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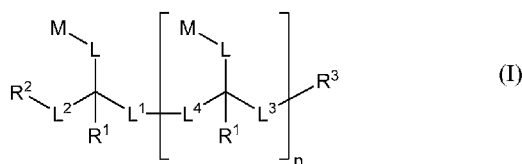
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(54) Title: IONIC POLYMERS COMPRISING BIOLOGICALLY ACTIVE COMPOUNDS



(57) Abstract: Compounds useful as biologically active compounds are disclosed. The compounds have the following structure (I): structure (I) or a stereoisomer, tautomer or salt thereof, wherein R^1 , R^2 , R^3 , L , L^1 , L^2 , L^3 , L^4 , M and n are as defined herein. Methods associated with preparation and use of such compounds are also provided.

IONIC POLYMERS COMPRISING BIOLOGICALLY ACTIVE COMPOUNDS

BACKGROUND

Field

Embodiments of the present invention are generally directed to
5 polymeric biologically active compounds, and methods for their preparation and use in various therapeutic methods.

Description of the Related Art

Targeted drug conjugates, unlike, e.g., chemotherapy, are intended to target only diseased cells and spare healthy cells. Typically, conjugates are composed
10 of a targeting molecule that is linked to a biologically active payload or drug. By combining the unique targeting capability with the therapeutic effectiveness of a biologically active drug, conjugates can deliver the drug only to the intended target and minimize potential side effects.

Antibody-drug conjugates (ADCs) are one class of targeted drug
15 conjugates that are of particular interest for cancer treatment. ADCs combine the targeting features of monoclonal antibodies with cancer-killing ability of cytotoxic agents to provide a therapeutic with several advantages over other chemotherapeutics. However, challenges related to the complexity of ADC constructs, specifically the chemical linker between antibody and drug, has caused significant difficulties for
20 development of new and effective therapeutics. Although the first ADC was approved in 2001, it took almost a decade before the next ADC was approved. As of today, only Adcetris® and Kadcyla® are commercially available globally (Zevalin® has been approved in China only). Pioneers Pfizer/Wyeth withdrew Mylotarg® in 2010 after safety issues were observed during a comparative clinical trial.

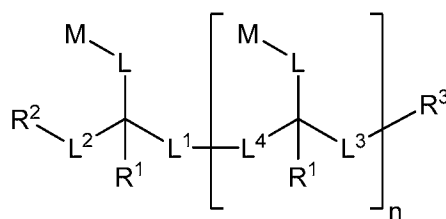
25 Thus, there exists a need in the art for potent, targeting drug conjugates having a large therapeutic index. Ideally, such drug conjugates should provide sensitive discrimination between healthy and diseased tissues (e.g., tumor cells). The present invention fulfills this need and provides further related advantages.

BRIEF SUMMARY

In brief, embodiments of the present invention are generally directed to compounds useful as a targeted drug conjugate, optionally comprising fluorescent and/or colored dyes that enable selective delivery to targets, such as tumor cells, as well as reagents for their preparation. Methods for preparation of such molecules as well as use of the same for providing therapeutic treatment to a patient in need thereof are also described.

Embodiments of the presently disclosed compounds include one or more biologically active moieties covalently linked to a backbone by a linker ("L"). Advantageously, embodiments of the present invention provide compounds that can be incorporated during polymer synthesis or attached post-synthetically. In addition, embodiments described herein allow incorporation of multiple biologically active moieties within the same compound as well as the optional inclusion of a targeting moiety and/or fluorescent dye.

In one embodiment, compounds having the following structure (I) are provided:



(I)

or a stereoisomer, tautomer or salt thereof, wherein R^1 , R^2 , R^3 , L , L^1 , L^2 , L^3 , L^4 , M and n are as defined herein. Compounds of structure (I) find utility in a number of applications, including use as therapeutic agents for various treatment methods.

In another embodiment, a method of treating a disease is provided, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structure (I) or a composition comprising a compound of structure (I), wherein each M independently comprises a biologically active moiety effective for treating the disease.

These and other aspects of the invention will be apparent upon reference to the following detailed description.

DETAILED DESCRIPTION

In the following description, certain specific details are set forth in order to provide a thorough understanding of various embodiments of the invention.

However, one skilled in the art will understand that the invention may be practiced
5 without these details.

Unless the context requires otherwise, throughout the present specification and claims, the word "comprise" and variations thereof, such as, "comprises" and "comprising" are to be construed in an open, inclusive sense, that is, as "including, but not limited to".

10 Reference throughout this specification to "one embodiment" or "an embodiment" means that a particular feature, structure or characteristic described in connection with the embodiment is included in at least one embodiment of the present invention. Thus, the appearances of the phrases "in one embodiment" or "in an embodiment" in various places throughout this specification are not necessarily all
15 referring to the same embodiment. Furthermore, the particular features, structures, or characteristics may be combined in any suitable manner in one or more embodiments.

"Amino" refers to the -NH_2 group.

"Carboxy" refers to the $\text{-CO}_2\text{H}$ group.

"Cyano" refers to the -CN group.

20 "Formyl" refers to the -C(=O)H group.

"Hydroxy" or "hydroxyl" refers to the -OH group.

"Imino" refers to the =NH group.

"Nitro" refers to the -NO_2 group.

"Oxo" refers to the =O substituent group.

25 "Sulphydryl" refers to the -SH group.

"Thioxo" refers to the =S group.

"Alkyl" refers to a straight or branched hydrocarbon chain group consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to twelve carbon atoms ($\text{C}_1\text{-C}_{12}$ alkyl), one to eight carbon atoms ($\text{C}_1\text{-C}_8$
30 alkyl) or one to six carbon atoms ($\text{C}_1\text{-C}_6$ alkyl), and which is attached to the rest of the molecule by a single bond, e.g., methyl, ethyl, *n*-propyl, 1-methylethyl (*iso*-propyl),

n-butyl, *n*-pentyl, 1,1-dimethylethyl (*t*-butyl), 3-methylhexyl, 2-methylhexyl, and the like. Unless stated otherwise specifically in the specification, alkyl groups are optionally substituted.

"Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation, and having from one to twelve carbon atoms, e.g., methylene, ethylene, propylene, *n*-butylene, ethenylene, propenylene, *n*-butenylene, propynylene, *n*-butynylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, alkylene is optionally substituted.

"Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond and having from two to twelve carbon atoms, e.g., ethenylene, propenylene, *n*-butenylene, and the like. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkenylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, alkenylene is optionally substituted.

"Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond and having from two to twelve carbon atoms, e.g., ethenylene, propenylene, *n*-butenylene, and the like. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a double bond or a single bond. The points of attachment of the alkynylene chain to the rest of the molecule and to the radical group can be through one carbon or any two carbons within the chain. Unless stated otherwise specifically in the specification, alkynylene is optionally substituted.

"Alkylether" refers to any alkyl group as defined above, wherein at least one carbon-carbon bond is replaced with a carbon-oxygen bond. The carbon-oxygen bond may be on the terminal end (as in an alkoxy group) or the carbon oxygen bond may be internal (i.e., C-O-C). Alkylethers include at least one carbon oxygen bond, but
5 may include more than one. For example, polyethylene glycol (PEG) is included within the meaning of alkylether. Unless stated otherwise specifically in the specification, an alkylether group is optionally substituted. For example, in some embodiments an alkylether is substituted with an alcohol or $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b and R_c is as defined for compounds of structure (I).

10 "Alkoxy" refers to a group of the formula $-OR_a$ where R_a is an alkyl group as defined above containing one to twelve carbon atoms. Unless stated otherwise specifically in the specification, an alkoxy group is optionally substituted.

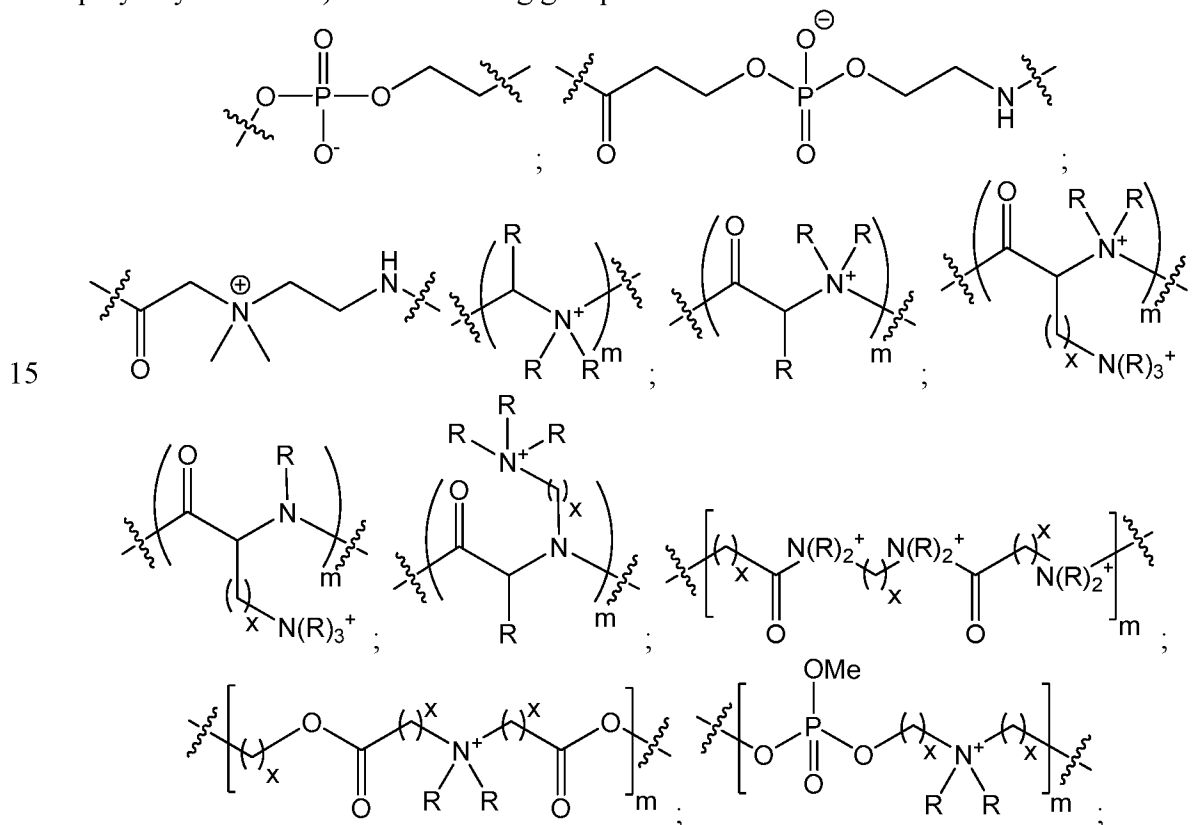
"Alkoxyalkylether" refers to a group of the formula $-OR_aR_b$ where R_a is an alkylene group as defined above containing one to twelve carbon atoms, and R_b is an
15 alkylether group as defined herein. Unless stated otherwise specifically in the specification, an alkoxyalkylether group is optionally substituted, for example substituted with an alcohol or $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b and R_c is as defined for compounds of structure (I).

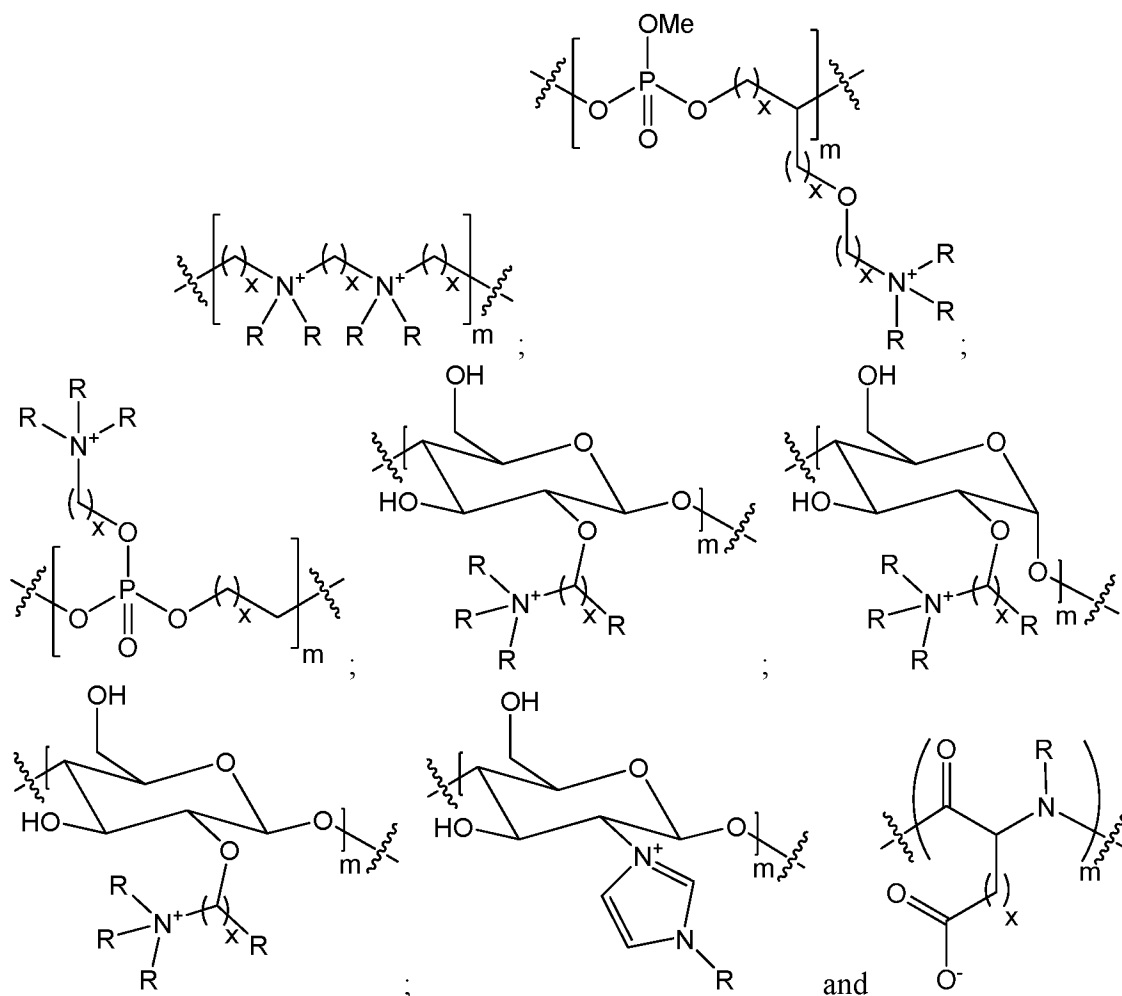
"Heteroalkyl" refers to an alkyl group, as defined above, comprising at
20 least one heteroatom (e.g., Si, N, O, P or S) within the alkyl group or at a terminus of the alkyl group. In some embodiments, the heteroatom is within the alkyl group (i.e., the heteroalkyl comprises at least one carbon-[heteroatom]_x-carbon bond, where x is 1, 2 or 3). In other embodiments, the heteroatom is at a terminus of the alkyl group and thus serves to join the alkyl group to the remainder of the molecule (e.g., M1-H-A),
25 where M1 is a portion of the molecule, H is a heteroatom and A is an alkyl group). Unless stated otherwise specifically in the specification, a heteroalkyl group is optionally substituted. Exemplary heteroalkyl groups include ethylene oxide (e.g., polyethylene oxide), optionally including phosphorous-oxygen bonds, such as phosphodiester bonds.

30 "Heteroalkoxy" refers to a group of the formula $-OR_a$ where R_a is a heteroalkyl group as defined above containing one to twelve carbon atoms. Unless

stated otherwise specifically in the specification, a heteroalkoxy group is optionally substituted.

"Heteroalkylene" refers to an alkylene group, as defined above, comprising at least one heteroatom (e.g., Si, N, O, P or S) within the alkylene chain or at a terminus of the alkylene chain. In some embodiments, the heteroatom is within the alkylene chain (i.e., the heteroalkylene comprises at least one carbon-[heteroatom]-carbon bond, where x is 1, 2 or 3). In other embodiments, the heteroatom is at a terminus of the alkylene and thus serves to join the alkylene to the remainder of the molecule (e.g., M1-H-A-M2, where M1 and M2 are portions of the molecule, H is a heteroatom and A is an alkylene). Unless stated otherwise specifically in the specification, a heteroalkylene group is optionally substituted. Exemplary heteroalkylene groups include amino acid and peptidyl linkers, ethylene oxide (e.g., polyethylene oxide) and the linking groups illustrated below:





wherein:

- 5 R is, at each occurrence, independently H or C₁-C₆ alkyl.

Multimers of the above linkers are included in various embodiments of heteroalkylene linkers.

- "Heteroalkenylene" is a heteroalkylene, as defined above, comprising at least one carbon-carbon double bond. Unless stated otherwise specifically in the specification, a heteroalkenylene group is optionally substituted.

"Heteroalkynylene" is a heteroalkylene comprising at least one carbon-carbon triple bond. Unless stated otherwise specifically in the specification, a heteroalkynylene group is optionally substituted.

- "Heteroatomic" in reference to a "heteroatomic linker" refers to a linker group consisting of one or more heteroatoms. Exemplary heteroatomic linkers include single atoms selected from the group consisting of Si, O, N, P and S, and multiple

heteroatoms for example a linker having the formula $-P(O^*)(=O)O-$ or $-OP(O^*)(=O)O-$ and multimers and combinations thereof.

"Phosphate" refers to the $-OP(=O)(R_a)R_b$ group, wherein R_a is OH, O^- or OR_c ; and R_b is OH, O^- , OR_c , a thiophosphate group or a further phosphate group,
 5 wherein R_c is a counter ion (e.g., Na^+ and the like).

"Phosphate ester" refers to the bivalent moiety $-OP(=O)(R_a)O-$ group, wherein R_a is OH, O^- or OR_c , wherein R_c is a counter ion (e.g., Na^+ and the like).

"Phosphoalkyl" refers to the $-OP(=O)(R_a)R_b$ group, wherein R_a is OH, O^- or OR_c ; and R_b is $-Oalkyl$, wherein R_c is a counter ion (e.g., Na^+ and the like).

10 Unless stated otherwise specifically in the specification, a phosphoalkyl group is optionally substituted. For example, in certain embodiments, the $-Oalkyl$ moiety in a phosphoalkyl group is optionally substituted with one or more of hydroxyl, amino, sulfhydryl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether, thiophosphoalkylether or $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b
 15 and R_c is as defined for compounds of structure (I).

"Phosphoalkylether" refers to the $-OP(=O)(R_a)R_b$ group, wherein R_a is OH, O^- or OR_c ; and R_b is $-Oalkylether$, wherein R_c is a counter ion (e.g., Na^+ and the like). Unless stated otherwise specifically in the specification, a phosphoalkylether group is optionally substituted. For example, in certain embodiments, the $-Oalkylether$
 20 moiety in a phosphoalkylether group is optionally substituted with one or more of hydroxyl, amino, sulfhydryl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether, thiophosphoalkylether or $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b and R_c is as defined for compounds of structure (I).

"Thiophosphate" refers to the $-OP(=R_a)(R_b)R_c$ group, wherein R_a is O or
 25 S, R_b is OH, O^- , S^- , OR_d or SR_d ; and R_c is OH, SH, O^- , S^- , OR_d , SR_d , a phosphate group or a further thiophosphate group, wherein R_d is a counter ion (e.g., Na^+ and the like) and provided that: i) R_a is S; ii) R_b is S^- or SR_d ; iii) R_c is SH, S^- or SR_d ; or iv) a combination of i), ii) and/or iii).

"Thiophosphoalkyl" refers to the $-OP(=R_a)(R_b)R_c$ group, wherein R_a is
 30 O or S, R_b is OH, O^- , S^- , OR_d or SR_d ; and R_c is $-Oalkyl$, wherein R_d is a counter ion (e.g., Na^+ and the like) and provided that: i) R_a is S; ii) R_b is S^- or SR_d ; or iii) R_a is S and

R_b is S^- or SR_d . Unless stated otherwise specifically in the specification, a thiophosphoalkyl group is optionally substituted. For example, in certain embodiments, the $-Oalkyl$ moiety in a thiophosphoalkyl group is optionally substituted with one or more of hydroxyl, amino, sulfhydryl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether, thiophosphoalkylether or $-OP(=R_a)(R_b)R_c$,
 5 wherein each of R_a , R_b and R_c is as defined for compounds of structure (I).

"Thiophosphoalkylether" refers to the $-OP(=R_a)(R_b)R_c$ group, wherein R_a is O or S, R_b is OH, O^- , S^- , OR_d or SR_d ; and R_c is $-Oalkylether$, wherein R_d is a counter ion (e.g., Na^+ and the like) and provided that: i) R_a is S; ii) R_b is S^- or SR_d ; or
 10 iii) R_a is S and R_b is S^- or SR_d . Unless stated otherwise specifically in the specification, a thiophosphoalkylether group is optionally substituted. For example, in certain embodiments, the $-Oalkylether$ moiety in a thiophosphoalkyl group is optionally substituted with one or more of hydroxyl, amino, sulfhydryl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether, thiophosphoalkylether or
 15 $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b and R_c is as defined for compounds of structure (I).

"Carbocyclic" refers to a stable 3- to 18-membered aromatic or non-aromatic ring comprising 3 to 18 carbon atoms. Unless stated otherwise specifically in the specification, a carbocyclic ring may be a monocyclic, bicyclic,
 20 tricyclic or tetracyclic ring system, which may include fused or bridged ring systems, and may be partially or fully saturated. Non-aromatic carbocyclyl radicals include cycloalkyl, while aromatic carbocyclyl radicals include aryl. Unless stated otherwise specifically in the specification, a carbocyclic group is optionally substituted.

"Cycloalkyl" refers to a stable non-aromatic monocyclic or polycyclic
 25 carbocyclic ring, which may include fused or bridged ring systems, having from three to fifteen carbon atoms, preferably having from three to ten carbon atoms, and which is saturated or unsaturated and attached to the rest of the molecule by a single bond. Monocyclic cycloalkyls include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example,
 30 adamantyl, norbornyl, decalinyl, 7,7-dimethyl-bicyclo-[2.2.1]heptanyl, and the like.

Unless stated otherwise specifically in the specification, a cycloalkyl group is optionally substituted.

"Aryl" refers to a ring system comprising at least one carbocyclic aromatic ring. In some embodiments, an aryl comprises from 6 to 18 carbon atoms.

- 5 The aryl ring may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems. Aryls include, but are not limited to, aryls derived from aceanthrylene, acenaphthylene, acephenanthrylene, anthracene, azulene, benzene, chrysene, fluoranthene, fluorene, *as*-indacene, *s*-indacene, indane, indene, naphthalene, phenalene, phenanthrene, pleiadene, pyrene, and triphenylene. Unless
10 stated otherwise specifically in the specification, an aryl group is optionally substituted.

- "Heterocyclic" refers to a stable 3- to 18-membered aromatic or non-aromatic ring comprising one to twelve carbon atoms and from one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Unless
15 stated otherwise specifically in the specification, the heterocyclic ring may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heterocyclic ring may be optionally oxidized; the nitrogen atom may be optionally quaternized; and the heterocyclic ring may be partially or fully saturated. Examples of aromatic heterocyclic rings are listed below in the definition of heteroaryls (i.e., heteroaryl being a subset of
20 heterocyclic). Examples of non-aromatic heterocyclic rings include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolynyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholynyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl,
25 pyrazolopyrimidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trioxanyl, trithianyl, triazinanyl, tetrahydropyranyl, thiomorpholynyl, thiamorpholynyl, 1-oxo-thiomorpholynyl, and 1,1-dioxo-thiomorpholynyl. Unless stated otherwise specifically in the specification, a heterocyclic group is optionally substituted.

