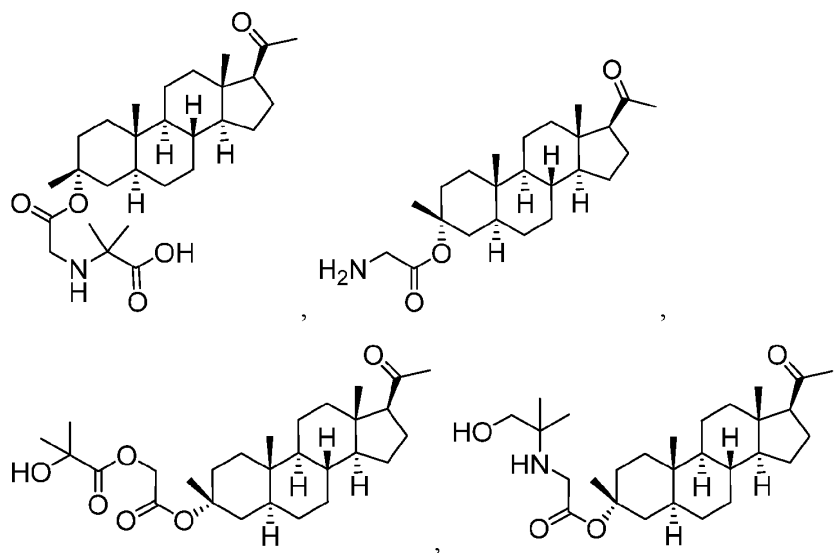
35. The compound of any one of claims 1, 2, 33, or 34, wherein the X group of Formula (I), or the R^6 group of Formula (IE), is a moiety selected from the group consisting of

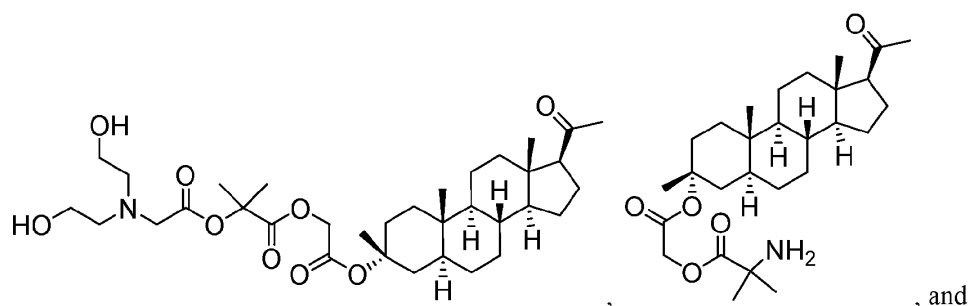


$\text{HO---CH}_2\text{---CH}_2\text{---O---COO---}$, wherein --- denotes the point of attachment of X to Z, or X to Y when Z is absent, in Formula (I); or the point of attachment of the R^6 group to the carbon atom of the $\text{---C(R}^A\text{)(R}^B\text{)---}$ group.

36. The compound of any one of the preceding claims, wherein the compound is a compound selected from Table 1.

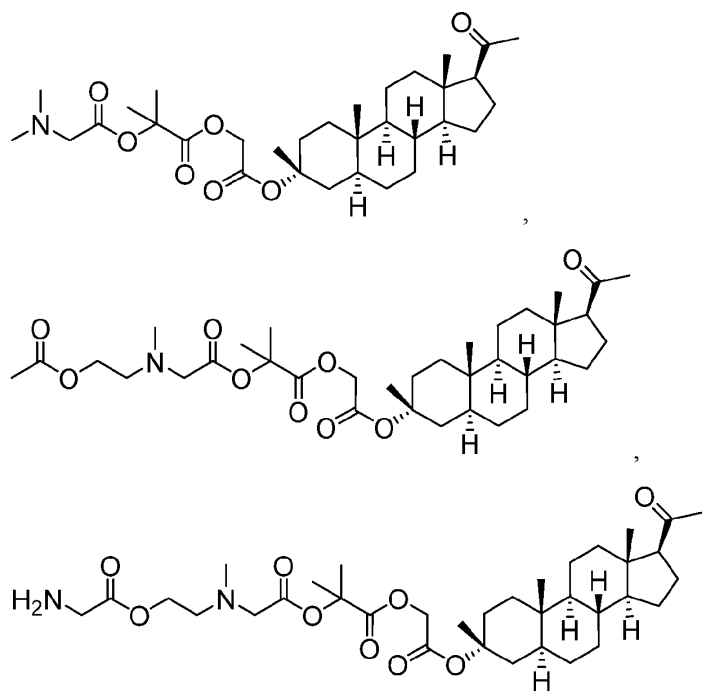
37. The compound of any one of claims 1-26 or 36, wherein the compound is selected from the group consisting of