- "Heteroaryl" refers to a 5- to 14-membered ring system comprising one
30 to thirteen carbon atoms, one to six heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, and at least one aromatic ring. For purposes of certain

embodiments of this invention, the heteroaryl radical may be a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which may include fused or bridged ring systems; and the nitrogen, carbon or sulfur atoms in the heteroaryl radical may be optionally oxidized; the nitrogen atom may be optionally quaternized. Examples include, but are

5 not limited to, azepinyl, acridinyl, benzimidazolyl, benzthiazolyl, benzindolyl, benzodioxolyl, benzofuranyl, benzooxazolyl, benzothiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzotriazolyl,

10 benzo[4,6]imidazo[1,2-*a*]pyridinyl, benzoxazolinonyl, benzimidazolthionyl, carbazolyl, cinnolinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indoliziny, isoxazolyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 1-oxidopyridinyl, 1-oxidopyrimidinyl, 1-oxidopyrazinyl, 1-oxidopyridazinyl,

15 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, pteridinonyl, purinyl, pyrrolyl, pyrazolyl, pyridinyl, pyridinonyl, pyrazinyl, pyrimidinyl, pyrimidinonyl, pyridazinyl, pyrrolyl, pyrido[2,3-*d*]pyrimidinonyl, quinazolinyl, quinazolinonyl, quinoxalinyl, quinoxalinonyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, thiazolyl, thiadiazolyl, thieno[3,2-*d*]pyrimidin-4-onyl, thieno[2,3-

20 *d*]pyrimidin-4-onyl, triazolyl, tetrazolyl, triazinyl, and thiophenyl (i.e. thienyl). Unless stated otherwise specifically in the specification, a heteroaryl group is optionally substituted.

"Fused" refers to a ring system comprising at least two rings, wherein the two rings share at least one common ring atom, for example two common ring atoms.

25 When the fused ring is a heterocyclyl ring or a heteroaryl ring, the common ring atom(s) may be carbon or nitrogen. Fused rings include bicyclic, tricyclic, tetracyclic, and the like.

The term "substituted" used herein means any of the above groups (e.g., alkyl, alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene,

30 heteroalkynylene, alkoxy, alkylether, alkoxyalkylether, heteroalkyl, heteroalkoxy, phosphoalkyl, phosphoalkylether, thiophosphoalkyl, thiophosphoalkylether,

carbocyclic, cycloalkyl, aryl, heterocyclic and/or heteroaryl) wherein at least one hydrogen atom (e.g., 1, 2, 3 or all hydrogen atoms) is replaced by a bond to a non-hydrogen atoms such as, but not limited to: a halogen atom such as F, Cl, Br, and I; an oxygen atom in groups such as hydroxyl groups, alkoxy groups, and ester groups; a sulfur atom in groups such as thiol groups, thioalkyl groups, sulfone groups, sulfonyl groups, and sulfoxide groups; a nitrogen atom in groups such as amines, amides, alkylamines, dialkylamines, arylamines, alkylarylamines, diarylamines, N-oxides, imides, and enamines; a silicon atom in groups such as trialkylsilyl groups, dialkylarylsilyl groups, alkyl-diarylsilyl groups, and triarylsilyl groups; and other heteroatoms in various other groups. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced by a higher-order bond (e.g., a double- or triple-bond) to a heteroatom such as oxygen in oxo, carbonyl, carboxyl, and ester groups; and nitrogen in groups such as imines, oximes, hydrazones, and nitriles. For example, "substituted" includes any of the above groups in which one or more hydrogen atoms are replaced with $-NR_gR_h$, $-NR_gC(=O)R_h$, $-NR_gC(=O)NR_gR_h$, $-NR_gC(=O)OR_h$, $-NR_gSO_2R_h$, $-OC(=O)NR_gR_h$, $-OR_g$, $-SR_g$, $-SOR_g$, $-SO_2R_g$, $-OSO_2R_g$, $-SO_2OR_g$, $=NSO_2R_g$, and $-SO_2NR_gR_h$. "Substituted" also means any of the above groups in which one or more hydrogen atoms are replaced with $-C(=O)R_g$, $-C(=O)OR_g$, $-C(=O)NR_gR_h$, $-CH_2SO_2R_g$, $-CH_2SO_2NR_gR_h$. In the foregoing, R_g and R_h are the same or different and independently hydrogen, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl. "Substituted" further means any of the above groups in which one or more hydrogen atoms are replaced by a bond to an amino, cyano, hydroxyl, imino, nitro, oxo, thioxo, halo, alkyl, alkoxy, alkylamino, thioalkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, haloalkyl, heterocyclyl, *N*-heterocyclyl, heterocyclylalkyl, heteroaryl, *N*-heteroaryl and/or heteroarylalkyl group. In some embodiments, the optional substituent is $-OP(=R_a)(R_b)R_c$, wherein each of R_a , R_b and R_c is as defined for compounds of structure (I). In addition, each of the foregoing substituents may also be optionally substituted with one or more of the above substituents.

"Conjugation" or "bio-conjugation" refers to a chemical strategy for forming a stable covalent bond between two molecules. The term "bio-conjugation" is generally used when one of the molecules is a biomolecule (e.g., an antibody). The product or compound resulting from such a strategy is a conjugate, is conjugated, or a grammatical equivalent.

"Fluorescent" refers to a molecule which is capable of absorbing light of a particular frequency and emitting light of a different frequency. Fluorescence is well-known to those of ordinary skill in the art.

"Colored" refers to a molecule which absorbs light within the colored spectrum (i.e., red, yellow, blue and the like).

A "linker" refers to a contiguous chain of at least one atom, such as carbon, oxygen, nitrogen, sulfur, phosphorous and combinations thereof, which connects a portion of a molecule to another portion of the same molecule or to a different molecule, moiety or solid support (e.g., microparticle). Linkers may connect the molecule via a covalent bond or other means, such as ionic or hydrogen bond interactions.

The term "biomolecule" refers to any of a variety of biological materials, including nucleic acids, carbohydrates, amino acids, polypeptides, glycoproteins, hormones, aptamers and mixtures thereof. More specifically, the term is intended to include, without limitation, RNA, DNA, oligonucleotides, modified or derivatized nucleotides, enzymes, receptors, prions, receptor ligands (including hormones), antibodies, antigens, and toxins, as well as bacteria, viruses, blood cells, and tissue cells. The visually detectable biomolecules of the invention (e.g., compounds of structure (I) having a biomolecule linked thereto) are prepared, as further described herein, by contacting a biomolecule with a compound having a reactive group that enables attachment of the biomolecule to the compound via any available atom or functional group, such as an amino, hydroxy, carboxyl, or sulfhydryl group on the biomolecule.

A "reactive group" is a moiety capable of reacting with a second reactive groups (e.g., a "complementary reactive group") to form one or more covalent bonds, for example by a displacement, oxidation, reduction, addition or cycloaddition reaction.

Exemplary reactive groups are provided in Table 1, and include for example, nucleophiles, electrophiles, dienes, dienophiles, aldehyde, oxime, hydrazone, alkyne, amine, azide, acylazide, acylhalide, nitrile, nitron, sulfhydryl, disulfide, sulfonyl halide, isothiocyanate, imidoester, activated ester, ketone, α,β -unsaturated carbonyl, alkene, maleimide, α -haloimide, epoxide, aziridine, tetrazine, tetrazole, phosphine, biotin, thiirane and the like.

The terms "visible" and "visually detectable" are used herein to refer to substances that are observable by visual inspection, without prior illumination, or chemical or enzymatic activation. Such visually detectable substances absorb and emit light in a region of the spectrum ranging from about 300 to about 900 nm. Preferably, such substances are intensely colored, preferably having a molar extinction coefficient of at least about 40,000, more preferably at least about 50,000, still more preferably at least about 60,000, yet still more preferably at least about 70,000, and most preferably at least about 80,000 $M^{-1}cm^{-1}$. Embodiments of compounds of the present disclosure may be detected by observation with the naked eye, or with the aid of an optically based detection device, including, without limitation, absorption spectrophotometers, transmission light microscopes, digital cameras and scanners. Visually detectable substances are not limited to those which emit and/or absorb light in the visible spectrum. Substances which emit and/or absorb light in the ultraviolet (UV) region (about 10 nm to about 400 nm), infrared (IR) region (about 700 nm to about 1 mm), and substances emitting and/or absorbing in other regions of the electromagnetic spectrum are also included with the scope of "visually detectable" substances.

For purposes of embodiments of the invention, the term "photostable visible dye" refers to a chemical moiety that is visually detectable, as defined hereinabove, and is not significantly altered or decomposed upon exposure to light. Preferably, the photostable visible dye does not exhibit significant bleaching or decomposition after being exposed to light for at least one hour. More preferably, the visible dye is stable after exposure to light for at least 12 hours, still more preferably at least 24 hours, still yet more preferably at least one week, and most preferably at least one month. Non-limiting examples of photostable visible dyes suitable for use in the compounds and methods of the invention include azo dyes, thioindigo dyes,

quinacridone pigments, dioxazine, phthalocyanine, perinone, diketopyrrolopyrrole, quinophthalone, and triarylcationium.

As used herein, the term "perylene derivative" is intended to include any substituted perylene that is visually detectable. However, the term is not intended to include perylene itself. The terms "anthracene derivative", "naphthalene derivative", and "pyrene derivative" are used analogously. In some preferred embodiments, a derivative (e.g., perylene, pyrene, anthracene or naphthalene derivative) is an imide, *bis*-imide or hydrazamimide derivative of perylene, anthracene, naphthalene, or pyrene.

"Solid support" refers to any solid substrate known in the art for solid-phase support of molecules, for example a "microparticle" refers to any of a number of small particles useful for attachment to compounds of the invention, including, but not limited to, glass beads, magnetic beads, polymeric beads, non-polymeric beads, and the like. In certain embodiments, a microparticle comprises polystyrene beads.

A "solid support residue" refers to the functional group remaining attached to a molecule when the molecule is cleaved from the solid support. Solid support residues are known in the art and can be easily derived based on the structure of the solid support and the group linking the molecule thereto.

A "targeting moiety" is a moiety that selectively binds or associates with a particular target, such as a tumor cell antigen. "Selectively" binding or associating means a targeting moiety preferentially associates or binds with the desired target relative to other targets. In some embodiments, the compounds disclosed herein include linkages to targeting moieties for the purpose of selectively binding or associating the compound with a tumor cell antigen (i.e., the target of the targeting moiety), thus allowing delivery of the biologically active moiety to the tumor cell. Exemplary targeting moieties include, but are not limited to, antibodies, antigens, nucleic acid sequences, enzymes, proteins, cell surface receptor antagonists, and the like. In some embodiments, the targeting moiety is a moiety, such as an antibody, that selectively binds or associates with a target feature on or in a cell, for example a target feature on a cell membrane or other cellular structure, thus allowing for delivery of a biologically active moiety to or into cells of interest. Small molecules that selectively bind or

associate with a desired biological target are also contemplated as targeting moieties in certain embodiments. One of skill in the art will understand other biological targets, and the corresponding targeting moiety, that will be useful in various embodiments.

"Physiologically cleavable linker" refers to a molecular linkage that can be split or separated a prescribed manner, resulting in two or more separate molecules while in the presence of an *in vivo* or *in vitro* environment of an organism or cell system. Generally, physiological conditions that induce such a cleavage or scission event may include a temperature ranging from about 20 to 40°C, an atmospheric pressure of about 1 atm (101 kPa or 14.7 psi), a pH of about 6 to 8, a glucose concentration of about 1 to 20 mM, atmospheric oxygen concentration, and earth gravity. In some embodiments, physiological conditions include enzymatic conditions (i.e., enzymatic cleavage). Bond cleavage or scission can be homolytic or heterolytic.

Embodiments of the invention disclosed herein are also meant to encompass all compounds of structure (I) being isotopically-labelled by having one or more atoms replaced by an atom having a different atomic mass or mass number. Examples of isotopes that can be incorporated into the disclosed compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, chlorine, and iodine, such as ²H, ³H, ¹¹C, ¹³C, ¹⁴C, ¹³N, ¹⁵N, ¹⁵O, ¹⁷O, ¹⁸O, ³¹P, ³²P, ³⁵S, ¹⁸F, ³⁶Cl, ¹²³I, and ¹²⁵I, respectively.

Isotopically-labeled compounds of structure (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described below and in the following Examples using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

"Optional" or "optionally" means that the subsequently described event or circumstances may or may not occur, and that the description includes instances where said event or circumstance occurs and instances in which it does not. For example, "optionally substituted alkyl" means that the alkyl group may or may not be

substituted and that the description includes both substituted alkyl groups and alkyl groups having no substitution.

"Salt" includes both acid and base addition salts.

"Acid addition salt" refers to those salts which are formed with inorganic acids such as, but not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as, but not limited to, acetic acid, 2,2-dichloroacetic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, camphoric acid, camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxyethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, 2-oxo-glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalene-1,5-disulfonic acid, naphthalene-2-sulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, oleic acid, orotic acid, oxalic acid, palmitic acid, pamoic acid, propionic acid, pyroglutamic acid, pyruvic acid, salicylic acid, 4-aminosalicylic acid, sebacic acid, stearic acid, succinic acid, tartaric acid, thiocyanic acid, *p*-toluenesulfonic acid, trifluoroacetic acid, undecylenic acid, and the like.

"Base addition salt" refers to those salts which are prepared from addition of an inorganic base or an organic base to the free acid. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as ammonia, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, diethanolamine, ethanolamine, deanol, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, benethamine, benzathine, ethylenediamine, glucosamine, methylglucamine,

theobromine, triethanolamine, tromethamine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. Particularly preferred organic bases are isopropylamine, diethylamine, ethanolamine, trimethylamine, dicyclohexylamine, choline and caffeine.

- 5 Crystallizations may produce a solvate of the compounds described herein. Embodiments of the present invention include all solvates of the described compounds. As used herein, the term "solvate" refers to an aggregate that comprises one or more molecules of a compound of the invention with one or more molecules of solvent. The solvent may be water, in which case the solvate may be a hydrate.
- 10 Alternatively, the solvent may be an organic solvent. Thus, the compounds of the present invention may exist as a hydrate, including a monohydrate, dihydrate, hemihydrate, sesquihydrate, trihydrate, tetrahydrate and the like, as well as the corresponding solvated forms. The compounds of the invention may be true solvates, while in other cases the compounds of the invention may merely retain adventitious
- 15 water or another solvent or be a mixture of water plus some adventitious solvent.

- Embodiments of the compounds of the invention (e.g., compounds of structure I), or their salts, tautomers or solvates may contain one or more stereocenters and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)- or, as (*D*)- or
- 20 (*L*)- for amino acids. Embodiments of the present invention are meant to include all such possible isomers, as well as their racemic and optically pure forms. Optically active (+) and (-), (*R*)- and (*S*)-, or (*D*)- and (*L*)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, for example, chromatography and fractional crystallization. Conventional techniques for the
- 25 preparation/isolation of individual enantiomers include chiral synthesis from a suitable optically pure precursor or resolution of the racemate (or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). When the compounds described herein contain olefinic double bonds or other features giving rise to geometric asymmetry, and unless specified otherwise, it is intended that
- 30 the compounds include both *E* and *Z* geometric isomers. Likewise, all tautomeric forms are also intended to be included.

A "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures, which are not interchangeable. The present invention contemplates various stereoisomers and mixtures thereof and includes "enantiomers", which refers to two stereoisomers whose
5 molecules are non-superimposable mirror images of one another.

A "tautomer" refers to a proton shift from one atom of a molecule to another atom of the same molecule. The present invention includes tautomers of any said compounds. Various tautomeric forms of the compounds are easily derivable by those of ordinary skill in the art.

10 The chemical naming protocol and structure diagrams used herein are a modified form of the I.U.P.A.C. nomenclature system, using the ACD/Name Version 9.07 software program and/or ChemDraw Ultra Version 11.0 software naming program (CambridgeSoft). Common names familiar to one of ordinary skill in the art are also used.

15 As noted above, in one embodiment of the present invention, compounds useful as covalent linkers between biologically active moieties and targeting moieties are provided. In other embodiments, compounds useful as synthetic intermediates for preparation of compounds comprising one or more biologically active moieties are provided. In general terms, embodiments of the present invention are directed to
20 polymers with pendant biologically active moieties. The biologically active moieties are linked by a linker having one or more positively or negatively charged moieties at the pH at which the compound is administered. Without wishing to be bound by theory, it is believed the length and specific characteristics (e.g., secondary structure, positive charge, etc.) of the linker helps to shield or suspend the biological activity until
25 release of the drug at the desired target, and in some embodiments may help to optimize solubility or other desirable properties. In another aspect, the linker provides a link between the biologically active moiety and a targeting moiety, which acts to increase accumulation of the biologically active moiety at the desired target. That is, the biological activity is only operative or increased due to accumulation at the intended
30 target, thus minimizing potential side effects of the therapeutic (e.g., cytotoxicity).

For example, the linker may comprise carboxylate, phosphate and/or thiophosphate moieties when a negative charge is desired. When positive charges are desired, linking groups containing primary or quaternary amine groups and/or other groups capable of holding a positive charge may be used. When a specific secondary structure is desired, linking groups with an amino acid sequence amenable to such a structure (e.g., alpha-helix or beta sheet) may be used. By “charged moieties” it is understood that the moieties will be charged at certain pH’s, for example at the pH at which the compound or conjugate is administered, but it is not a requirement that the “charged moieties” be charged at all pH’s.

- 10 In some embodiments is provided a compound comprising:
- i) a polymer backbone;
 - ii) one or more charged moieties on the polymer backbone; and
 - iii) at least one biologically active moiety, or fragment thereof, a prodrug of a biologically active moiety, or fragment thereof,
 - 15 iv) an optional fluorescent dye, an imaging agent, or a radioisotope binding site;

wherein the one or more charged moieties are in a position on the polymer backbone and provided that at least one of the charged moieties is not a phosphate ester. In other embodiments at least one of the charged moieties is not an amino acid, for example in some embodiments the compounds do not include peptide-like backbones.

In some embodiments, the charged moieties are positively charged. For example, in some embodiments the charged moieties comprise a protonated amine or quaternary amine functional group.

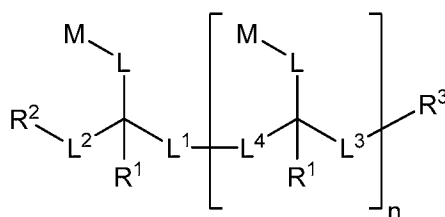
25 In other embodiments, the charged moieties are negatively charged. For example, in some embodiments the charged moieties comprise a carboxylic acid or sulfate functional group.

The charged moieties may be included in the compound in a variety of different manners. For example, in some embodiments the charged moieties are within the polymer backbone (i.e., part of the polymer backbone). In other embodiments, the charged moieties are covalently bound pendent to the backbone via an optional linker.

The polymer backbone can be formed from any type of monomer, and include all the same monomers (homopolymer) or a mixture of different monomers (copolymer). In some embodiments, the polymer backbone comprises a backbone resulting from polymerization of: a phosphoramidite and an alcohol; an amine and an epoxide; an amine and an aldehyde; N-carboxyanhydride, or a combination thereof.

In other embodiments, the polymer backbone comprises a polyamide, a polyamine, dextran, cellulose, chitosan, polyacrylate, polysulfate or polycarboxylic acid.

In some embodiments is provided a compound having the following structure (I):



(I)

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

M is, at each occurrence, independently a biologically active moiety, or fragment thereof, a prodrug of a biologically active moiety, or fragment thereof, a fluorescent dye, an imaging agent, or a radioisotope binding site, provided at least one occurrence of M is not a fluorescent dye;

L is a physiologically cleavable linker;

L¹, L² and L³ are, at each occurrence, independently an optional alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene or heteroatomic linker;

L⁴ is, at each occurrence, independently an alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene or heteroalkynylene linker comprising one or more charged moieties, provided at least one charged moiety is not a phosphate ester;

R¹ is, at each occurrence, independently H, alkyl or alkoxy;

R^2 and R^3 are each independently -H, -OH, -SH, alkyl, alkoxy, alkylether, heteroalkyl, alkylaminyl, alkylcarbonyl, alkoxycarbonyl, $-OP(=R_a)(R_b)R_c$, Q or a protected form thereof, or L' ;

R_a is O or S;

5 R_b is OH, SH, O^- , S^- , OR_d or SR_d ;

R_c is OH, SH, O^- , S^- , OR_d , OL' , SR_d , alkyl, alkoxy, heteroalkyl, heteroalkoxy, alkylether, alkoxyalkylether, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether or thiophosphoalkylether;

R_d is a counter ion;

10 Q is, at each occurrence, independently a moiety comprising a reactive group, or protected form thereof, capable of forming a covalent bond with a complementary reactive group Q' on a targeting moiety;

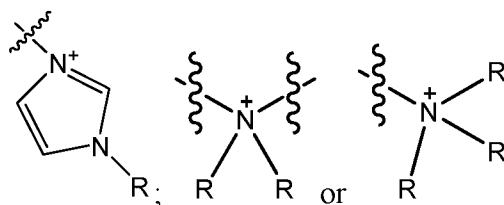
L' is, at each occurrence, independently a linker comprising a covalent bond to Q, a targeting moiety, a linker comprising a covalent bond to a targeting moiety, a solid support or solid support residue, a linker comprising a covalent bond to a solid support or solid support residue or a linker comprising a covalent bond to a further compound of structure (I); and

n is an integer of one or greater. The various linkers and substituents (e.g., M, Q, R^1 , R^2 , R^3 , L, L^1 , L^2 , L^3 , L^4 and L') in the compound of structure (I) are optionally substituted with one more substituent. For example, in some embodiments the optional substituent is selected to optimize the water solubility, permeability, retention, or other property of the compound of structure (I). In certain embodiments, each alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene or heteroatomic linker or alkyl, alkoxy, alkylether, heteroalkyl, 25 alkylaminyl, alkylcarbonyl or alkoxycarbonyl in the compound of structure (I) is optionally substituted with one more substituents selected from the group consisting of hydroxyl, alkoxy, alkylether, alkoxyalkylether, sulfhydryl, amino, alkylamino, carboxyl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether and thiophosphoalkylether. In certain embodiments the optional 30 substituent is $-OP(=R_a)(R_b)R_c$, wherein R_a is O or S, R_b is OH, SH, O^- , S^- , OR_d or SR_d , R_c is OH, SH, O^- , S^- , OR_d , SR_d , alkyl, alkoxy, heteroalkyl, heteroalkoxy, alkylether,

alkoxyalkylether, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether or thiophosphoalkylether, and R_d is a counter ion. In certain embodiments, substituents are selected to increase cellular or tissue permeation. In related embodiments, substituents are selected to increase cellular or tissue retention. In some embodiments, the alkyl, alkoxy, alkylether, heteroalkyl, alkylaminyl, alkylcarbonyl and alkyloxycarbonyl are optionally substituted with hydroxyl, amino, sulfhydryl, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether or thiophosphoalkylether, or combinations thereof

In some embodiments, at least one occurrence of M comprises a biologically active moiety. In other embodiments, M, at each occurrence, independently comprises a biologically active moiety.

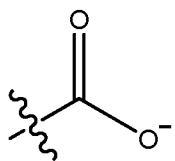
In some embodiments, the charged moieties are positively charged. In more specific embodiments, the charged moieties comprise a protonated amine or quaternary amine functional group. In more specific embodiments, the charged moieties independently have one of the following structures:



wherein:

R is, at each occurrence, independently H or C_1 - C_6 alkyl.

In other embodiments, the charged moieties are negatively charged. In certain embodiments, the charged moieties comprise a carboxylic acid, phosphate or sulfate functional group. In some embodiments, the charged moieties have the following structure:

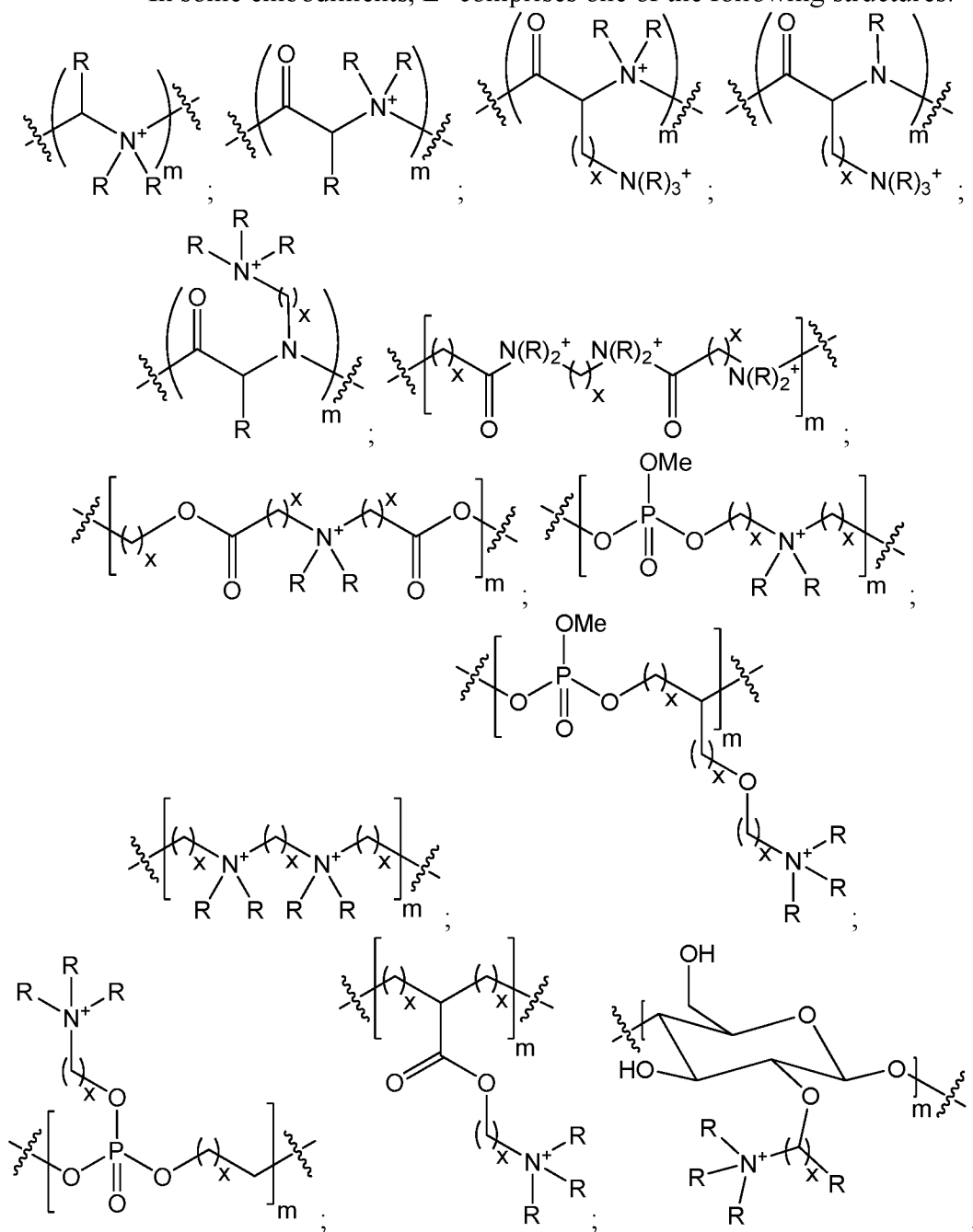


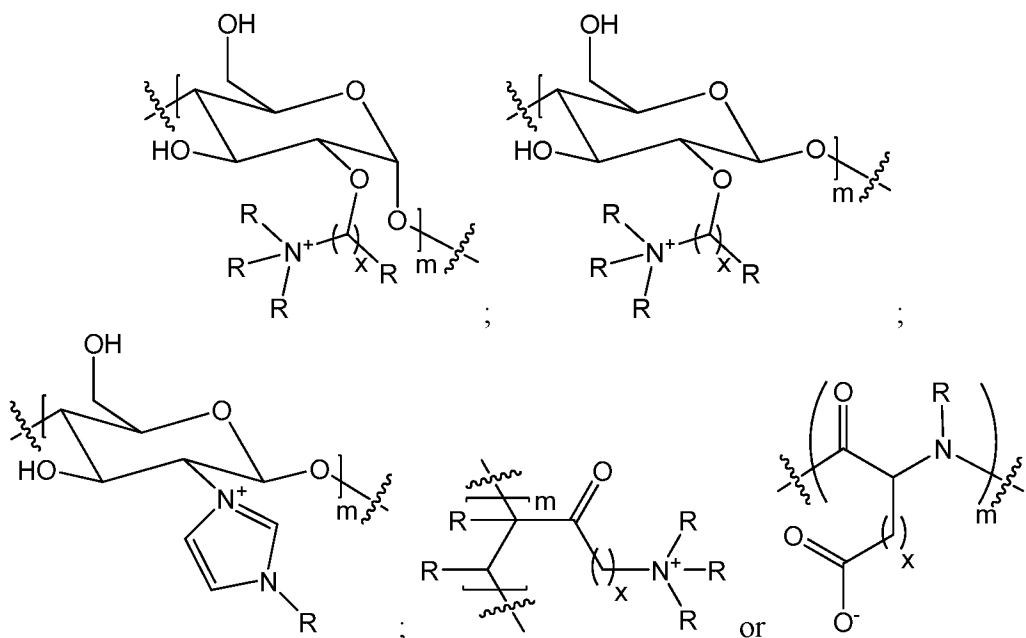
In some embodiments, the charged moieties comprise a combination of positively charged and negatively charged moieties.

In certain embodiments, the charged moieties are pendant to the backbone of the compound (e.g., attached to a linker via an alkylene or heteroalkylene linker). In some embodiments, the charged moiety is part of the backbone of the compound (e.g., part of the contiguous chain of the linker).

5

In some embodiments, L^4 comprises one of the following structures:





wherein:

R is, at each occurrence, independently H or C₁-C₆ alkyl;

5 x is an integer from 0 to 6; and

m is an integer of 1 or greater, provided that m is selected such that the compound comprises at least two charged moieties.

In some embodiments, L², L³ and L⁴ are, at each occurrence, independently C₁-C₆ alkylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene.

10 The linker L can be used as a point of attachment of the M moiety to the remainder of the compound. For example, in some embodiments a synthetic precursor to the compound of structure (I) is prepared, and the M moiety is attached to the synthetic precursor using any number of *facile* methods known in the art, for example methods referred to as "click chemistry." For this purpose any reaction which is rapid
15 and substantially irreversible can be used to attach M to the synthetic precursor to form a compound of structure (I). Exemplary reactions include the copper catalyzed reaction of an azide and alkyne to form a triazole (Huisgen 1,3-dipolar cycloaddition), reaction of a diene and dienophile (Diels-Alder), strain-promoted alkyne-nitrone cycloaddition, reaction of a strained alkene with an azide, tetrazine or tetrazole, alkene and azide [3+2]
20 cycloaddition, alkene and tetrazine inverse-demand Diels-Alder, alkene and tetrazole photoreaction and various displacement reactions, such as displacement of a leaving group by nucleophilic attack on an electrophilic atom. Exemplary displacement

reactions include reaction of an amine with: an activated ester (e.g., an N-hydroxysuccinimide ester); an isocyanate; an isothiocyanate or the like. In some embodiments the reaction to form L may be performed in an aqueous environment.

Accordingly, in some embodiments L is at each occurrence a linker comprising a functional group capable of formation by reaction of two complementary reactive groups, for example a functional group which is the product of one of the foregoing "click" reactions. In various embodiments, for at least one occurrence of L, the functional group can be formed by reaction of an aldehyde, oxime, hydrazone, alkyne, amine, azide, acylazide, acylhalide, nitrile, nitron, sulfhydryl, disulfide, sulfonyl halide, isothiocyanate, imidoester, activated ester (e.g., N-hydroxysuccinimide ester), ketone, α,β -unsaturated carbonyl, alkene, maleimide, α -haloimide, epoxide, aziridine, tetrazine, tetrazole, phosphine, biotin or thiirane functional group with a complementary reactive group, for example, reaction of an amine with an N-hydroxysuccinimide ester or isothiocyanate.

In some embodiments, L is at each occurrence a linker comprising a functional group capable of formation by reaction of two complementary reactive groups. In certain related embodiments, L is, at each occurrence, independently a linker comprising an amide bond, an ester bond, a disulfide bond, a double bond, a triple bond, an ether bond, a ketone, a diol, a cyano, a nitro, a heterocyclic, a heteroaryl or combinations thereof.

In other embodiments, for at least one occurrence of L, the functional group can be formed by reaction of an alkyne and an azide. In other embodiments, for at least one occurrence of L, the functional group can be formed by reaction of an amine (e.g., primary amine) and an N-hydroxysuccinimide ester or isothiocyanate.

In more embodiments, for at least one occurrence of L, the functional group comprises an alkene, ester, amide, thioester, disulfide, carbocyclic, heterocyclic or heteroaryl group. In more embodiments, for at least one occurrence of L, the functional group comprises an alkene, ester, amide, thioester, thiourea, disulfide, carbocyclic, heterocyclic or heteroaryl group. In other embodiments, the functional group comprises an amide or thiourea. In some more specific embodiments, for at least one occurrence of L, L is a linker comprising a triazolyl functional group. While in

other embodiments, for at least one occurrence of L, L is a linker comprising an amide or thiourea functional group.

Some embodiments provide an L that is able to be cleaved under the appropriate conditions (e.g., physiological conditions). Accordingly, in some
 5 embodiments, L comprises an amide bond, an ester bond, a disulfide bond, a hydrazone, a phosphotriester, a diester, β -glucuronide, a double bond, a triple bond, an ether bond, a ketone or oxo, a diol, a cyano, a nitro, a heterocycle, a heteroaryl or combinations thereof.

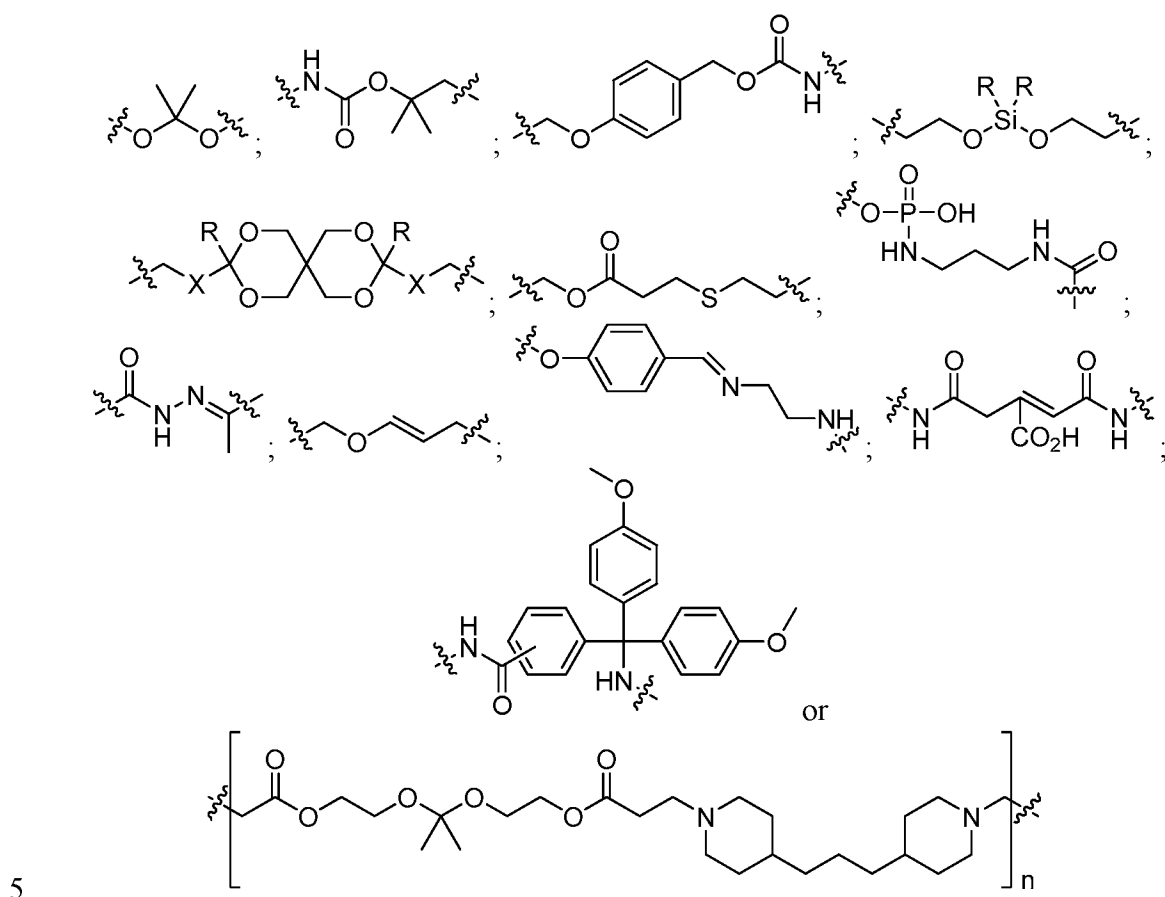
In some embodiments, L comprises *tert*-butyloxycarbonyl,
 10 paramethoxybenzyl, dialkyl or diaryldialkoxysilane, orthoester, acetal, β -thiopropionate, ketal, phosphoramidate, hydrazone, vinyl ether, imine, aconityl, trityl, polyketal, bisarylhydrazone, diazobenzene, vivinal diol, pyrophosphate diester, or valine citrulline.

In certain embodiments, L is, at each occurrence, independently a linker
 15 that is cleavable at a pH ranging from 6 to 8. For example, in some embodiments L is a linker that is cleavable at pH 6.0, 6.1, 6.2, 6.3, 6.4, 6.5, 6.6, 6.7, 6.8, 6.9, 7.0, 7.1, 7.2, 7.3, 7.4, 7.5, 7.6, 7.7, 7.8, 7.9, 8.0, 8.1, or 8.0.

In certain embodiments, L is, at each occurrence, independently a linker that is cleavable at a temperature ranging from 20°C to 40°C, from 25°C to 35°C, from
 20 30°C to 35°C, from 30°C to 37°C, from 35°C to 37°C, from 35°C to 40°C, from 32°C to 38°C. In certain embodiments, L is, at each occurrence, independently a linker that is cleavable at a temperature of about 20°C, about 21°C, about 22°C, about 23°C, about 24°C, about 25°C, about 26°C, about 27°C, about 28°C, about 29°C, about 30°C, about 31°C, about 32°C, about 33°C, about 34°C, about 35°C, about 36°C, about 37°C, about
 25 38°C, about 39°C, or about 40°C.

In certain embodiments, L is, at each occurrence, independently a linker that is cleavable by an enzyme. For example, in some embodiments, the enzyme is a hydrolase, an oxidoreductase or a lyase. In certain embodiments, the enzyme is an EC 4.1 (e.g., EC 4.1.1, EC 4.1.2, EC 4.1.3 or EC 4.1.99), EC 4.2, EC 4.3, EC 4.4, EC 4.5,
 30 EC 4.6, or EC 4.99 enzyme.

In certain embodiments, L comprises one of the following structures:



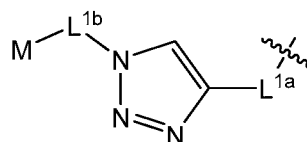
wherein:

R is H, methyl, ethyl, isopropyl, tert-butyl, or phenyl;

X is O or CH₂; and

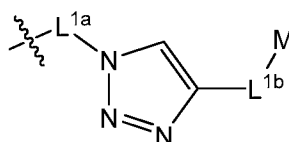
n is an integer greater than 0.

10 In still other embodiments, for at least one occurrence of L, L-M has the
following structure:



wherein L^{1a} and L^{1b} are each independently optional linkers.

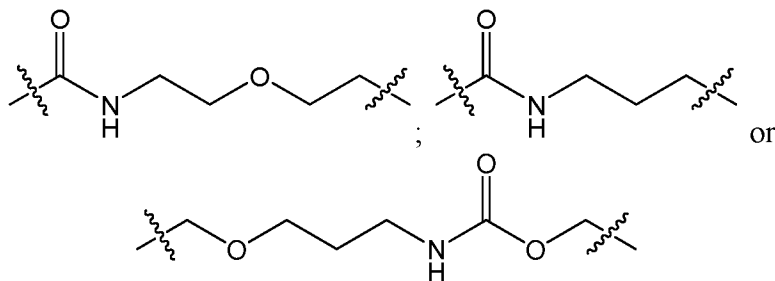
In different embodiments, for at least one occurrence of L, L-M has the
15 following structure:



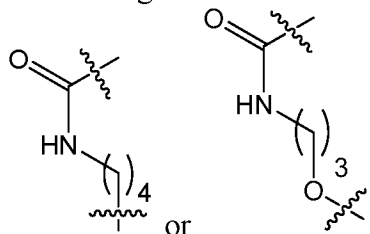
wherein L^{1a} and L^{1b} are each independently optional linkers.

In various embodiments of the foregoing, L^{1a} or L^{1b} , or both, is absent. In other embodiments, L^{1a} or L^{1b} , or both, is present.

In some embodiments L^{1a} and L^{1b} , when present, are each independently
 5 alkylene or heteroalkylene. For example, in some embodiments L^{1a} and L^{1b} , when present, independently have one of the following structures:



In still other different embodiments of structure (I), L is at each
 10 occurrence, independently an optional alkylene or heteroalkylene linker. In certain embodiments, L has one of the following structures:



In more embodiments, L^2 and L^3 are, at each occurrence, independently C_1 - C_6 alkylene, C_2 - C_6 alkenylene or C_2 - C_6 alkynylene.

In some different embodiments of any of the foregoing compounds, R^1
 15 is, at each occurrence, H. In some embodiments, R^1 is, at each occurrence, methyl.

In certain related embodiments, one of R^2 or R^3 is OH or -
 $OP(=R_a)(R_b)R_c$, and the other of R^2 or R^3 is Q or a linker comprising a covalent bond to
 Q. In some of those embodiments, Q comprises a nucleophilic reactive group, an
 20 electrophilic reactive group or a cycloaddition reactive group. In more specific
 embodiments, Q comprises a sulfhydryl, disulfide, activated ester (e.g., N-succinimide
 ester, imidoester or polyfluorophenyl ester), isothiocyanate, azide (e.g., alkyl azide or
 acyl azide), alkyne, alkene, diene, dienophile, acid halide, sulfonyl halide, phosphine,
 α -haloamide, biotin, amino or maleimide functional group.

In certain embodiments, one of R^2 or R^3 is L' , and L' is a linker comprising a covalent bond to a solid support. In some of those embodiments, the solid support is a polymeric bead or non-polymeric bead.

In certain other embodiments, one of R^2 or R^3 is L' , and L' is a targeting moiety or a linker to a targeting moiety. In some of those embodiments, L' is a linker to a targeting moiety, the linker comprising a heteroalkylene linker.

In other various embodiments, R^2 and R^3 are each independently OH or $-OP(=R_a)(R_b)R_c$. In some different embodiments, R^2 or R^3 is OH or $-OP(=R_a)(R_b)R_c$, and the other of R^2 or R^3 is Q or L' .

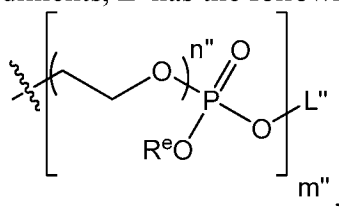
In still more different embodiments of any of the foregoing compounds of structure (I), R^2 and R^3 are each independently $-OP(=R_a)(R_b)R_c$. In some of these embodiments, R_c is OL' .

In some more specific embodiments, L' is a targeting moiety or a linker to a targeting moiety. In related embodiments, L' is a linker to a targeting moiety. In some embodiments, the linker is a peptidyl linker or a linker comprising an alkylene oxide or phosphodiester moiety, or combinations thereof.

In other embodiments, R^2 and R^3 are each independently $-OP(=R_a)(R_b)OL'$, and L' is an alkylene or heteroalkylene linker to: Q, a targeting moiety, an analyte (e.g., analyte molecule), a solid support, a solid support residue, an amino acid, nucleoside or a further compound of structure (I).

The linker L' can be any linker suitable for attaching Q, a targeting moiety, an analyte (e.g., analyte molecule), a solid support, a solid support residue, a nucleoside or a further compound of structure (I) to the compound of structure (I). Advantageously, certain embodiments include use of L' moieties selected to increase or optimize water solubility of the compound. In certain embodiments, L' is a heteroalkylene moiety. In some other certain embodiments, L' comprises an alkylene oxide or phosphodiester moiety, or combinations thereof.

In certain embodiments, L' has the following structure:



wherein:

m'' and n'' are independently an integer from 1 to 10;

R^e is H, an electron pair or a counter ion;

L'' is the targeting moiety or a linkage to the targeting moiety.

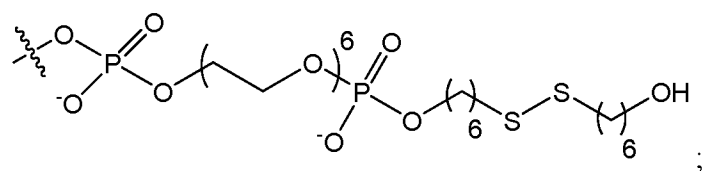
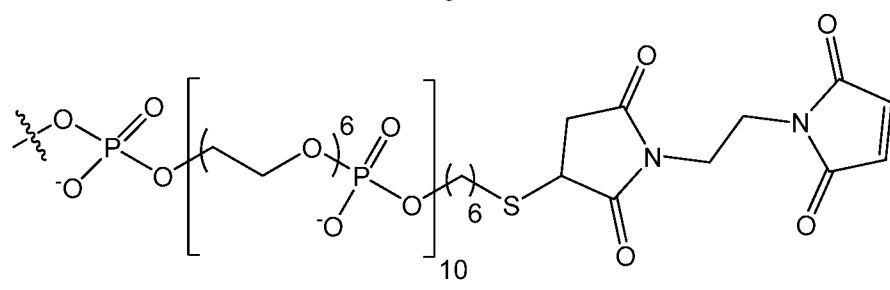
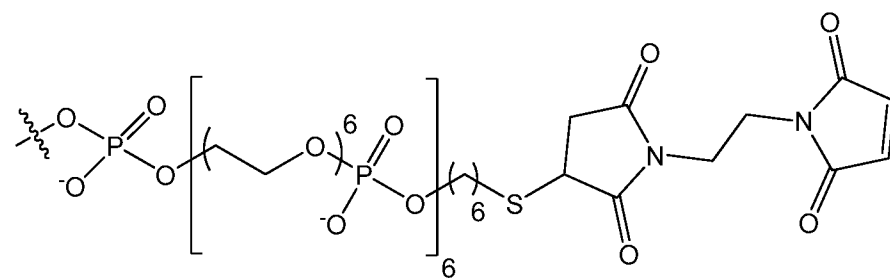
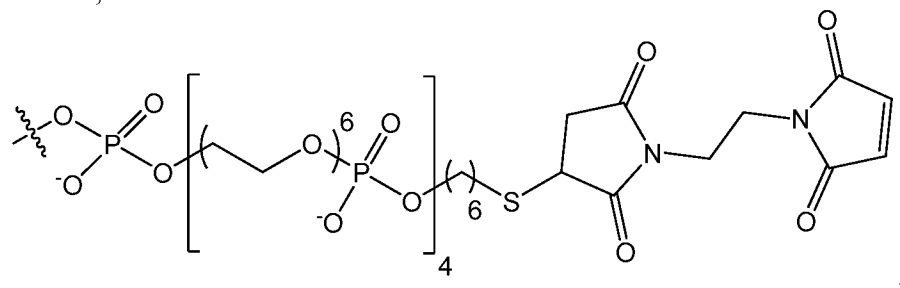
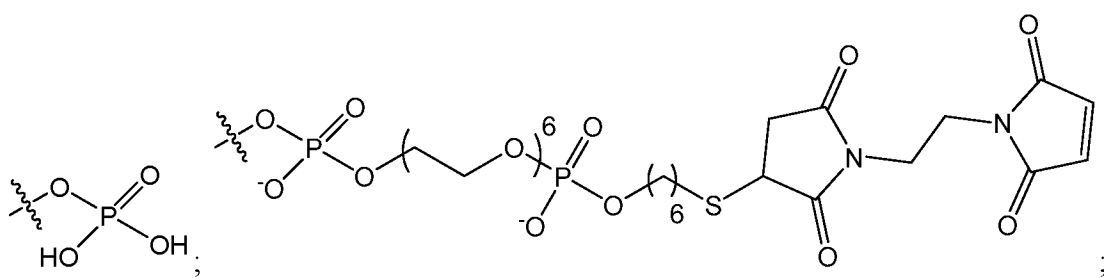
5 In some embodiments, m'' is an integer from 4 to 10, for example 4, 6 or 10. In other embodiments n'' is an integer from 3 to 6, for example 3, 4, 5 or 6.