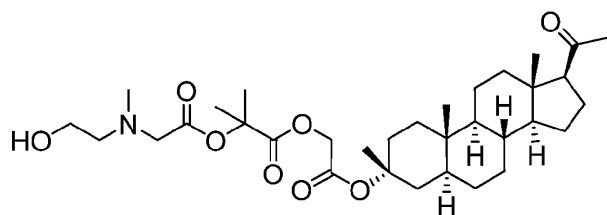




pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomers thereof.

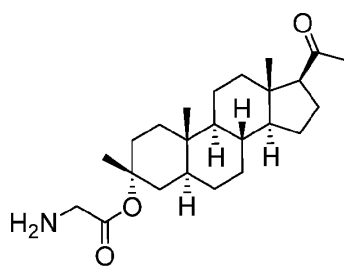
38. The compound of any one of claims 1-26 or 36, wherein the compound is selected from the group consisting of





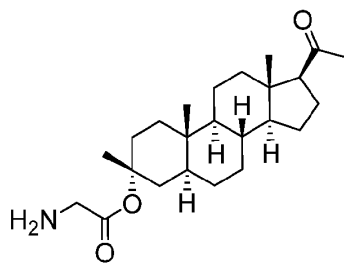
, and pharmaceutically acceptable salts, solvates, hydrates, tautomers, and stereoisomers thereof.

39. The compound of any one of claims 1-4, 6, 13, 14, 16, 36, or 37, wherein the compound is



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

40. The compound of any one of claims 1-38, wherein the compound is not



or a pharmaceutically acceptable salt, solvate, hydrate, tautomer, or stereoisomer thereof.

41. The compound of any one of the preceding claims, wherein the compound has a higher aqueous solubility and or hydrophilicity relative to ganaxolone, e.g., as determined by logS, logP, logD, topological polar surface area (TPSA), acid pKa, base pKa, or a combination thereof.

42. The compound of any one of the preceding claims, wherein the compound is substantially converted to ganaxolone by a metabolic process, e.g., following administration to a subject.

43. The compound of any one of the preceding claims, wherein the compound has a higher bioavailability of ganaxolone, relative to ganaxolone delivered by the same route of administration at an equivalent amount, e.g., as determined by serum concentration of ganaxolone (e.g., $C_{\max}$ or AUC).
44. The compound of any one of the preceding claims, wherein the compound provides higher serum concentrations of ganaxolone (e.g., $C_{\max}$ or AUC) and/or a longer half-life of ganaxolone, e.g., following administration to a subject, relative to ganaxolone delivered by the same route of administration at an equivalent amount.
45. A pharmaceutical composition, comprising a compound of any one of the preceding claims, and a pharmaceutically acceptable excipient.
46. A method of treating a disease or disorder in a subject, comprising administering to a subject in need thereof a compound of any one of claims 1-44, or a pharmaceutical composition of claim 45.
47. The method of claim 46, wherein the administering comprises oral administration or intravenous administration.
48. A composition for use in treating a disease or disorder in a subject, comprising a therapeutically effective amount of a compound of any one of claims 1-44, or a pharmaceutical composition of claim 45.
49. Use of a compound of any one of claims 1-44, or a pharmaceutical composition of claim 45, for the production of a medicament effective for treating a disease or disorder in a subject.
50. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is a neurological disorder.

51. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is a seizure disorder, an epilepsy disorder, a genetic epilepsy disorder, an epilepsy-related disorder, a central nervous system disorder, a neurological disorder, or a neurodegenerative disorder.
52. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is status epilepticus (SE).
53. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is CDKL5 Deficiency Disorder.
54. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is Tuberous Sclerosis Complex.
55. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is PCDH19-related epilepsy.
56. The method of claim 46 or 47, the composition for use of claim 48, or the use of claim 49, wherein the disease or disorder is Lennox-Gastaut syndrome.