In certain embodiments, the targeting moiety is an antibody or cell surface receptor antagonist. In related embodiments, the antibody or cell surface receptor antagonist is an epidermal growth factor receptor (EGFR) inhibitor, a
10 hepatocyte growth factor receptor (HGFR) inhibitor, an insulin-like growth factor receptor (IGFR) inhibitor, a folate, or a MET inhibitor. In certain embodiments, the antibody or cell surface receptor antagonist is a tyrosine kinase inhibitor (e.g., gefitinib, erlotinib), lapatinib, Vandetanib, neratinib, osimertinib, Tivantinib (ARQ197), Crizotinib, Cabozantinib, tyrphostins (e.g., AG538, AG1024), pyrrolo(2,3-d)-
15 pyrimidine derivatives (e.g., NVP-AEW541), monoclonal antibody (e.g., figitumumab, cetuximab, panitumumab, necitumumab, ganitumab, cixutumumab, dalotuzumab, robatumumab, onartuzumab, K1, labetuzumab, milatuzumab, lorvotuzumab, inotuzumab), BMS-777607, PF-02341066, PF-04217903, AMG-458, MK-2461, JNJ-38877605, GSK 1363089 (foretinib), XL880, XL 184, ARQ197, E7050, or
20 INCB28060.

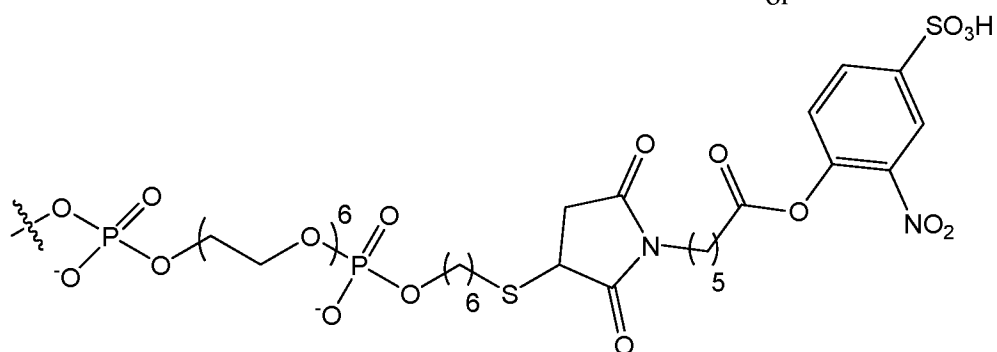
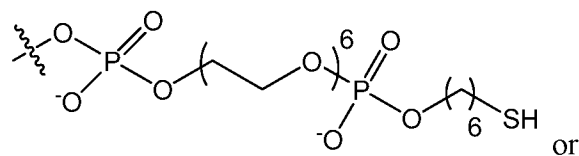
In certain embodiments, the antibody or cell surface receptor antagonist targets EGFR (e.g., EGFRvIII), HER 2, folate receptors, CD19, CD20, CD22, CD27L, CD30, CD33, CD37, CD56, CD66e, CD70, CD74, CD79b, CA6, CD138, CA 6, mesothelin, nectin 4, STEAP1, MUC16, MaPi2b, GCC, Trop-2, AGS-5, ENPP3,
25 carbonic anhydrase IX, GPNMB, PDMA,

In some other embodiments, L'' is an alkylene or heteroalkylene moiety. In some other certain embodiments, L'' comprises an alkylene oxide, phosphodiester moiety, a peptidyl linker, sulfhydryl, disulfide or maleimide moiety or combinations thereof.

30 In other more specific embodiments of any of the foregoing compounds of structure (I), R^2 or R^3 has one of the following structures:



5



Certain embodiments of compounds of structure (I) can be prepared according to solid-phase synthetic methods analogous to those known in the art for preparation of peptides. Accordingly, in some embodiments, L' is a linkage to a solid support, a solid support residue, a peptide or an amino acid. Various solid supports (e.g., polystyrene, polyamide, PEG-based), protecting groups (e.g., Fmoc, Boc, triphenylmethyl), activating groups (e.g., carbodiimides, triazoles) and other materials are readily available, and in some embodiments can be employed for preparation of compounds of structure (I). The solid support residue can be removed or modified post synthesis.

10 In still other embodiments, Q is, at each occurrence, independently a moiety comprising a reactive group capable of forming a covalent bond with an analyte molecule or a solid support. In other embodiments, Q is, at each occurrence, independently a moiety comprising a reactive group capable of forming a covalent bond with a complementary reactive group Q'. For example, in some embodiments, Q' is
15 present on a further compound of structure (I) (e.g., in the R² or R³ position), and Q and Q' comprise complementary reactive groups such that reaction of the compound of structure (I) and the further compound of structure (I) results in covalently bound dimer of the compound of structure (I). Multimer compounds of structure (I) can also be prepared in an analogous manner and are included within the scope of embodiments of
20 the invention.

The type of Q group and connectivity of the Q group to the remainder of the compound of structure (I) is not particularly limited, provided that Q comprises a moiety having appropriate reactivity for forming the desired bond.

In certain embodiments, Q is a moiety which is not susceptible to
25 hydrolysis under aqueous conditions, but is sufficiently reactive to form a bond with a corresponding group on an analyte molecule or solid support (e.g., an amine, azide or alkyne).

Certain embodiments of compounds of structure (I) comprise Q groups commonly employed in the field of bio-conjugation. For example in some
30 embodiments, Q comprises a nucleophilic reactive group, an electrophilic reactive group or a cycloaddition reactive group. In some more specific embodiments, Q

comprises a sulfhydryl, disulfide, activated ester, isothiocyanate, azide, alkyne, alkene, diene, dienophile, acid halide, sulfonyl halide, phosphine, α -haloamide, biotin, amino or maleimide functional group. In some embodiments, the activated ester is an N-succinimide ester, imidoester or polyfluorophenyl ester. In other embodiments, the

5 alkyne is an alkyl azide or acyl azide.

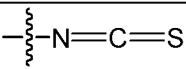
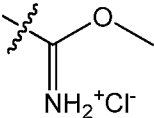
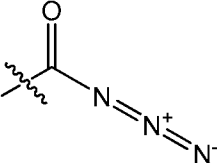
The Q groups can be conveniently provided in protected form to increase storage stability or other desired properties, and then the protecting group removed at the appropriate time for coupling with, for example, a targeting moiety or analyte. Accordingly, Q groups include "protected forms" of a reactive group, including any of

10 the reactive groups described above and in the Table 1 below. A "protected form" of Q refers to a moiety having lower reactivity under predetermined reaction conditions relative to Q, but which can be converted to Q under conditions, which preferably do not degrade or react with other portions of the compound of structure (I). One of skill in the art can derive appropriate protected forms of Q based on the particular Q and

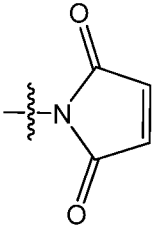
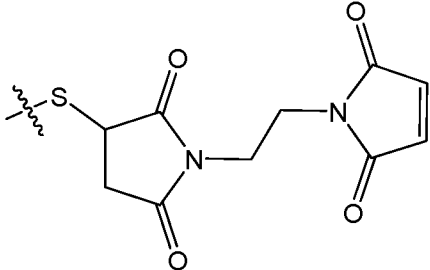
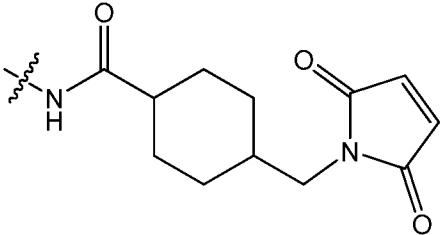
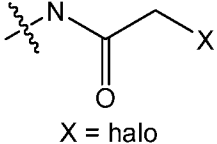
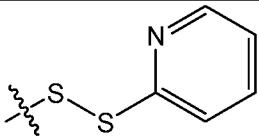
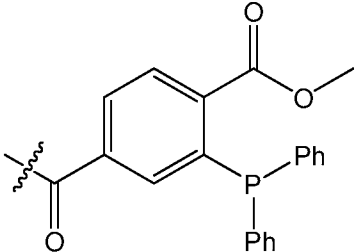
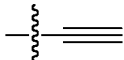
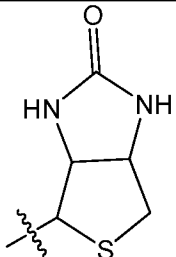
15 desired end use and storage conditions. For example, when Q is -SH, a protected form of Q includes a disulfide, which can be reduced to reveal the -SH moiety using commonly known techniques and reagents (e.g., TCEP).

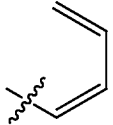
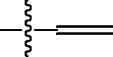
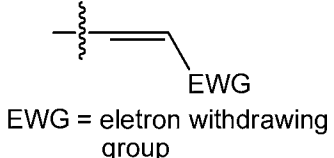
Exemplary Q moieties are provided in Table 1 below.

Table 1. Exemplary Q Moieties

Structure	Class
	Sulfhydryl
	Isothiocyanate
	Imidoester
	Acyl Azide

Structure	Class
	Activated Ester
	Activated Ester
	Activated Ester
	Activated Ester
	Activated Ester
	Activated Ester
X = halo	Sulfonyl halide

Structure	Class
	Maleimide
	Maleimide
	Maleimide
 X = halo	α -haloimide
	Disulfide
	Phosphine
	Azide
	Alkyne
	Biotin

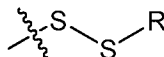
Structure	Class
	Diene
	Alkene/dienophile
	Alkene/dienophile
-NH ₂	Amino

It should be noted that in some embodiments, wherein Q is -SH, the -SH moiety will tend to form disulfide bonds with another sulfhydryl group, for example on another compound of structure (I). Accordingly, some embodiments include

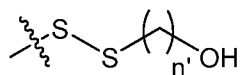
5 compounds of structure (I), which are in the form of disulfide dimers, the disulfide bond being derived from -SH Q groups.

In other embodiments, the Q moiety is conveniently masked (e.g., protected) as a disulfide moiety, which can later be reduced to provide an activated Q moiety for binding to a desired targeting moiety. For example, the Q moiety may be

10 masked as a disulfide having the following structure:



wherein R is an optionally substituted alkyl group. For example, in some embodiments, Q is provided as a disulfide moiety having the following structure:

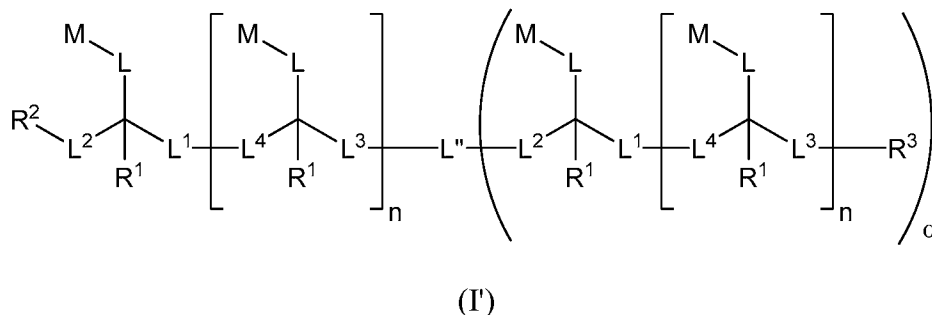


15 wherein n' is an integer from 1 to 10, for example, in some embodiments n' is 4, 5, 6 or 7.

Also included within the scope of certain embodiments are compounds of structure (I), wherein one, or both, of R² and R³ comprises a linkage to a further compound of structure (I). For example, wherein one or both of R² and R³ are

20 -OP(=R_a)(R_b)R_c, and R_c is OL', and L' is a linker comprising a covalent bond to a further compound of structure (I). Such compounds can be prepared by preparing a

first compound of structure (I) having for example about 10 "M" moieties (i.e., $n = 9$) and having an appropriate "Q" for reaction with a complementary Q' group on a second compound of structure (I). In this manner, compounds of structure (I), having any number of "M" moieties, for example 100 or more, can be prepared without the need for sequentially coupling each monomer. Exemplary embodiments of such compounds of structure (I) have the following structure (I')



wherein:

each occurrence of R^1 , R^2 , R^3 , L , L^1 , L^2 , L^3 , L^4 , M and n are independently as defined for a compound of structure (I);

L'' is a linker comprising a functional group resulting from reaction of a Q moiety with a corresponding Q' moiety; and

α is an integer greater than 1, for example from 1 to 100, or 1 to 10.

Other compounds of structure (I') are derivable by those of ordinary skill in the art, for example by dimerizing or polymerizing compounds of structure (I) provided herein.

In some other embodiments, one of R^2 or R^3 is OH or $-\text{OP}(=\text{R}_a)(\text{R}_b)\text{R}_c$, and the other of R^2 or R^3 is a linker comprising a covalent bond to a targeting moiety or a linker comprising a covalent bond to a solid support. For example, in some embodiments the targeting moiety is an antibody or cell surface receptor antagonist. In still different embodiments, the solid support is a polymeric bead or non-polymeric bead.

The value for m is another variable that can be selected based on the desired solubility, permeation effect or therapeutic application. In some embodiments, m is, at each occurrence, independently an integer from 1 to 20. In some embodiments, m is, at each occurrence, independently an integer from 1 to 10. In other embodiments,

m is, at each occurrence, independently an integer from 1 to 5, for example 1, 2, 3, 4 or 5.

The solubility, permeation or retention can also be tuned by selection of different values of n. In certain embodiments, n is an integer from 1 to 100. In other
 5 embodiments, n is an integer from 1 to 10. In some embodiments n is 1. In some embodiments n is 2. In some embodiments n is 3. In some embodiments n is 4. In some embodiments n is 5. In some embodiments n is 6. In some embodiments n is 7. In some embodiments n is 8. In some embodiments n is 9. In some embodiments n is 10.

10 Tumor cell antigens include tumor-specific antigens and tumor-associated antigens, for example EGFR, HER 2, folate receptors, CD 20, CD 33, oncofetal antigens (e.g., alphafetoprotein, carcinoembryonic antigen, immature laminin receptor, TAG-72), CA-125, MUC-1, epithelial tumor antigen, tyrosinase, melanoma-associated antigen (MAGE), and abnormal products of RAS or p53. Tumor cell
 15 antigens may also include antigens characterized as oncofetal, oncoviral (e.g., HPV E6, E7), overexpressed/accumulated (e.g., BING-4, calcium activated chloride channel 2, 9D7, Ep-CAM, EphA3, HER2, telomerase, mesothelin, SAP-1, survivin), cancer-tetis (e.g., BAGE family, CAGE family, GAGE family, MAGE family, SAGE family, XAGE family), lineage-restricted, mutated, post-translationally altered, idiotypic, CT9
 20 or CT10 (e.g., NY-ESO-1/LAGE-1, PRAME).

In some embodiments, M is at each occurrence, independently an NSAID, a kinase inhibitor, an anthracycline, EGFR inhibitor or an alkylating agent.

In some embodiments, at least one M is an anti-cancer drug. In certain specific embodiments, M is at each occurrence, independently an anti-cancer drug, and
 25 the targeting moiety is an antibody specific for a tumor cell antigen. In some embodiments, the tumor cell antigen is an EGFR, a HER 2, a folate receptor, CD 20 or CD 33.

Anti-cancer drug, as used herein, includes derivatives. That is, an anti-cancer drug that has been modified or derivatized such that the drug can be conjugated
 30 or attached to another molecule (e.g., to include Q moieties). For example, maytansine is a cancer drug and maytansinoids are cancer drug derivatives.

In certain embodiments, the anti-cancer drug is an epidermal growth factor receptor (EGFR) inhibitor, phosphatidylinositol kinase (PI3K) inhibitor, insulin-like growth factor receptor (IGF1R) inhibitor, Janus kinase (JAK) inhibitor, a Met kinase inhibitor, a SRC family kinase inhibitor, a mitogen-activated protein kinase (MEK) inhibitor, an extracellular-signal-regulated kinase (ERK) inhibitor, a topoisomerase inhibitors (such as irinotecan, or such as etoposide, or such as doxorubicin), taxanes (such as anti-microtubule agents including paclitaxel and docetaxel), anti-metabolite agents (such as 5-FU or such as gemcitabine), alkylating agents (such as cisplatin or such as cyclophosphamide), or a taxane.

Anti-cancer drugs that can be modified and incorporated into embodiments of compounds of the present disclosure include, for example, auristatin F; auristatin E; maytansine; calicheamicin; paclitaxel; doxorubicin; cryptophycin; erlotinib; CC-1065; carzelesin; SJG-136; DSB-120; afatinib; Iressa or methotrexate.

Other non-limiting examples of anti-cancer drugs include Gleevec® (Imatinib Mesylate), Velcade® (bortezomib), Casodex (bicalutamide), Iressa® (gefitinib), and Adriamycin, alkylating agents such as thiotepa and cyclophosphamide (CYTOXAN®); alkyl sulfonates such as busulfan, improsulfan and piposulfan; aziridines such as benzodopa, carboquone, meturedopa, and uredopa; ethylenimines and methylamelamines including altretamine, triethylenemelamine, triethylenephosphoramidate, triethylenethiophosphoramidate and trimethylolomelamine; nitrogen mustards such as chlorambucil, chlornaphazine, cholophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard; nitrosureas such as carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine; antibiotics such as aclacinomysins, actinomycin, authramycin, azaserine, bleomycins, cactinomycin, calicheamicin, carabycin, carminomycin, carzinophilin, Casodex®, chromomycins, dactinomycin, daunorubicin, detorubicin, 6-diazo-5-oxo-L-norleucine, doxorubicin, epirubicin, esorubicin, idarubicin, marcellomycin, mitomycins, mycophenolic acid, nogalamycin, olivomycins, peplomycin, potfiromycin, puromycin, quelamycin, rodorubicin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin; anti-metabolites such as methotrexate and 5-fluorouracil (5-FU); folic acid

analogues such as denopterin, methotrexate, pteropterin, trimetrexate; purine analogs such as fludarabine, 6-mercaptopurine, thiamiprine, thioguanine; pyrimidine analogs such as ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, androgens such as calusterone, dromostanolone

5 propionate, epitiostanol, mepitiothane, testolactone; anti-adrenals such as aminogluthethimide, mitotane, trilostane; folic acid replenisher such as frolinic acid; aceglutone; aldophosphamide glycoside; aminolevulinic acid; amsacrine; bestrabucil; bisantrene; edatraxate; defofamine; demecolcine; diaziquone; elfomithine; elliptinium acetate; etoglucid; gallium nitrate; hydroxyurea; lentinan; lonidamine; mitoguazone;

10 mitoxantrone; mopidamol; nitracrine; pentostatin; phenamet; pirarubicin; podophyllinic acid; 2-ethylhydrazide; procarbazine; PSK.RTM.; razoxane; sizofiran; spirogermanium; tenuazonic acid; triaziquone; 2,2',2''-trichlorotriethylamine; urethan; vindesine; dacarbazine; mannomustine; mitobronitol; mitolactol; pipobroman; gacytosine; arabinoside ("Ara-C"); cyclophosphamide; thiotepa; taxanes, e.g. paclitaxel

15 (TAXOLTM, Bristol-Myers Squibb Oncology, Princeton, N.J.) and docetaxel (TAXOTERETM, Rhone-Poulenc Rorer, Antony, France); retinoic acid; esperamicins or capecitabine. Also included as suitable cancer drugs are anti-hormonal agents that act to regulate or inhibit hormone action on tumors such as anti-estrogens including for example tamoxifen, (NolvadexTM), raloxifene, aromatase inhibiting 4(5)-imidazoles, 4-

20 hydroxytamoxifen, trioxifene, keoxifene, LY 117018, onapristone, and toremifene (Fareston); and anti-androgens such as flutamide, nilutamide, bicalutamide, leuprolide, and goserelin; chlorambucil; gemcitabine; 6-thioguanine; mercaptopurine; methotrexate; platinum analogs such as cisplatin and carboplatin; vinblastine; platinum; etoposide (VP-16); ifosfamide; mitomycin C; mitoxantrone; vincristine; vinorelbine;

25 navelbine; novantrone; teniposide; daunomycin; aminopterin; xeloda; ibandronate; camptothecin-11 (CPT-11); topoisomerase inhibitor RFS 2000; difluoromethylornithine (DMFO).

In certain embodiments, at least one M is a tyrosine kinase inhibitor (e.g., gefitinib, erlotinib), lapatinib, Vandetanib, neratinib, osimertinib, Tovantinib

30 (ARQ197), Crizotinib, Cabozantinib, tyrphostins (e.g., AG538, AG1024), pyrrolo(2,3-d)-pyrimidine derivatives (e.g., NVP-AEW541), monoclonal antibody (e.g.,

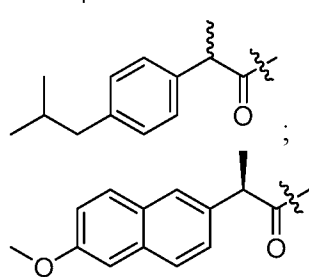
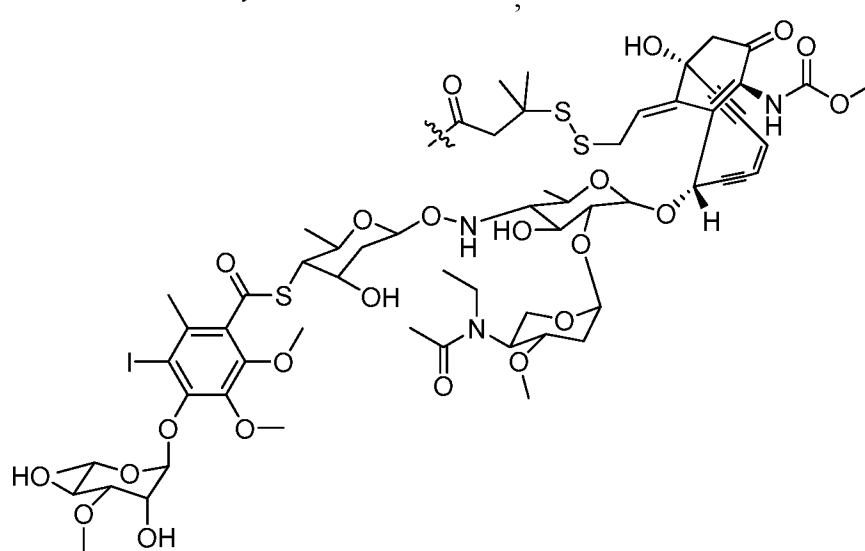
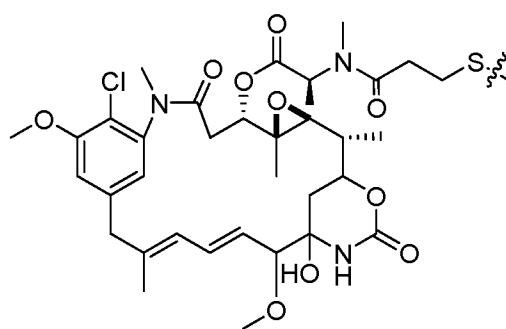
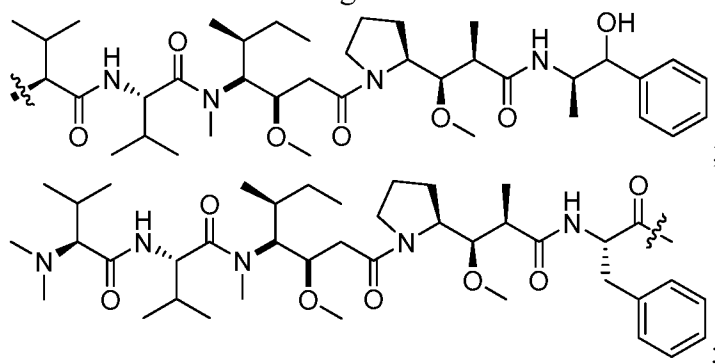
figitumumab, cetuximab, panitumumab, necitumumab, ganitumab, cixutumumab, dalotuzumab, robatumumab, onartuzumab, K1, labetuzumab, milatuzumab, lorvotuzumab, inotuzumab), BMS-777607, PF-02341066, PF-04217903, AMG-458, MK-2461, JNJ-38877605, GSK 1363089 (foretinib), XL880, XL 184, ARQ197, E7050, 5 or INCB28060.

Where desired, embodiments of the compounds or composition of the present disclosure can be used in combination with commonly prescribed anti-cancer drugs such as Herceptin®, Avastin®, Erbitux®, Rituxan®, Taxol®, Arimidex®, Taxotere®, ABVD, AVICINE, Abagovomab, Acridine carboxamide, Adecatumumab, 10 17-N-Allylamino-17-demethoxygeldanamycin, Alpharadin, Alvocidib, 3-Aminopyridine-2-carboxaldehyde thiosemicarbazone, Amonafide, Anthracenedione, Anti-CD22 immunotoxins, Antineoplastic, Antitumorigenic herbs, Apaziquone, Atiprimod, Azathioprine, Belotecan, Bendamustine, BIBW 2992, Biricodar, Brostallicin, Bryostatin, Buthionine sulfoximine, CBV (chemotherapy), Calyculin, cell- 15 cycle nonspecific antineoplastic agents, Dichloroacetic acid, Discodermolide, Elsamitucin, Enocitabine, Epothilone, Eribulin, Everolimus, Exatecan, Exisulind, Ferruginol, Forodesine, Fosfestrol, ICE chemotherapy regimen, IT-101, Imexon, Imiquimod, Indolocarbazole, Irofulven, Laniquidar, Larotaxel, Lenalidomide, Lucanthone, Lurtotecan, Mafosfamide, Mitozolomide, Nafoxidine, Nedaplatin, 20 Olaparib, Ortataxel, PAC-1, Pawpaw, Pixantrone, Proteasome inhibitor, Rebeccamycin, Resiquimod, Rubitecan, SN-38, Salinosporamide A, Sapacitabine, Stanford V, Swainsonine, Talaporfin, Tariquidar, Tegafur-uracil, Temodar, Tesetaxel, Triplatin tetranitrate, Tris(2-chloroethyl)amine, Troxacitabine, Uramustine, Vadimezan, Vinflunine, ZD6126 or Zosuquidar.

25 M is selected based on the desired therapeutic and/or optical properties, for example based on treating a specific disease or condition (e.g., cancer) or producing a particular color and/or fluorescence emission wavelength. In some embodiments, M is the same at each occurrence; however, it is important to note that each occurrence of M need not be an identical M, and certain embodiments include compounds wherein M 30 is not the same at each occurrence. For example, in some embodiments, each M is not the same and the different M moieties are selected to have different therapeutic

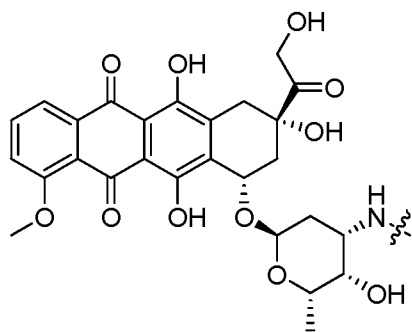
properties (e.g., cytotoxic and anti-inflammatory). In some embodiments, each M is not the same and the different M moieties are selected to have the same or similar therapeutic properties (e.g., cytotoxicity). In certain embodiments, each M is independently selected from the following:

5



10

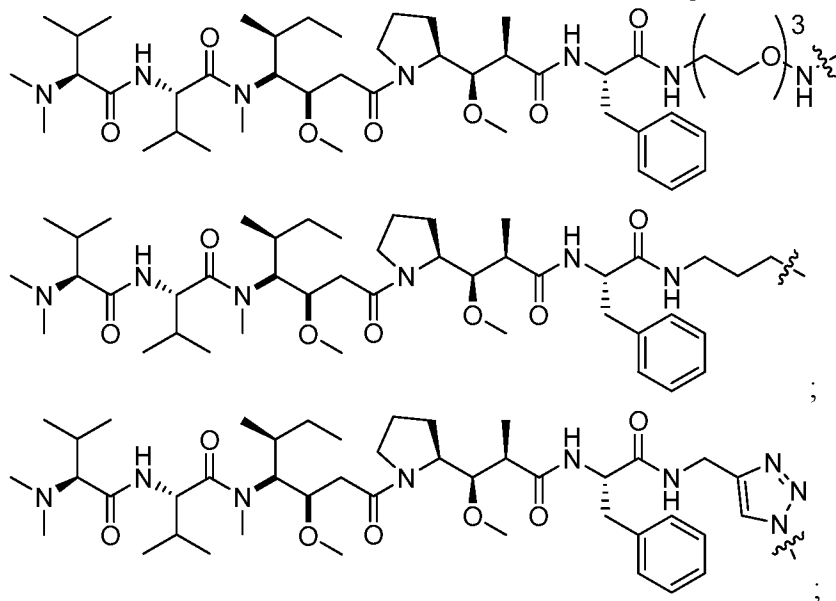
and

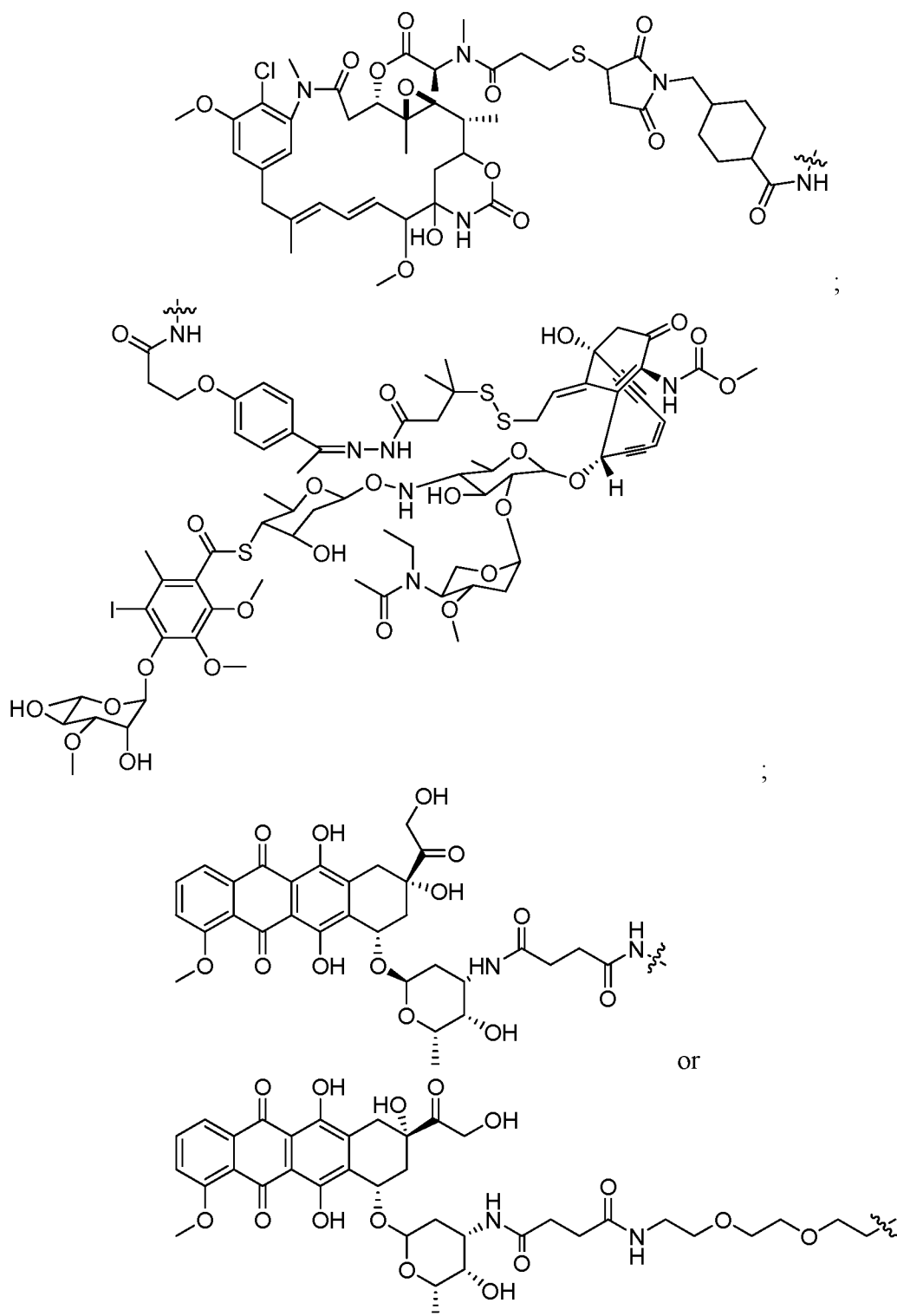


Although depicted having specific points of attachment (i.e., $\sim$) with the remainder of the molecule for ease of illustration, the M moiety may be attached via any available point. One of skill in the art can determine an appropriate attachment

5 point.

In certain embodiments, L-M has one of the following structures:





5 In still more embodiments of any of the foregoing, M is the same. In other embodiments, each M is different. In still more embodiments, one or more M is the same and one or more M is different.

In some embodiments selected occurrences of M are not the same and the different M moieties are selected to have absorbance and/or emissions for use in

fluorescence resonance energy transfer (FRET) methods. For example, in such embodiments the different M moieties are selected such that absorbance of radiation at one wavelength causes emission of radiation at a different wavelength by a FRET mechanism. Exemplary M moieties can be appropriately selected by one of ordinary skill in the art based on the desired end use. Exemplary M moieties for FRET methods include fluorescein and 5-TAMRA (5-carboxytetramethylrhodamine, succinimidyl ester) dyes.

M may be attached to the remainder of the molecule from any position (i.e., atom) on M. One of skill in the art will recognize means for attaching M to the remainder of molecule. Exemplary methods include the "click" reactions described herein.

In some embodiments, at least one M is a fluorescent or colored moiety. Any fluorescent and/or colored moiety may be used, for examples those known in the art and typically employed in colorimetric, UV, and/or fluorescent assays may be used. Examples of M moieties which are useful in various embodiments of the invention include, but are not limited to: Xanthene derivatives (e.g., fluorescein, rhodamine, Oregon green, eosin or Texas red); Cyanine derivatives (e.g., cyanine, indocarbocyanine, oxacarbocyanine, thiocarbocyanine or merocyanine); Squaraine derivatives and ring-substituted squaraines, including Seta, SeTau, and Square dyes; Naphthalene derivatives (e.g., dansyl and prodan derivatives); Coumarin derivatives; oxadiazole derivatives (e.g., pyridyloxazole, nitrobenzoxadiazole or benzoxadiazole); Anthracene derivatives (e.g., anthraquinones, including DRAQ5, DRAQ7 and CyTRAK Orange); Pyrene derivatives such as cascade blue; Oxazine derivatives (e.g., Nile red, Nile blue, cresyl violet, oxazine 170); Acridine derivatives (e.g., proflavin, acridine orange, acridine yellow); Arylmethine derivatives: auramine, crystal violet, malachite green; and Tetrapyrrole derivatives (e.g., porphin, phthalocyanine or bilirubin). Other exemplary M moieties include: Cyanine dyes, xanthate dyes (e.g., Hex, Vic, Nedd, Joe or Tet); Yakima yellow; Redmond red; tamra; texas red and alexa fluor® dyes.

In still other embodiments of any of the foregoing, at least one M comprises three or more aryl or heteroaryl rings, or combinations thereof, for example

four or more aryl or heteroaryl rings, or combinations thereof, or even five or more aryl or heteroaryl rings, or combinations thereof. In some embodiments, at least one M comprises six aryl or heteroaryl rings, or combinations thereof. In further embodiments, the rings are fused. For example in some embodiments, at least one M comprises three or more fused rings, four or more fused rings, five or more fused rings, or even six or more fused rings.

In some embodiments, at least one M is cyclic. For example, in some embodiments at least one M is carbocyclic. In other embodiment, at least one M is heterocyclic. In still other embodiments of the foregoing, at least one M, at each occurrence, independently comprises an aryl moiety. In some of these embodiments, the aryl moiety is multicyclic. In other more specific examples, the aryl moiety is a fused-multicyclic aryl moiety, for example which may comprise at least 3, at least 4, or even more than 4 aryl rings.

In other embodiments of any of the foregoing compounds of structure (I) or (I'), at least one M comprises at least one heteroatom. For example, in some embodiments, the heteroatom is nitrogen, oxygen or sulfur.

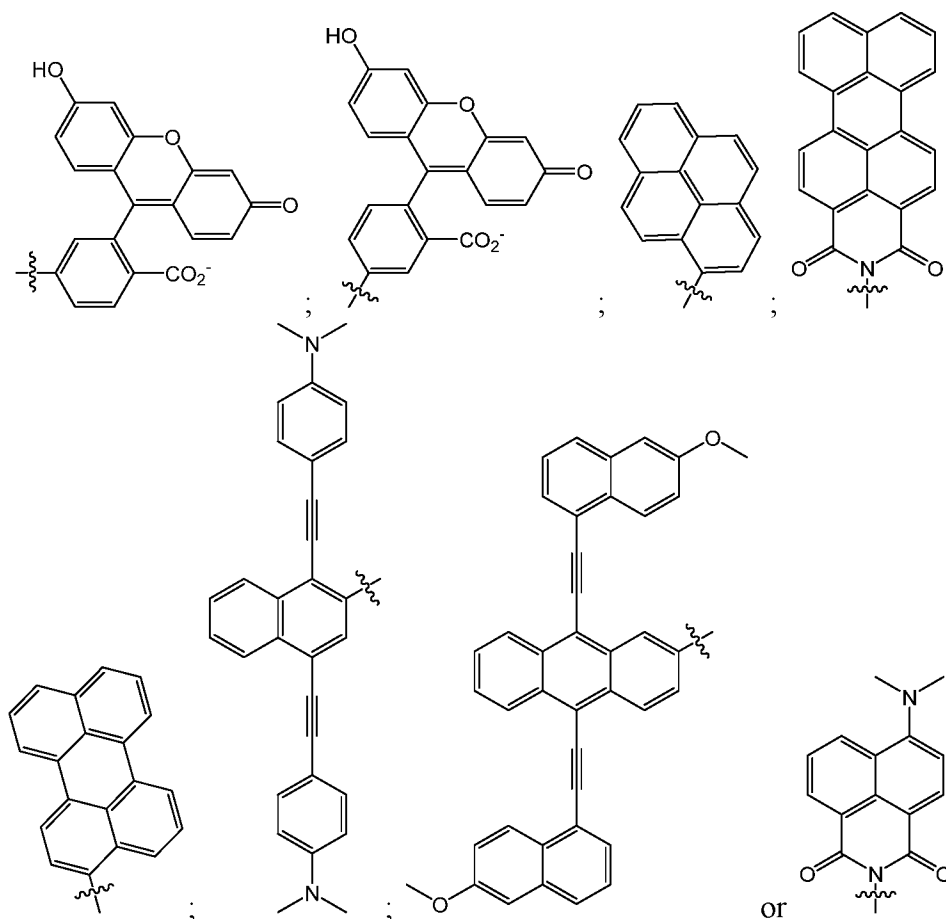
In still more embodiments of any of the foregoing, at least one M comprises at least one substituent. For example, in some embodiments the substituent is a fluoro, chloro, bromo, iodo, amino, alkylamino, arylamino, hydroxy, sulfhydryl, alkoxy, aryloxy, phenyl, aryl, methyl, ethyl, propyl, butyl, isopropyl, t-butyl, carboxy, sulfonate, amide, or formyl group.

In some even more specific embodiments of the foregoing, at least one M is a dimethylaminostilbene, quinacridone, fluorophenyl-dimethyl-BODIPY, his-fluorophenyl-BODIPY, acridine, terrylene, sexiphenyl, porphyrin, benzopyrene, (fluorophenyl-dimethyl-difluorobora-diaza-indacene)phenyl, (bis-fluorophenyl-difluorobora-diaza-indacene)phenyl, quaterphenyl, bi-benzothiazole, ter-benzothiazole, bi-naphthyl, bi-anthracyl, squaraine, squarylium, 9, 10-ethynylanthracene or ter-naphthyl moiety. In other embodiments, at least one M is p-terphenyl, perylene, azobenzene, phenazine, phenanthroline, acridine, thioxanthrene, chrysene, rubrene, coronene, cyanine, perylene imide, or perylene amide or a derivative thereof. In still more embodiments, at least one M is a coumarin dye, resorufin dye,

dipyrrometheneboron difluoride dye, ruthenium bipyridyl dye, energy transfer dye, thiazole orange dye, polymethine or N-aryl-1,8-naphthalimide dye.

In some embodiments, at least one M is pyrene, perylene, perylene monoimide or 6-FAM or a derivative thereof. In some other embodiments, at least one

5 M has one of the following structures:



Although M moieties comprising carboxylic acid groups are depicted in the anionic form (CO_2^-) above, one of skill in the art will understand that this will vary depending on pH, and the protonated form (CO_2H) is included in various embodiments.

In some specific embodiments, the compound is a compound selected from Table 2.

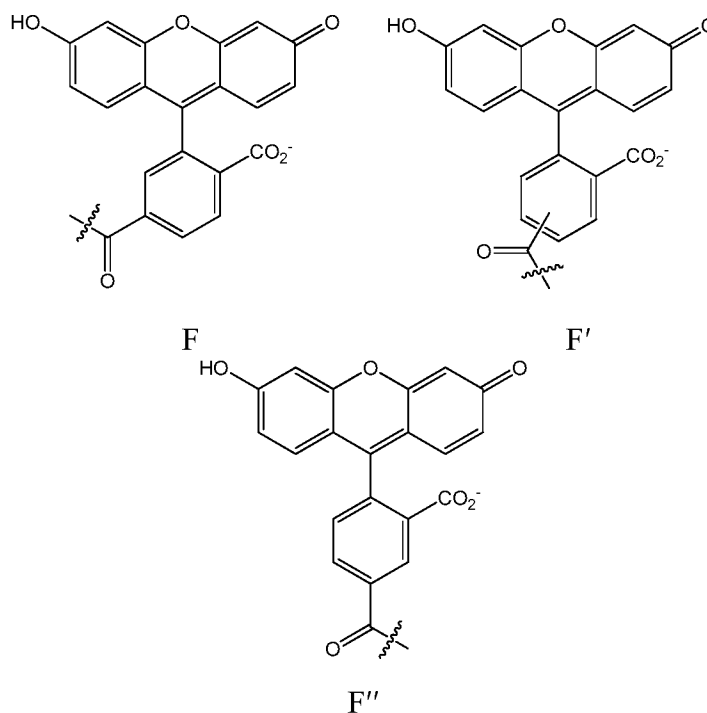
Table 2. Exemplary Compounds of Structure I

#	Structure
I-1	
I-2	
I-3	
I-4	

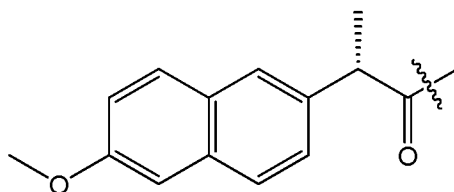
#	Structure
I-5	$\text{R}^2 \left[\text{C}(=\text{O}) \text{CH}_2 \text{N}^+(\text{CH}_3)_3 \text{CH}_2 \text{CH}_2 \text{NH} \text{C}(=\text{O}) \text{CH}_2 \text{NH} \text{C}(=\text{O}) \text{CH}(\text{M}) \text{CH}_2 \text{N} \text{H} \right] \text{R}^3_y$
I-6	$\text{R}^2 \left[\text{C}(=\text{O}) \text{CH}_2 \text{N}^+(\text{CH}_3)_3 \text{CH}_2 \text{CH}_2 \text{NH} \text{C}(=\text{O}) \text{CH}(\text{M}) \text{CH}_2 \text{N} \text{H} \right] \text{R}^3_y$
I-7	$\text{R}^2 \left[\text{C}(=\text{O}) \text{CH}_2 \text{N}^+(\text{CH}_3)_3 \text{CH}_2 \text{CH}_2 \text{NH} \text{C}(=\text{O}) \text{CH}(\text{M}) \text{CH}_2 \text{N} \text{H} \right] \text{R}^3_y$
I-8	$\text{R}^2 \left[\text{C}(=\text{O}) \text{CH}_2 \text{N}^+(\text{CH}_3)_3 \text{CH}_2 \text{CH}_2 \text{NH} \text{C}(=\text{O}) \text{CH}(\text{M}) \text{CH}_2 \text{N} \text{H} \right] \text{R}^3_y$

#	Structure
I-9	

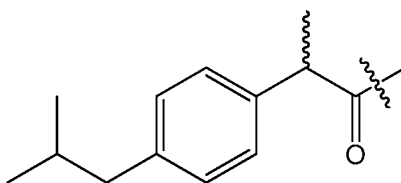
As used in Tables 2 and throughout the application R^2 , R^3 , L, M and n have the definitions provided for compounds of structure (I) unless otherwise indicated. As used in Table 2, in some embodiments, x is, at each occurrence, independently an integer of 1 or greater, and y is an integer of 2 or greater. In some embodiments, x is an integer of 2 or greater. R^2 , R^3 and L^1 are as defined herein. In some embodiments, M is, at each occurrence, independently F, F', F'', N', I', D', or D'', provided that at least one M is N', I', D', or D''. F, F' and F'' refer to a fluorescein moiety having the following structures, respectively:



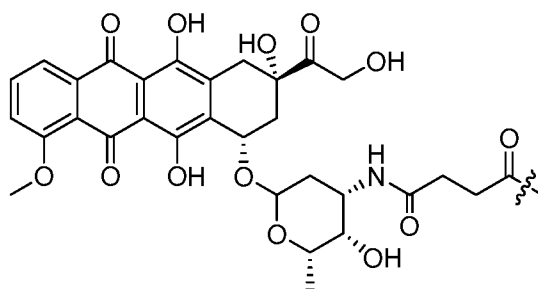
" N' " refers to the following structure:



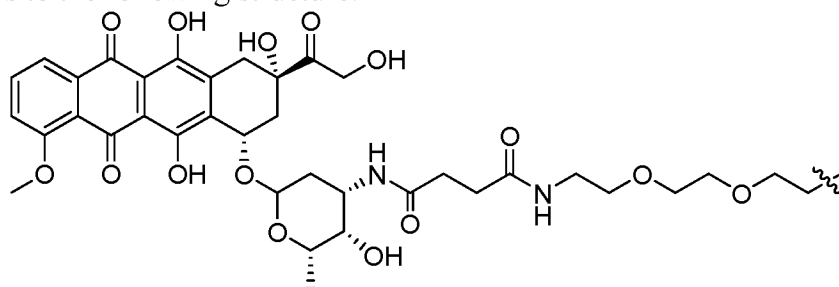
" I' " refers to the following structure:



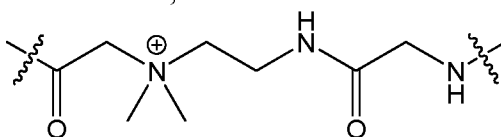
5 " D' " refers to the following structure:



" D' " refers to the following structure:

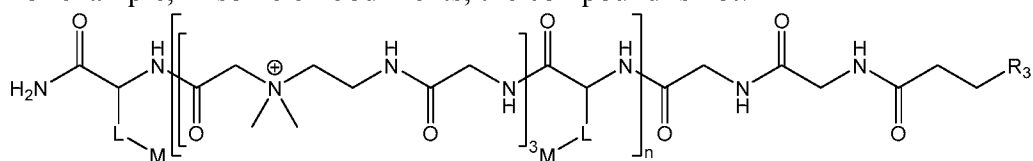


In some embodiments, L⁴ does not include the following structure:



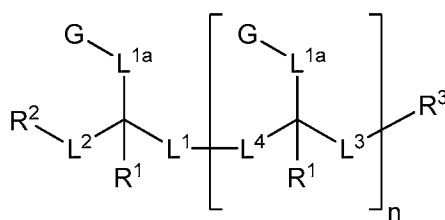
10

For example, in some embodiments, the compound is not:



Some embodiments include any of the foregoing compounds, including the specific compounds provided in Table 2, conjugated to a targeting moiety, such as an antibody. In some embodiments, one compound of structure (I) is conjugated to an antibody. In some embodiments, 1-2 compounds of structure (I) are conjugated to an antibody. In some embodiments, 2 compounds of structure (I) are conjugated to an antibody. In some embodiments, 3 compounds of structure (I) are conjugated to an antibody. In some embodiments, 4 compounds of structure (I) are conjugated to an antibody. In some embodiments, 5 compounds of structure (I) are conjugated to an antibody. In some embodiments, no more than 5 compounds of structure (I) are conjugated to an antibody.

In various embodiments, reactive polymers can be used to prepare compounds of structure (I). In certain embodiments, these reactive polymers are synthetic intermediates that comprise a moiety useful for reacting with a complementary moiety to form a covalent bond between M and the reactive polymer via any number of synthetic methodologies (e.g., the "click" reactions described above), thereby forming a compound of structure (I). Accordingly, in various embodiments a compound of structure (I) is formed using a reactive polymer having the following structure (II):



20

(II)

or a stereoisomer, salt or tautomer thereof, wherein:

G is, at each occurrence, independently a moiety comprising a reactive group, or protected analogue thereof, capable of forming a covalent bond with a complementary reactive group;

L^{1a} , L^1 , L^2 and L^3 are, at each occurrence, independently an optional alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene or heteroatomic linker;

L^4 is, at each occurrence, independently an alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene or heteroalkynylene linker comprising one or more charged moieties, provided at least one charged moiety is not a phosphate ester;

5 R^1 is, at each occurrence, independently H, alkyl or alkoxy;;

R^2 and R^3 are each independently -H, -OH, -SH, alkyl, alkoxy, alkylether, heteroalkyl, alkylaminyl, alkylcarbonyl, alkoxy carbonyl, $-OP(=R_a)(R_b)R_c$, Q or a protected form thereof, or L' ;

R_a is O or S;

10 R_b is OH, SH, O^- , S^- , OR_d or SR_d ;

R_c is OH, SH, O^- , S^- , OR_d , OL' , SR_d , alkyl, alkoxy, heteroalkyl, heteroalkoxy, alkylether, alkoxyalkylether, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether or thiophosphoalkylether;

R_d is a counter ion;

15 Q is, at each occurrence, independently a moiety comprising a reactive group, or protected form thereof, capable of forming a covalent bond with a complementary reactive group Q' on a targeting moiety;

L' is, at each occurrence, independently a linker comprising a covalent bond to Q, a targeting moiety, a linker comprising a covalent bond to a targeting moiety, a solid support or solid support residue, a linker comprising a covalent bond to a solid support or solid support residue or a linker comprising a covalent bond to a further compound of structure (II); and

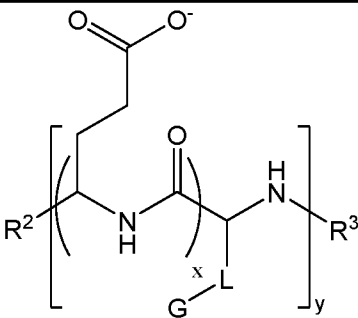
n is an integer of one or greater.

In some embodiments, the reactive polymer is selected from Table 3,
25 below.

Table 3. Exemplary Compounds of Structure II

#	Structure
II-1	
II-2	
II-3	
II-4	

#	Structure
II-5	
II-6	
II-7	
II-8	

#	Structure
II-9	

In various embodiments, G in the compounds of Table 3 is alkynyl, such as ethynyl. In other embodiments, G in the compounds of Table 3 is an azide. In other embodiments, G in the compounds of Table 3 is amino (NH₂). In other embodiments, G in the compounds of Table 3 is an isothiocyanate. In other embodiments, G in the compounds of Table 3 is an activated ester, such as an ester of N-hydroxysuccinimide.

Certain embodiments are directed to a therapeutically effective fluorescent compound provided at least one occurrence of M is not a fluorescent dye and at least one occurrence of M is a fluorescent dye. Therapeutically effective fluorescent compounds include compounds comprising at least one biologically active moiety or fragment thereof or a prodrug of a biologically active moiety, or fragment thereof, which emit a fluorescent signal upon excitation with light, such as ultraviolet light.

For ease of illustration, various compounds comprising phosphorous moieties (e.g., phosphate and the like) are depicted in the anionic state (e.g., -OPO(OH)O⁻, -OPO₃²⁻). One of skill in the art will readily understand that the charge is dependent on pH and the uncharged (e.g., protonated or salt, such as sodium or other cation) forms are also included in the scope of embodiments of the invention.

Compositions comprising any of the foregoing compounds and one or more targeting moiety (e.g., antibody or cell surface receptor antagonist) are provided in various other embodiments. In some embodiments, use of such compositions in methods for treating a disease the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of structure (I) or a composition comprising a compound of structure (I) wherein each M is independently a biologically active moiety effective for treating the disease are also provided.

Pharmaceutical Compositions

One embodiment provides a composition comprising the compound according any one of the embodiments disclosed herein and a pharmaceutically acceptable carrier.

- 5 Another embodiment provides a composition comprising a plurality of conjugates, the conjugates comprising a compound of claim 1 covalently bound to an antibody via a single linkage, wherein the plurality of conjugates has at least 90% structural homogeneity. "Structural homogeneity" means compounds having the same structure, including attachment point to the antibody. In more specific embodiments,
- 10 the plurality of conjugates has at least 95% structural homogeneity. In related embodiments, the plurality of conjugates has greater than 99% structural homogeneity. In certain embodiments, one of R^2 and R^3 is $-OP(=R_a)(R_b)OL'$ or L' , and L' is the antibody or a linker comprising a covalent bond to the antibody.

- Other embodiments are directed to pharmaceutical compositions. The
- 15 pharmaceutical composition comprises any one (or more) of the foregoing compounds and a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated for oral administration. In other embodiments, the pharmaceutical composition is formulated for injection. In still more embodiments, the pharmaceutical compositions comprise a compound as disclosed herein and an
- 20 additional therapeutic agent (e.g., anticancer agent). Non-limiting examples of such therapeutic agents are described herein below.

- Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of
- 25 example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

- In certain embodiments, a compound as described herein is administered in a local rather than systemic manner, for example, via injection of the compound
- 30 directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for

example subcutaneously or intramuscularly) or by intramuscular injection.

Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such

embodiments, the liposomes are targeted to and taken up selectively by the organ. In

- 5 yet other embodiments, the compound as described herein is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, the compound described herein is administered topically.

- The compounds according to embodiments of the invention are effective
- 10 over a wide dosage range. For example, in the treatment of adult humans, dosages from 0.01 to 1000 mg, from 0.5 to 100 mg, from 1 to 50 mg per day, and from 5 to 40 mg per day are examples of dosages that are used in some embodiments. An exemplary dosage is 10 to 30 mg per day. The exact dosage will depend upon the route of administration, the form in which the compound is administered, the subject to be treated, the body
- 15 weight of the subject to be treated, and the preference and experience of the attending physician.

- In some embodiments, a compound of the invention is administered in a single dose. Typically, such administration will be by injection, e.g., intravenous injection, in order to introduce the agent quickly. However, other routes are used as
- 20 appropriate. A single dose of a compound of the invention may also be used for treatment of an acute condition.

- In some embodiments, a compound of the invention is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, or more than six times per day. In other embodiments,
- 25 dosing is about once a month, once every two weeks, once a week, or once every other day. In another embodiment a compound of the invention and another agent are administered together about once per day to about 6 times per day. In another embodiment the administration of a compound of the invention and an agent continues for less than about 7 days. In yet another embodiment the administration continues for
- 30 more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, continuous dosing is achieved and maintained as long as necessary.

Administration of embodiments of the compounds of the invention may continue as long as necessary. In some embodiments, a compound of the invention is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a compound of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day.

- 5 In some embodiments, a compound of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic effects.

In some embodiments, the compounds of the invention are administered in dosages. It is known in the art that due to intersubject variability in compound pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy.

- 10 Dosing for an embodiment of a compound of the invention may be found by routine experimentation in light of the instant disclosure.

In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more

- 15 physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: Remington:
20 The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980; and
25 Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999).

- Provided herein are pharmaceutical compositions comprising a compound of structure (I) and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In certain embodiments, the compounds described are administered as pharmaceutical compositions in which compounds of structure (I) are mixed with other
30 active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this

disclosure. In specific embodiments, the pharmaceutical compositions include one or more compounds of structure (I).

A pharmaceutical composition, as used herein, refers to a mixture of a compound of structure (I) with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the compound to an organism. In some embodiments, practicing the methods of treatment or use provided herein, therapeutically effective amounts of compounds of structure (I) provided herein are administered in a pharmaceutical composition to a mammal having a disease, disorder or medical condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. The compounds described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

In one embodiment, one or more compounds of structure (I) is formulated in an aqueous solutions. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more compound of structure (I) is/are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the compounds described herein are formulated for other parenteral injections, appropriate formulations include aqueous or non-aqueous solutions. In specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

In another embodiment, compounds described herein are formulated for oral administration. Compounds described herein are formulated by combining the active compounds with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, the compounds described herein are formulated in oral dosage

forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the compounds described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

In certain embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other

embodiments, soft capsules contain one or more active compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

5 In other embodiments, therapeutically effective amounts of at least one of the compounds described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the compounds described herein are formulated for parental injection, including
10 formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical compositions are formulated in a form suitable for parenteral injection as sterile suspensions, solutions or
15 emulsions in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active compounds in water-soluble form. In additional embodiments, suspensions of the active compounds (e.g., compounds of structure (I))
20 are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as
25 sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

30 In still other embodiments, the compounds of structure (I) are administered topically. The compounds described herein are formulated into a variety

of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

5 In yet other embodiments, the compounds of structure (I) are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for
10 continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of the compounds of structure (I) is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the compounds of structure (I). In specific embodiments, the rate of absorption is slowed by using rate-controlling
15 membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption. Absorption enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the
20 compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

 In other embodiments, the compounds of structure (I) are formulated for administration by inhalation. Various forms suitable for administration by inhalation
25 include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of any of compound of structure (I) are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant (e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific
30 embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of,

such as, by way of example only, gelatin for use in an inhaler or insufflator is formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

In still other embodiments, the compounds of structure (I) are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are optionally used as suitable. Pharmaceutical compositions comprising a compound of structure (I) are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and at least one compound of structure (I), described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. In addition, the methods and pharmaceutical compositions described herein include the use of N-oxides, crystalline forms (also known as polymorphs), as well as active metabolites of these compounds having the same type of activity. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In

addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

5 Methods for the preparation of compositions comprising the compounds described herein include formulating the compounds with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in
10 which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior
15 to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

 In some embodiments, a pharmaceutical composition comprising at least one compound of structure (I) illustratively takes the form of a liquid where the agents
20 are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

25 In certain embodiments, useful aqueous suspensions contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example
30 from carboxymethylcellulose, carbomer (acrylic acid polymer),

poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a compound of structure (I). The term
5 "solubilizing agent" generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

Furthermore, useful pharmaceutical compositions optionally include one
10 or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an
15 amount required to maintain pH of the composition in an acceptable range.

Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or
20 bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and
25 quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60)
30 hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

In certain embodiments, aqueous suspension compositions are packaged
5 in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of
10 delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as N-methylpyrrolidone are also employed. In additional embodiments, the compounds described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments,
15 sustained-release capsules release the compounds for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other
20 general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h)
25 arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

In some embodiments, the concentration of one or more compounds provided in the pharmaceutical compositions is less than 100%, 90%, 80%, 70%, 60%,
30 50%, 40%, 30%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%,

0.07%, 0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%,
0.006%, 0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%,
0.0006%, 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v or v/v.

In some embodiments, the concentration of one or more compounds is
5 greater than 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 19.75%, 19.50%, 19.25%
19%, 18.75%, 18.50%, 18.25% 18%, 17.75%, 17.50%, 17.25% 17%, 16.75%, 16.50%,
16.25% 16%, 15.75%, 15.50%, 15.25% 15%, 14.75%, 14.50%, 14.25% 14%, 13.75%,
13.50%, 13.25% 13%, 12.75%, 12.50%, 12.25% 12%, 11.75%, 11.50%, 11.25% 11%,
10.75%, 10.50%, 10.25% 10%, 9.75%, 9.50%, 9.25% 9%, 8.75%, 8.50%, 8.25% 8%,
10 7.75%, 7.50%, 7.25% 7%, 6.75%, 6.50%, 6.25% 6%, 5.75%, 5.50%, 5.25% 5%,
4.75%, 4.50%, 4.25%, 4%, 3.75%, 3.50%, 3.25%, 3%, 2.75%, 2.50%, 2.25%, 2%,
1.75%, 1.50%, 1.25%, 1%, 0.5%, 0.4%, 0.3%, 0.2%, 0.1%, 0.09%, 0.08%, 0.07%,
0.06%, 0.05%, 0.04%, 0.03%, 0.02%, 0.01%, 0.009%, 0.008%, 0.007%, 0.006%,
0.005%, 0.004%, 0.003%, 0.002%, 0.001%, 0.0009%, 0.0008%, 0.0007%, 0.0006%,
15 0.0005%, 0.0004%, 0.0003%, 0.0002%, or 0.0001% w/w, w/v, or v/v.

In some embodiments, the concentration of one or more compounds is in
the range from approximately 0.0001% to approximately 50%, approximately 0.001%
to approximately 40 %, approximately 0.01% to approximately 30%, approximately
0.02% to approximately 29%, approximately 0.03% to approximately 28%,
20 approximately 0.04% to approximately 27%, approximately 0.05% to approximately
26%, approximately 0.06% to approximately 25%, approximately 0.07% to
approximately 24%, approximately 0.08% to approximately 23%, approximately 0.09%
to approximately 22%, approximately 0.1% to approximately 21%, approximately 0.2%
to approximately 20%, approximately 0.3% to approximately 19%, approximately 0.4%
25 to approximately 18%, approximately 0.5% to approximately 17%, approximately 0.6%
to approximately 16%, approximately 0.7% to approximately 15%, approximately 0.8%
to approximately 14%, approximately 0.9% to approximately 12%, approximately 1%
to approximately 10% w/w, w/v or v/v.

In some embodiments, the concentration of one or more compounds is in
30 the range from approximately 0.001% to approximately 10%, approximately 0.01% to
approximately 5%, approximately 0.02% to approximately 4.5%, approximately 0.03%

to approximately 4%, approximately 0.04% to approximately 3.5%, approximately 0.05% to approximately 3%, approximately 0.06% to approximately 2.5%, approximately 0.07% to approximately 2%, approximately 0.08% to approximately 1.5%, approximately 0.09% to approximately 1%, approximately 0.1% to approximately 0.9% w/w, w/v or v/v.

In some embodiments, the amount of one or more compounds is equal to or less than 10 g, 9.5 g, 9.0 g, 8.5 g, 8.0 g, 7.5 g, 7.0 g, 6.5 g, 6.0 g, 5.5 g, 5.0 g, 4.5 g, 4.0 g, 3.5 g, 3.0 g, 2.5 g, 2.0 g, 1.5 g, 1.0 g, 0.95 g, 0.9 g, 0.85 g, 0.8 g, 0.75 g, 0.7 g, 0.65 g, 0.6 g, 0.55 g, 0.5 g, 0.45 g, 0.4 g, 0.35 g, 0.3 g, 0.25 g, 0.2 g, 0.15 g, 0.1 g, 0.09 g, 0.08 g, 0.07 g, 0.06 g, 0.05 g, 0.04 g, 0.03 g, 0.02 g, 0.01 g, 0.009 g, 0.008 g, 0.007 g, 0.006 g, 0.005 g, 0.004 g, 0.003 g, 0.002 g, 0.001 g, 0.0009 g, 0.0008 g, 0.0007 g, 0.0006 g, 0.0005 g, 0.0004 g, 0.0003 g, 0.0002 g, or 0.0001 g.

In some embodiments, the amount of one or more compounds is more than 0.0001 g, 0.0002 g, 0.0003 g, 0.0004 g, 0.0005 g, 0.0006 g, 0.0007 g, 0.0008 g, 0.0009 g, 0.001 g, 0.0015 g, 0.002 g, 0.0025 g, 0.003 g, 0.0035 g, 0.004 g, 0.0045 g, 0.005 g, 0.0055 g, 0.006 g, 0.0065 g, 0.007 g, 0.0075 g, 0.008 g, 0.0085 g, 0.009 g, 0.0095 g, 0.01 g, 0.015 g, 0.02 g, 0.025 g, 0.03 g, 0.035 g, 0.04 g, 0.045 g, 0.05 g, 0.055 g, 0.06 g, 0.065 g, 0.07 g, 0.075 g, 0.08 g, 0.085 g, 0.09 g, 0.095 g, 0.1 g, , 0.15 g, 0.2 g, , 0.25 g, 0.3 g, , 0.35 g, 0.4 g, , 0.45 g, 0.5 g, 0.55 g, 0.6 g, , 0.65 g, 0.7 g, 0.75 g, 0.8 g, 0.85 g, 0.9 g, 0.95 g, 1 g, 1.5 g, 2 g, 2.5, 3 g, 3.5, 4 g, 4.5 g, 5 g, 5.5 g, 6 g, 6.5g, 7 g, 7.5g, 8 g, 8.5 g, 9 g, 9.5 g, or 10 g.

In some embodiments, the amount of one or more compounds ranges from 0.0001 to 10 g, 0.0005 to 9 g, 0.001 to 8 g, 0.005 to 7 g, 0.01 to 6 g, 0.05 to 5 g, 0.1 to 4 g, 0.5 to 4 g, or 1 to 3 g.

25 Methods of Treatment

In still other embodiments, the compounds are useful in various methods of treating a disease or condition. Accordingly, one embodiment provides a method of treating a disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound according to any one of the embodiments disclosed herein or a composition according to any one of the

embodiments disclosed herein, wherein each M is independently a biologically active moiety effective for treating the disease. In some embodiments, the disease is cancer, and each M is independently an anti-cancer drug.

For example, in certain embodiments the disclosure provides a method
5 of treating solid tumors, multiple myeloma, gliomas, clear cell renal cell carcinoma, prostate cancer, ovarian cancer, non-small cell lung cancer, GI malignancies, acute lymphoblastic leukemia, acute myelogenous leukemia, renal cell carcinoma, colorectal carcinoma, epithelial cancers, pancreatic and gastric cancers, renal cell carcinoma, non-Hodgkin's lymphoma, metastatic renal cell carcinoma, malignant mesothelioma,
10 pancreatic, ovarian, and/or lung adenocarcinoma, B-cell malignancies, breast cancer, melanoma, recurrent multiple myeloma, small cell lung cancer, CD22-positive B cell malignancies, Hodgkin's lymphoma/anaplastic large cell lymphoma, or HER2-positive breast cancer.

Certain embodiments also relate to a method of treating a
15 hyperproliferative disorder in a mammal (e.g., a human) that comprises administering to said mammal a therapeutically effective amount of a compound, or a pharmaceutically acceptable salt, ester, prodrug, solvate, hydrate or derivative thereof. In some embodiments, said method relates to the treatment of cancer such as acute myeloid leukemia, cancer in adolescents, adrenocortical carcinoma childhood, AIDS-related
20 cancers (e.g., Lymphoma and Kaposi's Sarcoma), anal cancer, appendix cancer, astrocytomas, atypical teratoid, basal cell carcinoma, bile duct cancer, bladder cancer, bone cancer, brain stem glioma, brain tumor, breast cancer, bronchial tumors, burkitt lymphoma, carcinoid tumor, atypical teratoid, embryonal tumors, germ cell tumor, primary lymphoma, cervical cancer, childhood cancers, chordoma, cardiac tumors,
25 chronic lymphocytic leukemia (CLL), chronic myelogenous leukemia (CML), chronic myeloproliferative disorders, colon cancer, colorectal cancer, craniopharyngioma, cutaneous T-cell lymphoma, extrahepatic ductal carcinoma in situ (DCIS), embryonal tumors, CNS cancer, endometrial cancer, ependymoma, esophageal cancer, esthesioneuroblastoma, Ewing sarcoma, extracranial germ cell tumor, extragonadal
30 germ cell tumor, eye cancer, fibrous histiocytoma of bone, gall bladder cancer, gastric cancer, gastrointestinal carcinoid tumor, gastrointestinal stromal tumors (GIST), germ

- cell tumor, gestational trophoblastic tumor, hairy cell leukemia, head and neck cancer, heart cancer, liver cancer, Hodgkin's lymphoma, hypopharyngeal cancer, intraocular melanoma, islet cell tumors, pancreatic neuroendocrine tumors, kidney cancer, laryngeal cancer, lip and oral cavity cancer, liver cancer, lobular carcinoma in situ
- 5 (LCIS), lung cancer, lymphoma, metastatic squamous neck cancer with occult primary, midline tract carcinoma, mouth cancer, multiple endocrine neoplasia syndromes, multiple myeloma/plasma cell neoplasm, mycosis fungoides, myelodysplastic syndromes, myelodysplastic/myeloproliferative neoplasms, multiple myeloma, merkel cell carcinoma, malignant mesothelioma, malignant fibrous
- 10 histiocytoma of bone and osteosarcoma, nasal cavity and paranasal sinus cancer, nasopharyngeal cancer, neuroblastoma, non-Hodgkin's lymphoma, non-small cell lung cancer (NSCLC), oral cancer, lip and oral cavity cancer, oropharyngeal cancer, ovarian cancer, pancreatic cancer, papillomatosis, paraganglioma, paranasal sinus and nasal cavity cancer, parathyroid cancer, penile cancer, pharyngeal
- 15 cancer, pleuropulmonary blastoma, primary central nervous system (CNS) lymphoma, prostate cancer, rectal cancer, transitional cell cancer, retinoblastoma, rhabdomyosarcoma, salivary gland cancer, skin cancer, stomach (gastric) cancer, small cell lung cancer, small intestine cancer, soft tissue sarcoma, T-Cell lymphoma, testicular cancer, throat cancer, thymoma and thymic
- 20 carcinoma, thyroid cancer, transitional cell cancer of the renal pelvis and ureter, trophoblastic tumor, unusual cancers of childhood, urethral cancer, uterine sarcoma, vaginal cancer, vulvar cancer, or Viral-Induced cancer. In some embodiments, said method relates to the treatment of a non-cancerous hyperproliferative disorder such as benign hyperplasia of the skin (e.g., psoriasis), restenosis, or prostate (e.g., benign
- 25 prostatic hypertrophy (BPH)).

Certain particular embodiments provide methods for treatment of lung cancers, the methods comprise administering an effective amount of any of the above described compounds (or a pharmaceutical composition comprising the same) to a subject in need thereof. In certain embodiments the lung cancer is a non-small cell lung

30 carcinoma (NSCLC), for example adenocarcinoma, squamous-cell lung carcinoma or large-cell lung carcinoma. In other embodiments, the lung cancer is a small cell lung

carcinoma. Other lung cancers treatable with the disclosed compounds include, but are not limited to, glandular tumors, carcinoid tumors and undifferentiated carcinomas.

Accordingly, in some embodiments of the foregoing methods, R^2 is a linker comprising a covalent linkage to a targeting moiety, such as an antibody or a cell surface receptor antagonist. For example, epidermal growth factor receptor (EGFR) inhibitor, a hepatocyte growth factor receptor (HGFR) inhibitor, an insulin-like growth factor receptor (IGFR) inhibitor, a folate, or a MET inhibitor.

In even more embodiments, the method further comprises inducing apoptosis.

Embodiments of the present compounds thus find utility in any number of methods, including, but not limited to: drug delivery; quantifying apoptosis; qualifying therapeutic drug delivery; quantifying apoptosis; and diagnosing and treating diseases, such as blood cancers.

In addition to the above methods, embodiments of the compounds of structure (I) find utility in various disciplines and methods, including but not limited to: cancer treatment and imaging, for example by including a targeting moiety, such as an antibody or sugar or other moiety that preferentially binds cancer cells, in a compound of structure (I) to; and/or drug delivery.

In some embodiments, the method of treatment comprises treating a tumor having tumor cells with tumor cell receptors. In some embodiments, the tumor cells have receptors ranging from 1,000 to 100,000, from 1,000 to 50,000, from 1,000 to 25,000 receptors, 1,000 to 10,000 receptors per cell. For example, in some embodiments the tumor cells have about 1,000, about 10,000, or less than 100,000 receptors per cell.

Methods of Preparation

It is understood that any embodiment of the compounds of structure (I), as set forth above, and any specific choice set forth herein for a R^1 , R^2 , R^3 , L, L^1 , L^2 , L^3 , L^4 , M and/or n variable in the compounds of structure (I), as set forth above, may be independently combined with other embodiments and/or variables of the compounds of structure (I) to form embodiments of the invention not specifically set forth above. In

addition, in the event that a list of choices is listed for any particular R^1 , R^2 , R^3 , L , L^1 , L^2 , L^3 , L^4 , M and/or n variable in a particular embodiment and/or claim, it is understood that each individual choice may be deleted from the particular embodiment and/or claim and that the remaining list of choices will be considered to be within the scope of the
5 invention.

It is understood that in the present description, combinations of substituents and/or variables of the depicted formulae are permissible only if such contributions result in stable compounds.

It will also be appreciated by those skilled in the art that in the process
10 described herein the functional groups of intermediate compounds may need to be protected by suitable protecting groups. Such functional groups include hydroxy, amino, mercapto and carboxylic acid. Suitable protecting groups for hydroxy include trialkylsilyl or diarylalkylsilyl (for example, t-butyl dimethylsilyl, t-butyl diphenylsilyl or trimethylsilyl), tetrahydropyranyl, benzyl, and the like. Suitable protecting groups for
15 amino, amidino and guanidino include t-butoxycarbonyl, benzyloxycarbonyl, and the like. Suitable protecting groups for mercapto include $-C(O)-R''$ (where R'' is alkyl, aryl or arylalkyl), p-methoxybenzyl, trityl and the like. Suitable protecting groups for carboxylic acid include alkyl, aryl or arylalkyl esters. Protecting groups may be added or removed in accordance with standard techniques, which are known to one skilled in
20 the art and as described herein. The use of protecting groups is described in detail in Green, T.W. and P.G.M. Wutz, Protective Groups in Organic Synthesis (1999), 3rd Ed., Wiley. As one of skill in the art would appreciate, the protecting group may also be a polymer resin such as a Wang resin, Rink resin or a 2-chlorotrityl-chloride resin.

Furthermore, all compounds of the invention which exist in free base or
25 acid form can be converted to their salts by treatment with the appropriate inorganic or organic base or acid by methods known to one skilled in the art. Salts of the compounds of the invention can be converted to their free base or acid form by standard techniques.

The following Reaction Schemes illustrate exemplary methods of
30 making compounds of this invention. It is understood that one skilled in the art may be able to make these compounds by similar methods or by combining other methods

known to one skilled in the art. It is also understood that one skilled in the art would be able to make, in a similar manner as described below, other compounds of structure (I) not specifically illustrated below by using the appropriate starting components and modifying the parameters of the synthesis as needed. In general, starting components
5 may be obtained from sources such as Sigma Aldrich, Lancaster Synthesis, Inc., Maybridge, Matrix Scientific, TCI, and Fluorochem USA, etc. or synthesized according to sources known to those skilled in the art (see, for example, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 5th edition (Wiley, December 2000)) or prepared as described in this invention.

10 The following examples are provided for purposes of illustration, not limitation.

EXAMPLES

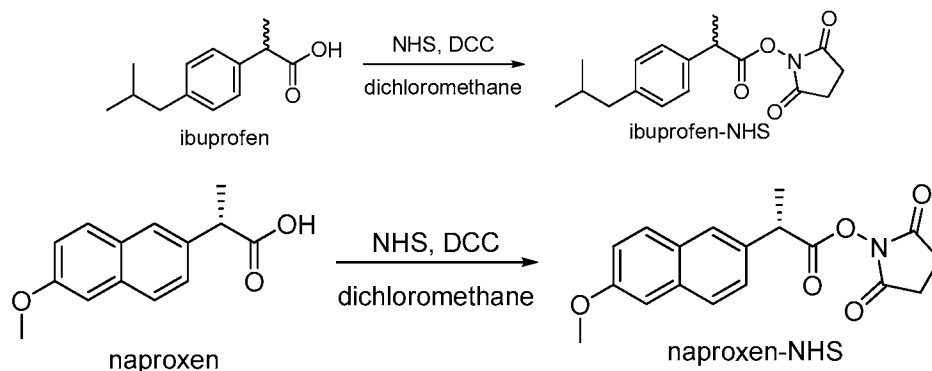
General Methods

¹H and NMR spectra are obtained on a JEOL 400 MHz spectrometer. ¹H
15 spectra are referenced against TMS. Reverse phase HPLC dye analysis is performed using a Waters Acquity UHPLC system with a 2.1mm × 50mm Acquity BEH-C18 column held at 45°C. Mass spectral analysis is performed on a Waters/Micromass Quattro micro MS/MS system (in MS only mode) using MassLynx 4.1 acquisition software. Mobile phase used for LC/MS on dyes is 100 mM 1,1,1,3,3,3-hexafluoro-2-
20 propanol (HFIP), 8.6 mM triethylamine (TEA), pH 8. Phosphoramidites and precursor molecules are analyzed using an Agilent Infinity 1260 UHPLC system with a diode array detector and High Performance Autosampler using an Aapptec[®] Spirit[™] Peptide C18 column (4.6mm × 100mm, 5μm particle size). Excitation and emission profiles experiments are recorded on a Cary Eclipse spectra photometer.

25 All reactions were carried out in oven dried glassware under a nitrogen atmosphere unless otherwise stated.

EXAMPLE 1

SYNTHESIS OF IBUPROFEN-NHS AND NAPROXEN-NHS



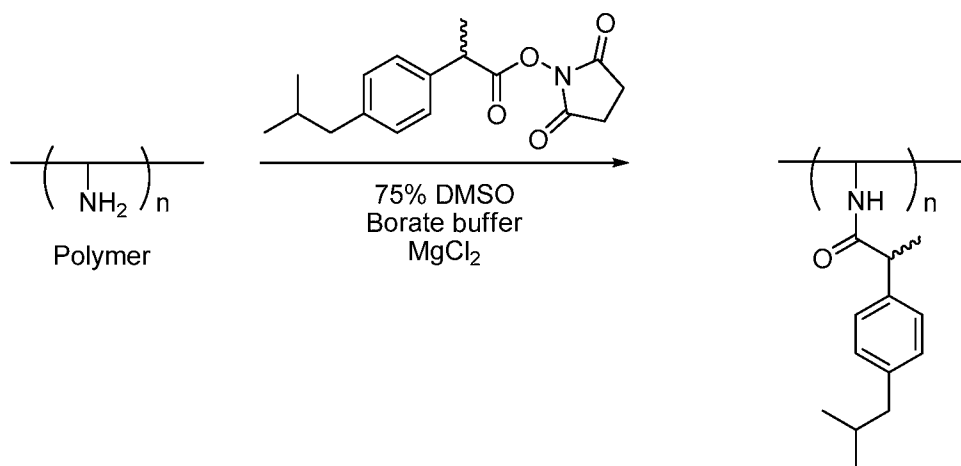
5

Ibuprofen-NHS and naproxen-NHS were synthesized using standard coupling conditions. That is, ibuprofen and naproxen were separately dissolved in dichloromethane and to the mixture was added N,N'-dicyclohexylcarbodiimide (DCC) and N-hydroxysuccinimide (NHS). Products were then purified as necessary and used in the next synthetic step. Ibuprofen-NHS is easily synthesized in one step on a multi-

10 gram scale.

EXAMPLE 2

SYNTHESIS OF IBUPROFEN POLYMER

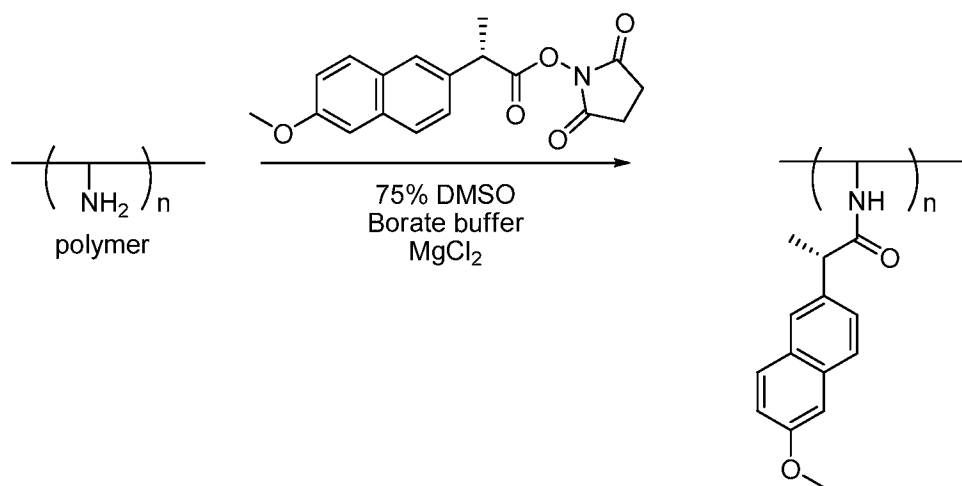


15 An exemplary polymer (e.g., having pendant amine functional groups) is coupled with ibuprofen-NHS as shown in the reaction sequence above. The reaction is carried out using a borate buffered $\text{H}_2\text{O}/\text{DMSO}$ mixture with magnesium chloride. The

reaction successfully adds an ibuprofen moiety to each of the amine functional groups to afford the desired product.

EXAMPLE 3

SYNTHESIS OF NAPROXEN POLYMER



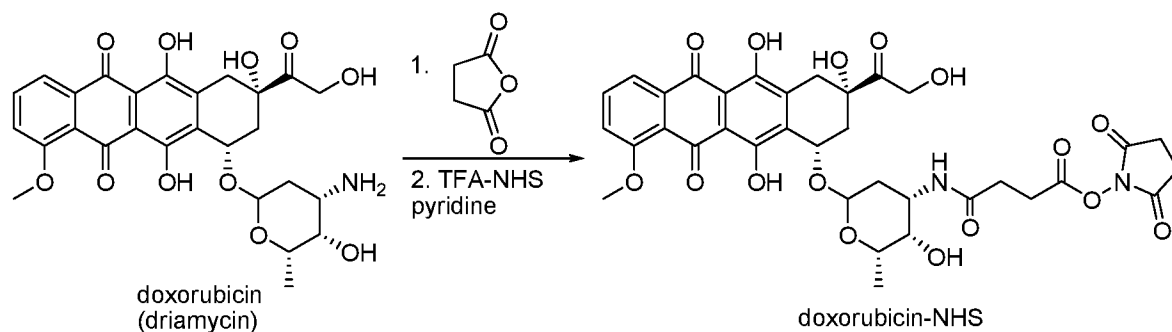
5

An exemplary polymer (e.g., having pendant amine functional groups) is coupled with naproxen-NHS as shown in the reaction sequence above. The reaction is carried out using a borate buffered $\text{H}_2\text{O}/\text{DMSO}$ mixture with magnesium chloride. The reaction successfully adds an ibuprofen moiety to each of the amine functional groups

10 to afford the desired product.

EXAMPLE 4

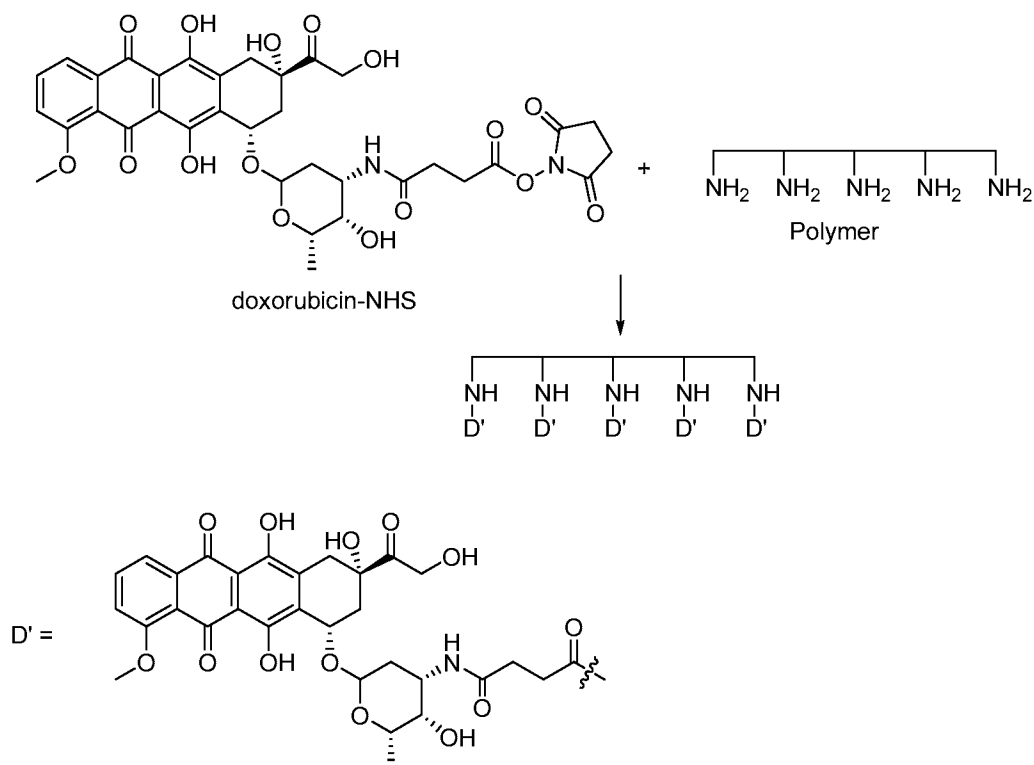
SYNTHESIS OF DOXORUBICIN-NHS



- 5 Doxorubicin was reacted with dihydrofuran-2,5-dione to afford a carboxylic acid containing intermediate. The intermediate was activated using TFA-NHS and pyridine to afford doxorubicin-NHS.

EXAMPLE 5

SYNTHESIS OF DOXORUBICIN POLYMER



10

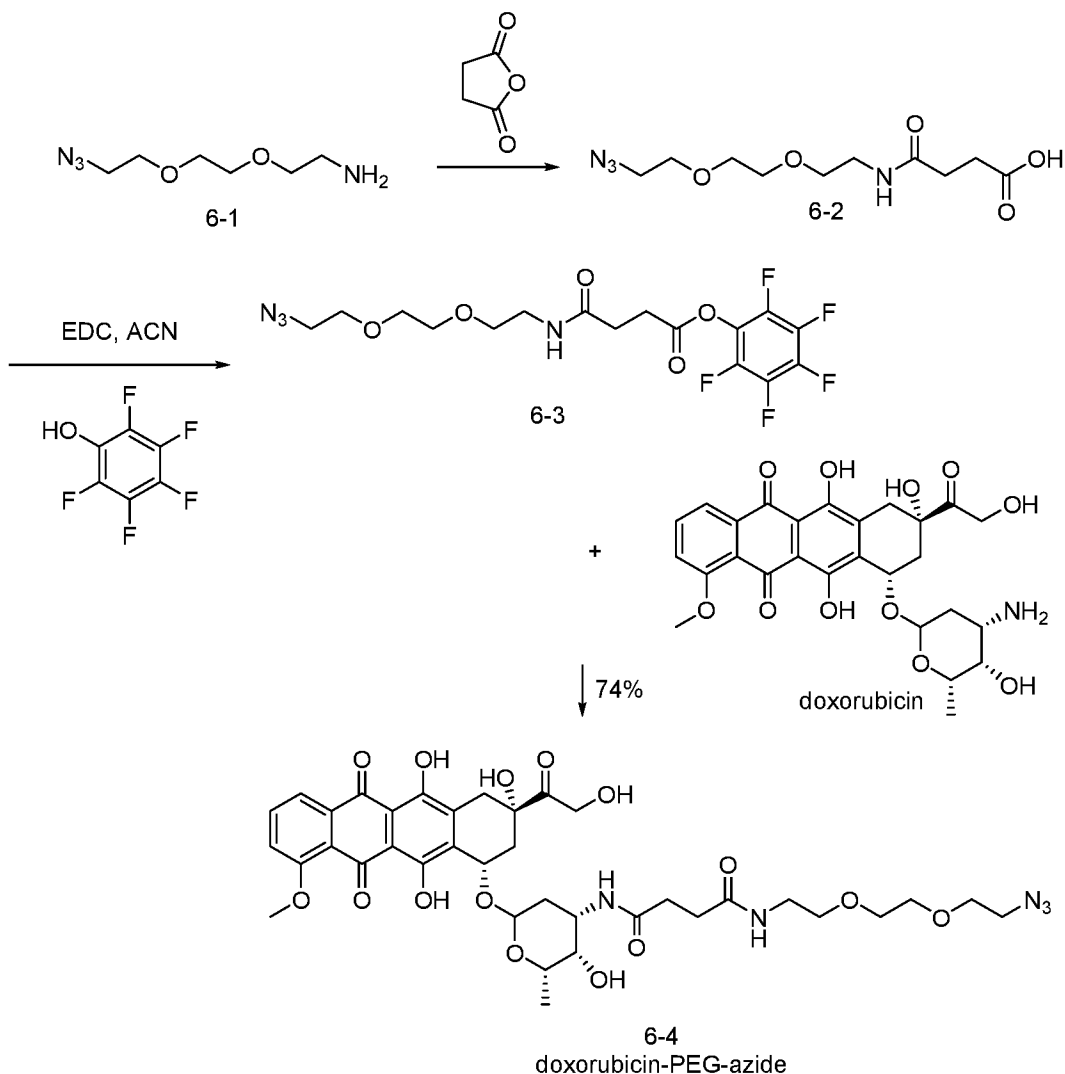
An exemplary polymer is coupled to doxorubicin-NHS. The reaction conditions require experimentation with different solvent mixtures because of the

limited solubility of doxorubicin derivatives. Reaction conditions alternatives include increasing organic solvent content, increasing reaction temperature and adding sodium dodecyl sulfate (SDS) to aid the reaction.

EXAMPLE 6

SYNTHESIS OF DOXORUBICIN-PEG-AZIDE

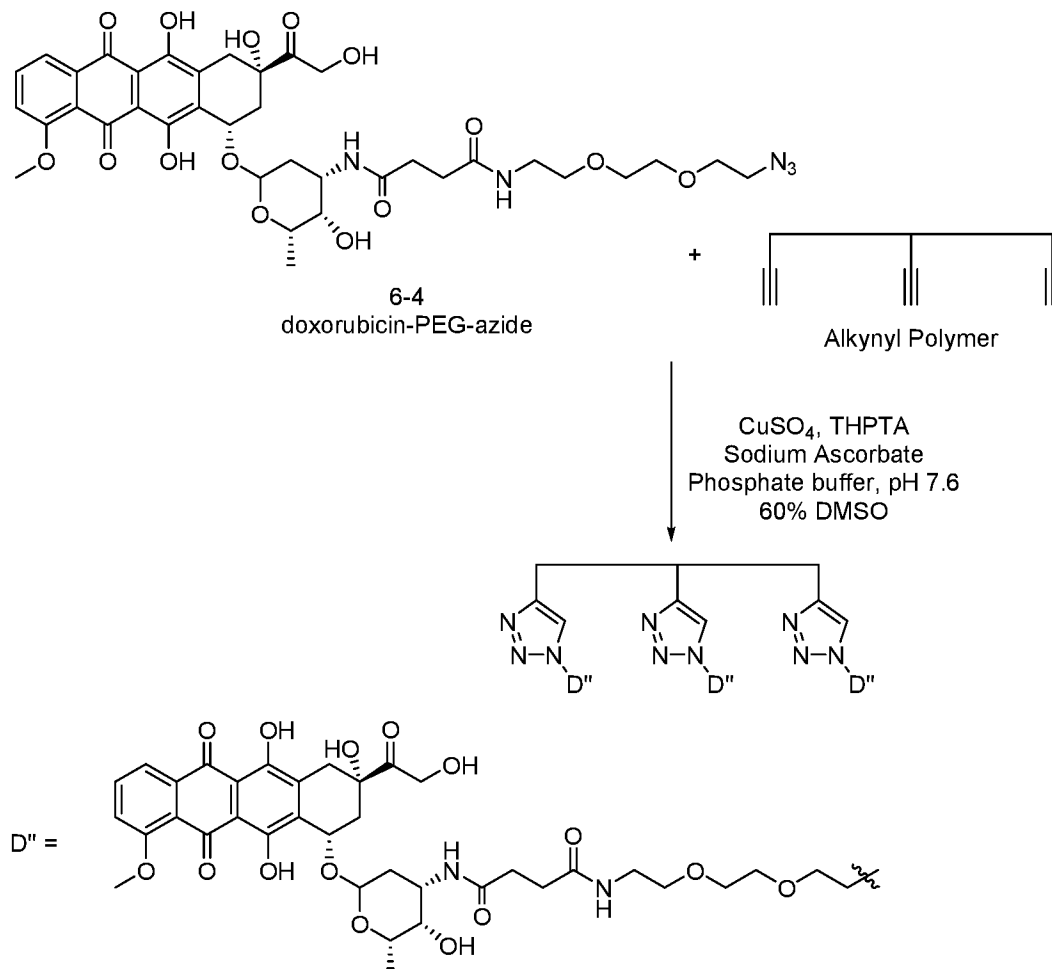
5



Doxorubicin-PEG-azide was synthesized according to the reaction sequence shown above on a 50 mg scale. Azide 6-1 was reacted with dihydrofuran-2,5-dione to afford intermediate 6-2, which was reacted with perfluorophenol to afford intermediate 6-3. Intermediate 6-3 was coupled to doxorubicin to afford the desired product, doxorubicin-PEG-azide in good yield (74%). The presence of the desired product was confirmed by LC-MS.

EXAMPLE 7

SYNTHESIS OF DOXORUBICIN POLYMER (COMPOUND 18)



An exemplary alkynyl-containing polymer is coupled to doxorubicin-

5 PEG-azide. Reaction conditions include CuSO₄, tris(3-hydroxypropyltriazolylmethyl)amine (THPTA), and sodium ascorbate. The reaction is carried out in phosphate buffered aqueous solvent with 60% DMS at a pH of 7.6. The reaction is run at room temperature and the presence of the desired product is confirmed by LC-MS.

10 Numerous advantages are afforded by embodiments disclosed herein, including the ability to control the number of biologically active moieties or fluorescent dye moieties that are coupled to the polymer and any subsequent targeting moiety. The composition of the polymer backbone can also be selected to afford desirable solubility properties, for example, by controlling the incorporation of charged moieties (e.g.,

15 number, frequency, spacing, etc.). In addition to the properties provided by the

composition of the backbone, the side chains can be selected to provide a source for tuning the solubility of the compounds disclosed herein.

The embodiments disclosed herein also provide compounds that can advantageously include multiple therapeutic agents, for example, for complimentary or synergistic therapeutic strategies. In addition, embodiments of the present disclosure provide combinations of therapeutic agents, targeting moieties, and dye moieties (e.g., fluorophores) that can be used for simultaneous targeting, treatment and detection. The ease of coupling polymer-drug constructs to targeting agents such as antibodies, antibody fragments, proteins or other clinically interesting agents provides utility to a wide variety of interesting applications (e.g., surface chemistries, assay development, etc.).

The compounds of certain embodiments also provide other desirable properties, including enhanced permeability and retention effects. In addition to providing necessary solubility characteristics, the chemical features of embodiments of the present compounds can be adjusted to modulate the compound's ability to permeate diseased cells/tissue and be retained within the same. These features allow effective delivery of biologically active agents by increasing permeation and increasing efficacy by enhancing retention.

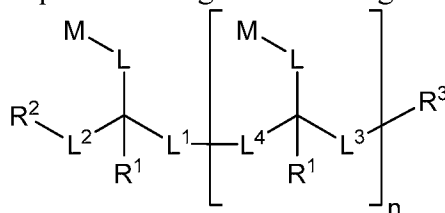
All of the U.S. patents, U.S. patent application publications, U.S. patent applications, foreign patents, foreign patent applications and non-patent publications referred to in this specification, including U.S. Provisional Patent Application No. 62/598,365, filed December 13, 2017, are incorporated herein by reference, in their entirety to the extent not inconsistent with the present description.

From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

What is claimed is:

1. A compound having the following structure (I):



(I)

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

M is, at each occurrence, independently a biologically active moiety, or fragment thereof, a prodrug of a biologically active moiety, or fragment thereof, a fluorescent dye, an imaging agent, or a radioisotope binding site, provided at least one occurrence of M is not a fluorescent dye;

L is a physiologically cleavable linker;

L^1 , L^2 and L^3 are, at each occurrence, independently an optional alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene, heteroalkynylene or heteroatomic linker;

L^4 is, at each occurrence, independently an alkylene, alkenylene, alkynylene, heteroalkylene, heteroalkenylene or heteroalkynylene linker comprising one or more charged moieties, provided at least one charged moiety is not a phosphate ester;

R^1 is, at each occurrence, independently H, alkyl or alkoxy;

R^2 and R^3 are each independently -H, -OH, -SH, alkyl, alkoxy, alkylether, heteroalkyl, alkylaminyl, alkylcarbonyl, alkoxy carbonyl, $-OP(=R_a)(R_b)R_c$, Q or a protected form thereof, or L' ;

R_a is O or S;

R_b is OH, SH, O^- , S^- , OR_d or SR_d ;

R_c is OH, SH, O^- , S^- , OR_d , OL' , SR_d , alkyl, alkoxy, heteroalkyl, heteroalkoxy, alkylether, alkoxyalkylether, phosphate, thiophosphate, phosphoalkyl, thiophosphoalkyl, phosphoalkylether or thiophosphoalkylether;

R_d is a counter ion;

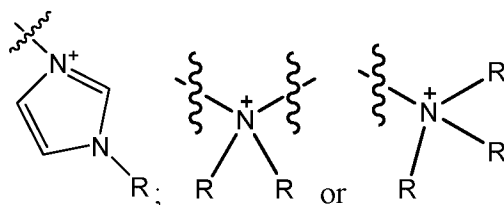
Q is, at each occurrence, independently a moiety comprising a reactive group, or protected form thereof, capable of forming a covalent bond with a complementary reactive group Q' on a targeting moiety;

L' is, at each occurrence, independently a linker comprising a covalent bond to Q, a targeting moiety, a linker comprising a covalent bond to a targeting moiety, a solid support or solid support residue, a linker comprising a covalent bond to a solid support or solid support residue or a linker comprising a covalent bond to a further compound of structure (I); and

n is an integer of one or greater.

2. The compound of claim 1, wherein the charged moieties are positively charged.

3. The compound of claim 2, wherein the charged moieties independently have one of the following structures:

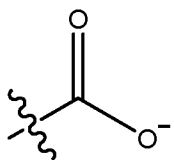


wherein:

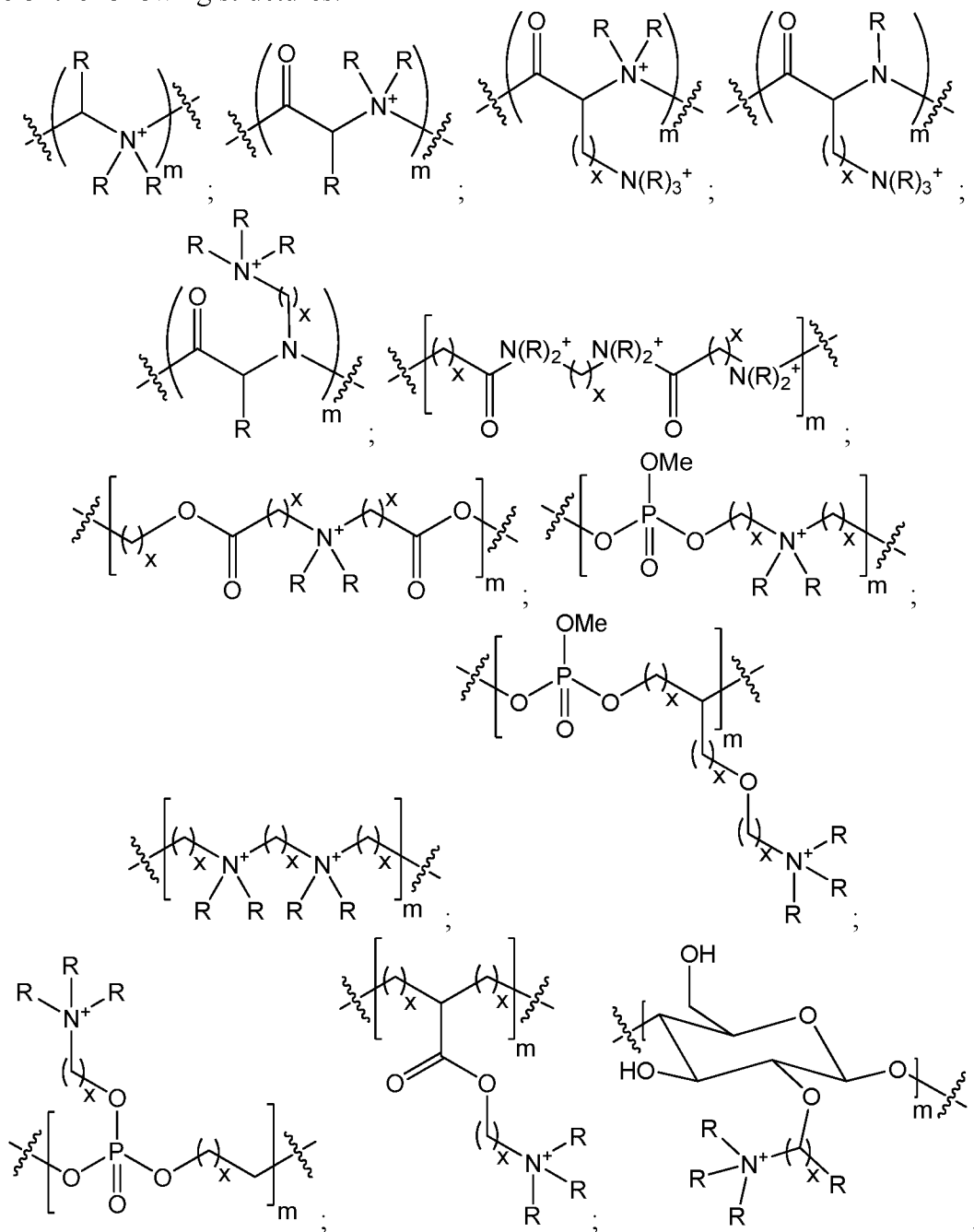
R is, at each occurrence, independently H or C₁-C₆ alkyl.

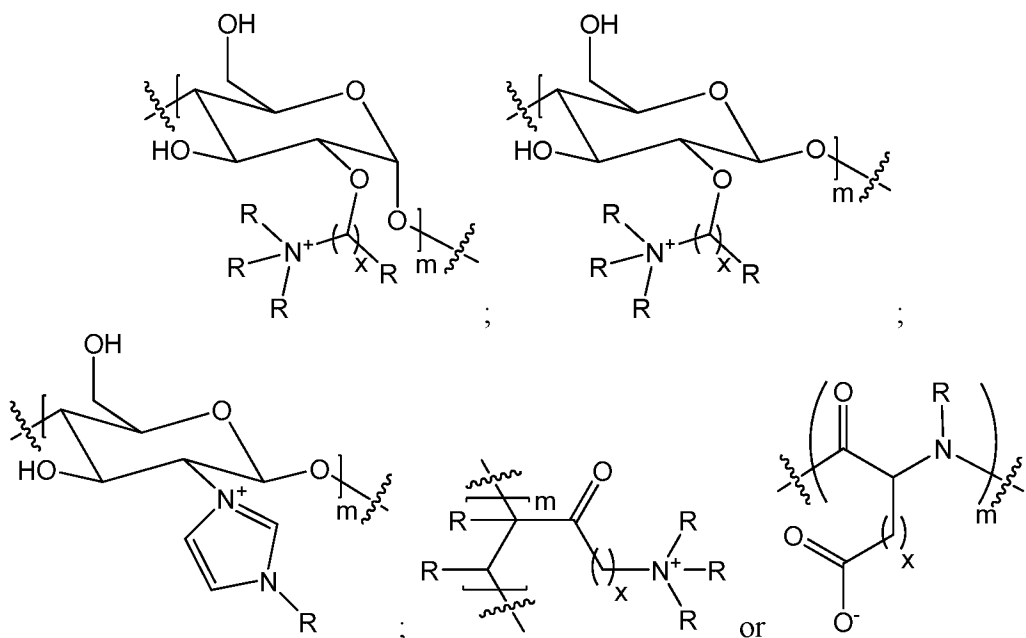
4. The compound of claim 1, wherein the charged moieties are negatively charged.

5. The compound of claim 4, wherein the charged moieties have the following structure:



6. The compound of any one of claims 1-5, wherein L^4 comprises one of the following structures:





wherein:

R is, at each occurrence, independently H or C₁-C₆ alkyl;

x is an integer from 0 to 6; and

m is an integer of 1 or greater.

7. The compound of any one of claims 1-6, wherein L is at each occurrence a linker comprising a functional group capable of formation by reaction of two complementary reactive groups.

8. The compound of any one of claims 1-7, wherein L is, at each occurrence, independently a linker comprising an amide bond, an ester bond, a disulfide bond, a double bond, a triple bond, an ether bond, a ketone, a diol, a cyano, a nitro, a heterocycle, a heteroaryl or combinations thereof.

9. The compound of any one of claims 1-8, wherein L², L³ and L⁴ are, at each occurrence, independently C₁-C₆ alkylene, C₂-C₆ alkenylene or C₂-C₆ alkynylene.

10. The compound of any one of claims 1-9, wherein R² and R³ are each independently -OH or -OP(=R_a)(R_b)R_c.

11. The compound of any one of claims 1-9, wherein one of R^2 or R^3 is -OH or -OP(=R_a)(R_b)R_c, and the other of R^2 or R^3 is Q or a linker comprising a covalent bond to Q.

12. The compound of any one of claims 1-9 or 11, wherein Q comprises a nucleophilic reactive group, an electrophilic reactive group or a cycloaddition reactive group.

13. The compound of claim 12, wherein Q comprises a sulfhydryl, disulfide, activated ester, isothiocyanate, azide, alkyne, alkene, diene, dienophile, acid halide, sulfonyl halide, phosphine, α -haloamide, biotin, amino or maleimide functional group.

14. The compound of claim 13, wherein the activated ester is an N-succinimide ester, imidoester or polyfluorophenyl ester.

15. The compound of claim 13, wherein the azide is an alkyl azide or acyl azide.

16. The compound of any one of claims 1-9 or 11, Q is a moiety selected from Table 1.

17. The compound of any one of claims 1-9, wherein one of R^2 or R^3 is L', and L' is a linker comprising a covalent bond to a solid support.

18. The compound of claim 17, wherein the solid support is a polymeric bead or non-polymeric bead.

19. The compound of any one of claims 1-9, wherein one of R^2 or R^3 is L', and L' is a targeting moiety or a linker to a targeting moiety.

20. The compound of claim 19, wherein L' is a linker to a targeting moiety, the linker comprising a heteroalkylene linker.
21. The compound of any one of claims 1-20, wherein the targeting moiety is an antibody or cell surface receptor antagonist.
22. The compound of claim 21, wherein the antibody or cell surface receptor antagonist is an epidermal growth factor receptor (EGFR) inhibitor, a hepatocyte growth factor receptor (HGFR) inhibitor, an insulin-like growth factor receptor (IGFR) inhibitor, a folate, or a MET inhibitor.
23. The compound of any one of claims 1-22, wherein n is an integer from 1 to 100.
24. The compound of any one of claims 1-23, wherein n is an integer from 1 to 10.
25. The compound of any one of claims 1-24, wherein M comprises at each occurrence, independently an NSAID, a kinase inhibitor, an anthracycline, an EGFR inhibitor or an alkylating agent.
26. The compound of any one of claims 1-24, wherein M comprises, at each occurrence, independently an anti-cancer drug, and the targeting moiety is an antibody specific for a tumor cell antigen.
27. The compound of claim 26, wherein the tumor cell antigen is an EGFR, a HER 2, a folate receptor, CD 20 or CD 33.
28. The compound of claim 1, wherein the compound is selected from a compound in Table 2.

29. A composition comprising the compound of any one of claims 1-28 and a pharmaceutically acceptable carrier.

30. A composition comprising a plurality of conjugates, the conjugates comprising a compound of claim 1 comprising a covalent bond to an antibody via a single linkage, wherein the plurality of conjugates has at least 90% structural homogeneity.

31. The composition of claim 30, wherein the plurality of conjugates has at least 95% structural homogeneity.

32. The composition of claim 30, wherein the plurality of conjugates has greater than 99% structural homogeneity.

33. The composition of any one of claims 29-32, wherein one of R^2 and R^3 is $-OP(=R_a)(R_b)OL'$ or L' , and L' is the antibody or a linker comprising a covalent bond to the antibody.

34. A method of treating a disease, the method comprising administering to a subject in need thereof a therapeutically effective amount of a compound of any one of claims 1-28 or a composition of any one of claims 29-33, wherein each M is independently a biologically active moiety effective for treating the disease.

35. The method of claim 34, wherein the disease is cancer, and each M is independently an anti-cancer drug.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2018/065432

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2018/065432

A. CLASSIFICATION OF SUBJECT MATTER		
INV.	C07F9/09 A61K47/59	C08G79/04 C08F220/34 C08L85/02 A61K47/58
ADD.		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED		
Minimum documentation searched (classification system followed by classification symbols) C09J C07F C08G C08F C08L		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2010/068862 A2 (UNIV MASSACHUSETTS [US]; EMRICK TODD [US]; CHEN XIANGJI [US]; MCRAE SA) 17 June 2010 (2010-06-17) Polymer "CP7" in figure 14B, disclosing a polymer-drug conjugate, whereby the drug is camphothecin, and whereby the polymer contains a repeating unit, that is a charged moiety. Random polymer with doxorubicin-linked to polymer backbone also comprising a charged moiety: page 37, scheme 3; page 37 Markush formula describing co-polymers with zwitterionic moieties as repeating units and with biological agents "A" attached via a linker to a repeating unit of the polymer backbone: claim 13 The co-polymer, where the terminal end of the polymer is featuring a targeting -/--	1-35
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
8 March 2019		20/03/2019
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Lange, Tim

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/065432

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	moiety "T", targeting towards a biological target the biological agent "A" is active to: claim 20 ----- WO 2017/196954 A1 (SONY CORP [JP]; SONY CORP AMERICA [US]) 16 November 2017 (2017-11-16) Polymer "I-4" featuring a drug "M" bound by linker "L1" to polymer backbone that contains an ammonium group as charged moiety. Markush formula (I) of claim 1 The group "M" represents fluorescent dyes (BODIPY analogues), polyaromatic compounds such as pyrenes and perylenes etc.: claims 43-49 -----	1-35
A	WO 01/91725 A2 (UNIV JOHNS HOPKINS [US]) 6 December 2001 (2001-12-06) Polyphosphate polymer featuring an ammonium groups as charged moieties in the polymer backbone, the ammonium group linked to a biologically active moiety, the biologically active compound being a sterole: scheme 4, page 49 and claim 35 Markush formulae describing such compounds: claims 11-15 The hydrophylic part (i.e. the charged group) can be integral to the polymer main chain or can be a pendent group linked to the main chain (claim 7) Use of polymer for controlled release of drug substance: claim 45 Biologically active substance can also be DNA, RNA, proteins and small therapeutic molecules: claim 53 ----- -/--	1

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2018/065432

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2016/077625 A1 (STAYTON PATRICK S [US]; CONVERTINE ANTHONY J [US]; RATNER DANIEL M [US]) 19 May 2016 (2016-05-19) A polymeric carrier as a macromolecular prodrug releasing a therapeutic agent: page 29, line 10 - page 30, line 24 A copolymer carrying Ciprofloxacin as therapeutic agent linked to the polymer backbone and a charged moiety linked to the polymer backbone: figures 8, 11 Further therapeutic agents: figures 17A-17G Markush formula describing a copolymer featuring a charged moiety "S" and a drug-carrying moiety $(-C(=O)-X-L1-C1-[L2-C2]_n-D)$, D being the drug: claim 26 embodiments for charged moiety "S": claim 52 -----	1-35
X	EP 2 272 897 A1 (UNIV TOKYO [JP]) 12 January 2011 (2011-01-12) A polymeric carrier as prodrug releasing a therapeutic agent, and where the polymer features a cationic repeating unit and a biologically active group carrying repeating unit: figure 1, page 17 and claim 4 -----	1-35
X,P	WO 2017/214165 A1 (SONY CORP [JP]; SONY CORP AMERICA [US]) 14 December 2017 (2017-12-14) Exemplary polymers I-1 on page 37 Polymer on page 52 and page 53/top Polymer page 55 Use of polymer for visual detection of analyte by fluorescence: claims 42-50 -----	1-35

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/US2018/065432

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010068862 A2	17-06-2010	AU 2009324490 A1 CA 2745302 A1 CA 2745307 A1 CN 102317332 A EP 2356167 A2 EP 2358770 A2 US 2011319569 A1 US 2011319570 A1 US 2016346400 A1 WO 2010068862 A2 WO 2010068864 A2	23-06-2011 17-06-2010 17-06-2010 11-01-2012 17-08-2011 24-08-2011 29-12-2011 29-12-2011 01-12-2016 17-06-2010 17-06-2010
WO 2017196954 A1	16-11-2017	EP 3455238 A1 WO 2017196954 A1	20-03-2019 16-11-2017
WO 0191725 A2	06-12-2001	AU 6525201 A US 2002045263 A1 WO 0191725 A2	11-12-2001 18-04-2002 06-12-2001
WO 2016077625 A1	19-05-2016	US 2018043029 A1 WO 2016077625 A1	15-02-2018 19-05-2016
EP 2272897 A1	12-01-2011	AU 2009224286 A1 CA 2718003 A1 CN 101970541 A EP 2272897 A1 JP 5467366 B2 JP WO2009113645 A1 KR 20100138910 A TW 200948384 A US 2011052917 A1 WO 2009113645 A1	17-09-2009 17-09-2009 09-02-2011 12-01-2011 09-04-2014 21-07-2011 31-12-2010 01-12-2009 03-03-2011 17-09-2009
WO 2017214165 A1	14-12-2017	NONE	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-35

Conjugates according to structure (I), where the variable M represents a biologically active moiety, a prodrug thereof, a fragment thereof, a fluorescent dye, an imaging agent or a radioisotope binding site; compositions therewith and methods of treatments.

1.1. claims: 25, 35(completely); 1-24, 28-34(partially)

Conjugates according to structure (I), where the variable M represents a biologically active moiety, compositions therewith and methods of treatments.

1.2. claims: 1-24, 28-34(all partially)

Conjugates according to structure (I), where the variable M represents a prodrug of a biologically active moiety, compositions therewith and methods of treatments.

1.3. claims: 1-24, 28-34(all partially)

Conjugates according to structure (I), where the variable M represents a fragment of a biologically active moiety, compositions therewith and methods of treatments.

1.4. claims: 1-24, 28-34(all partially)

Conjugates according to structure (I), where the variable M represents a fluorescent dye, compositions therewith and methods of treatments.

1.5. claims: 1-24, 28-34(all partially)

Conjugates according to structure (I), where the variable M represents an imaging agent, compositions therewith and methods of treatments.

1.6. claims: 1-24, 28-34(all partially)

Conjugates according to structure (I), where the variable M represents a radioisotope binding site, compositions therewith and methods of treatments
